TITLE PAGE

Protocol Title: A Two Part, Randomized, Open-label, Cross over Study in Healthy Elderly Participants to Evaluate the Relative Bioavailability of Hydrobromide Salt Tablet Formulations of Danirixin in the Fed and Fasted States, and to Evaluate the Effect of Food and Gastric Acid Secretion Suppression on Danirixin Pharmacokinetics Following Administration of Hydrobromide Salt Tablets.

Protocol Number: 207573 / 01

Short Title: GSK1325756 Relative Bioavailability Study in Healthy Elderly Participants

Compound Number: GSK1325756

Study Phase: I
Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): IND:108168

Approval Date: 22-FEB-2018

SPONSOR SIGNATORY:

PPD

22 Feb 2018

Aili L.Lazaar, MD PPD
Director Discovery Medicine, Respiratory Therapy Area Unit

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment -01	*22-FEB-2018*	2017N316476_01
Original Protocol	*21-Dec-2017*	2017N316476_00

Amendment 22-FEB-2018

Overall Rationale for the Amendment: This amendment modifies the design of Part A incorporating a fasted group for each of the 4 treatments in addition to the fed groups. Additional clarifications have been made where necessary throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
Synopsis (Section 1) – and throughout document	• Changed Strata/Stratum to Group	• Prevent confusion over the use of the term stratum/strata which is generally related to randomization
Synopsis (Section 1)	• Updated Part A from a single group to two groups	• Update study design to have fed and fasted groups in Part A
Synopsis (Section 1)	• Clarified OMP dosing and completion of OMP diary	• Provide additional clarity on timing of OMP dosing relative to screening visit and completion of diary
Schedule of Activities (Section 2)	• Updated Part A from a single group to two groups	• Update study design to have fed and fasted groups in Part A
Schedule of Activities (Section 2)	• Update minor inconsistencies in the table and footnotes	• Correct minor inconsistencies
Schedule of Activities (Section 2)	• Changed Strata/Stratum to Group	• Prevent confusion over the use of the term stratum/strata which is generally related to randomization
Schedule of Activities (Section 2)	• Clarified OMP dosing	• Provide additional clarity on timing of OMP dosing relative to screening visit
Objectives and Endpoints (Section 4)	• Updated Part A from a single group to two groups	• Update study design to have fed and fasted groups in Part A
Overall Design (Section 5.1)	• Updated Part A from a single group to two groups	• Update study design to have fed and fasted groups in Part A
Overall Design (Section 5.1)	• Clarified OMP dosing	• Provide additional clarity on timing of OMP dosing relative to screening visit
Number of	• Updated Part A from a	• Update study design to have fed

Section # and Name	Description of Change	Brief Rationale
Participants (Section 5.2)	single group to two groups	and fasted groups in Part A
Exclusion Criteria (Section 6.2)	• Removal of exclusion criteria related to TB	• Included in original protocol in error
Exclusion Criteria (Section 6.2)	• Changed pregnancy test from urine to serum	• Error in original protocol
Exclusion Criteria (Section 6.2)	• Updated details related to prohibited and allowed concomitant medications	• Clarified the information in the original protocol
Exclusion Criteria (Section 6.2)	• Removed exclusion criteria related to presence of HBcAb	• Study drug is not an immunosuppressant; therefore, criteria is not applicable.
Method of treatment assignment (Section 7.3)	• Updated to include the addition of fed and fasted groups in Part A	• Updated based on revised study design
Statistical Considerations and Sample size determination (Section 10 and 10.1)	• Updated to reflect revised study design	• Updated based on revised study design
All sections	• Additional minor clarifications added	• To clarify protocol

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1. SYNOPSIS

Protocol Title:

A Two Part, Randomized, Open-label, Cross over Study in Healthy Elderly Participants to Evaluate the Relative Bioavailability of Hydrobromide Salt Tablet Formulations of Danirixin in the Fed and Fasted States, and to Evaluate the Effect of Food and Gastric Acid Secretion Suppression on Danirixin Pharmacokinetics Following Administration of Hydrobromide Salt Tablets.

Short Title:

GSK1325756 Relative Bioavailability Study in Healthy Elderly Participants

Rationale:

Part A of this study will provide an understanding of the PK of 3 test tablet formulations of the HBr salt of danirixin in healthy elderly participants in fed and fasted conditions in comparison to the current HBr salt tablet formulation. The current formulation is a hemihydrate salt tablet formulation manufactured using roller compaction (RC). The test formulations are manufactured by direct compression (DC) and will investigate the performance of these DC tablets, as well as the inclusion of the excipient hydroxypropyl methylcellulose (HPMC). Formulation selection for Part B will occur following review of the PK data collected in Part A.

Part B of this study will provide an understanding of the PK using the selected formulation from Part A in the fed and fasted state; during gastric acid suppression and in the monohydrate state under fed conditions in a population of healthy elderly participants. Danirixin is currently administered with food, therefore the investigation of food effect for the selected formulation could potentially enable dosing without food. Additionally, omeprazole (OMP) is being administered with the selected formulation to investigate a potential PK interaction as gastric pH has been shown to alter PK exposure and this study will further enable us to investigate OMPs influence in the presence and absence of food. Finally, the monohydrate tablet simulates a hemihydrate to monohydrate tablet in stressed conditions.

The outcome of this study will contribute to the selection of the most appropriate formulation/dosing regimen for future studies.

Objectives and Endpoints:

Objectives	Endpoints
Part A: • To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed and fasted states.	• Danirixin PK parameters: AUC(0-inf) and Cmax.
• To provide safety and tolerability information for oral administration of the different formulations of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters
• To estimate the secondary pharmacokinetic parameters of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed and fasted states.	• Danirixin PK parameters: AUC(0-t), AUC(0-24), tmax, t1/2, tlast and tlag.
Part B: • To estimate the effect of food on the single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the effect of OMP on the single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects in various fed and fasted states.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax,

Objectives	Endpoints
formulation of the HBr tablet (MONO), in healthy elderly subjects in the fed state.	t1/2, tlast and tlag.
• To provide safety and tolerability information for oral administration of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters

Overall Design:

This is a Phase I, two part (Part A and Part B each part contains 2 Groups), randomized, open-label, single dose, cross-over study conducted with healthy elderly participants. Part A will support the selection of the formulation and Part B will address the Proton Pump Inhibitor (PPI) effect, food effect and PK of the monohydrate.

Part A

In Part A, approximately 16 healthy elderly participants will be enrolled such that approximately 13 subjects complete dosing and critical assessments for all planned treatment periods. The 16 participants will be randomized and designated to go into one of two (2) groups, Group 1 and Group 2. Group 1 will be administered danirixin in the fed state in all treatment periods. Group 2 will be administered danirixin in the fasted state in all treatment periods. Participants will undergo a screening period ~30 days prior to the first dose of study treatment, followed by 4 treatment periods with at least a 5 day washout period between each treatment and a follow-up period of 3-10 days following the last dose of danirixin.

Eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the last dose of danirixin, participants will return to the clinic for the final follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. A study design schematic for Part A is presented in Table 1.

Table 1 Part A Group 1 and 2 Study Design

Screening Period *Within 30 Days of Day 1*	Treatment Period 1	5- Day Washout	Treatment Period 2	5 Day Washout	Treatment Period 3	5 Day Washout	Treatment Period 4	Early Discontinuation/ Follow-Up Visit 3-10 days after last dose of DNX

Part B

In Part B, approximately 24 healthy elderly participants will be enrolled such that approximately 20 subjects (10 subjects per group) complete dosing and critical assessments for all planned treatment periods in Group 1 and 2.

In Part B Group 2 eligible participants will take omeprazole (OMP), 40 mg from Day -4 relative to treatment period 1, Day 1 first dose of danirixin through all periods and washouts until the final treatment period 3 PK assessment (48hr post dose). Participants will be provided with a participant diary to document daily recordings of OMP dosing occurring outside of the unit.

For Part B Group 2, once screened, eligible participants will be instructed to return to the clinic on Day -4 relative to the first dose of danirixin on Day 1 (Period 1) for a qualification visit. During this visit, clinical safety assessments will be performed as specified in the Section 2 Schedule of Activities of the protocol. Once assessments are complete, eligible participants will be administered a single of dose of OMP in the clinic. Participants will be discharged with OMP and will take OMP on Day -3 and Day -2 at home. OMP will be administered in the clinic on Day -1, Day 1, Day 2 and Day 3 of each treatment period. OMP will be taken on an outpatient daily bases on all other days through each period until the Period 3 post dose 48h PK assessment.

For Group 1 and 2, eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the last dose of danirixin, participants will return to the clinic for the final follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. Study design schematics are presented in Table 2 and Table 3 for Part B Group 1 and 2, respectively.

Table 2 Part B Group 1 Study Design

Screening Period *Within 30 Days of Day* 1	Treatment Period 1	5- Day Washout	Treatment Period 2	5 Day Washout	Treatment Period 3	5 Day Washout	Treatment Period 4	Early Discontinuation Follow-Up Visit 3-10 days after last dose of DNX

Table 3 Part B Group 2 Study Design

Screening Period Within *30 Days of Day* 1	Day -4	Treatment Period 1	5- Day Washout	Treatment Period 2	5 Day Washout	Treatment Period 3	Early Discontinuation Follow-Up Visit 3 - 10 days after last dose of DNX
	OMP taken daily through all treatment and washout periods, ending with final assessments for Treatment period 3						

Number of Participants:

In Part A, approximately 16 participants will be randomized such that approximately 13 evaluable participants complete the study. Participants will be randomized and designated to go into one of two (2) groups, Group 1 and Group 2. There will be approximately 8 participants in each group.

In Part B, a total of approximately 24 participants (12 participants per group) will be randomized per group such that approximately 10 evaluable participants complete each group.

Table 4 Part A Treatment Descriptions

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
A	1 x 50 mg danirixin HBr tablet (600 mg RC formulation) reference formulation; fed state high fat meal (heavy)	single dose
B	1 x 50 mg danirixin HBr tablet (475mg DC formulation); fed state high fat meal (heavy)	single dose
C	1 x 50 mg danirixin HBr tablet (600 mg DC formulation); fed state high fat meal (heavy)	single dose
D	1 x 50 mg danirixin HBr tablet (600 mg DC tablet formulation with 5% HPMC); fed state high fat meal (heavy)	single dose
AO	1 x 50 mg danirixin HBr tablet (600 mg RC formulation) reference formulation; fasted	single dose
BO	1 x 50 mg danirixin HBr tablet (475mg DC formulation); fasted	single dose
CO	1 x 50 mg danirixin HBr tablet (600 mg DC formulation); fasted	single dose
DO	1 x 50 mg danirixin HBr tablet (600 mg DC tablet formulation with 5% HPMC); fasted	single dose

Table 5 Part B Group 1 Treatment Descriptions (without OMP)

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
E	1 x danirixin Selected formulation; fasted	single dose
F	1 x danirixin Selected formulation; fed state normal meal (light)	single dose
G	1 x danirixin selected formulation; fed state high fat meal (heavy)	single dose

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
H	1 x 50 mg danirixin monohydrate formulation; fed state high fat meal (heavy)	single dose

Table 6 Part B Group 2 Treatment Descriptions (with OMP)

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
I	1 x danirixin selected formulation; fasted with 40mg OMP	single dose
J	1 x danirixin selected formulation; fed state normal meal (light) with 40mg OMP	single dose
K	1 x danirixin selected formulation; fed state high fat meal (heavy) with 40mg OMP	single dose

2. SCHEDULE OF ACTIVITIES (SOA) PART A (GROUP 1 AND GROUP 2) AND PART B (GROUP 1)

Periods 1-4

Procedure	Screening (up to 30 days prior to Day 1) [1]	Study Day (Treatment Periods 1-4) [2]															Early Discontinuation /Follow-up (3 to 10 days post-last dose)
			1														
		Day -1	Pre-dose	0h	0.5h	1h	1.5h	2h	3h	4h	6h	8h	10h	12h	24h	48h	
Informed Consent	X																
Inclusion and Exclusion Criteria	X	X															
Demographics	X																
Full Physical Exam including Height and Weight	X																
Brief Physical Exam		X															X
Medical History (includes substance usage)	X	X															
Pregnancy Test, (WOCBP)[3]	X	X															

Procedure	**Screening (up to 30 days prior to Day 1)** [1]	**Study Day (Treatment Periods 1-4)** [2]														**Early Discontinuation /Follow-up (3 to 10 days post-last dose)**
			1													
		Day -1	**Pre-dose**	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
FSH and estradiol (if needed)	X																
HIV, Hep B and Hep C Screen	X																
Urine Drug Screen	X	X															
Alcohol Screen-Breathalyzer	X	X															
Urine Cotinine Screen	X	X															
Admission to Unit		X															
Laboratory Assessments (include liver chemistries)	X	X															X
12-lead ECG [4]	X	X						X									X
Vital Signs[5]	X		X												X	X	X
Randomization			X														

Procedure	**Screening (up to 30 days prior to Day 1)** [1]	**Study Day (Treatment Periods 1-4)** [2]														**Early Discontinuation /Follow-up (3 to 10 days post-last dose)**
			1													
		Day -1	**Pre-dose**	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
Meal [6]			X														
Danirixin Administration [7]				X													
Pharmacokinetic Sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	
SAE Review	←==========→																
AE Review		X	←==========→														
Concomitant Medication Review		X	←==========→														
Discharge															X		

1. Screening must be performed within 30 days prior to receiving the dose of Danirixin on Day 1 of period 1.
2. Treatment periods 1-4 will include a minimum 5 day wash-out from day of dosing between each treatment
3. Serum pregnancy test (where applicable) will be performed at the screening visit and a urine pregnancy test at all other time points specified.
4. Triplicate ECGs at screening and on Day -1 of each treatment period only. Single ECGs at other timepoints (performed at a similar time of day as Day 1 Pre-dose), unless a reading meets the QTc stopping criteria, in which case two further measurements will be taken at the same time point and the average values captured.
5. Triplicate BP and HR at screening and pre-dose on Day 1 of each treatment period only. Single measurements at other timepoints (performed at a similar time of day as Day 1 Pre-dose). HR and BP assessments only performed at the 24 and 48 hr post dose and early discontinuation/follow-up visit timepoints.

6. Meal (where applicable) to be started and completed 30 minutes prior to of danirixin dosing. Meal to consist of 900-1000 calories and be composed of proper caloric content of protein/fat/carbohydrates per FDA guidance and subjects will be required to consume at least 90% of meal.
7. When danirixin dosing occurs in the fasted state, subjects will be provided with a light snack and then will fast from all food and drink (except water) from 10 hours prior to dosing until 4hrs post-dose on Day 1 in each treatment period at which time lunch will be provided. An evening meal will be provided at approximately 9 h post dose. At all other times during residency in the clinic, meals will be provided at appropriate times.

Part B – Group 2

Periods 1-3

Procedure		**Study Day (Treatment Periods -1-3)** [2]																**Early Discontinuation /Follow-up (3 to 10 days post-last dose)**
	Screening (Up to 30 days prior to Day 1) [1]	**Qualification Visit** **Day -4**[9]	**Day** **-1**	**1**														
				Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
Informed Consent	X																	
Inclusion and Exclusion	X		X															
Demographics	X																	
Full Physical Exam including Height and Weight	X																	
Brief Physical Exam			X															X
Medical History (includes substance usage)	X		X															
Pregnancy Test,[3] (WOCBP)	X	X	X															

Procedure		**Study Day (Treatment Periods -1-3)** [2]															**Early Discontinuation /Follow-up (3 to 10 days post-last dose)**
	Screening (Up to 30 days prior to Day 1) [1]	**Qualification Visit Day -4**[9]	**Day -1**	**1**													
				Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
FSH and estradiol (if needed)	X																	
HIV, Hep B and Hep C Screen	X																	
Urine Drug Screen	X	X	X															
Alcohol Screen-Breathalyzer	X	X	X															
Urine Cotinine Screen	X	X	X															
Admission to Unit			X															
Laboratory Assessments (include liver chemistries)	X		X															X
12-lead ECG [4]	X		X						X									X
Vital Signs [5]	X			X												X	X	X
Randomization				X														

Procedure		**Study Day (Treatment Periods -1-3)** [2]															**Early Discontinuation /Follow-up (3 to 10 days post-last dose)**
	Screening (Up to 30 days prior to Day 1) [1]	**Qualification Visit Day -4**[9]	**Day -1**	**1**													
				Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
Meal[6]				X														
Danirixin Administration[7]					X													
Omeprazole Administration [8]		X	X		X											X	X	
Diary Card completion for Omeprazole Dosing		←==========→																
Pharmacokinetic Sampling				X		X	X	X	X	X	X	X	X	X	X	X	X	
SAE Review	←==========→																	
AE Review			X	←==========→														
Concomitant Medication Review			X	←==========→														

Procedure		**Study Day (Treatment Periods -1-3)** [2]															**Early Discontinuation /Follow-up (3 to 10 days post-last dose)**
	Screening (Up to 30 days prior to Day 1) [1]	**Qualification Visit** **Day -4**[9]	**Day** **-1**	**1**													
				Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
Discharge																X		

1. Screening must be performed within 30 days prior to receiving the dose of Danirixin on Day 1 of period 1.
2. Treatment periods 1-3 will include a minimum 5 day wash-out from day of dose between each treatment.
3. Serum pregnancy test (where applicable) will be performed at the screening visit and a urine pregnancy test at all other time points specified.
4. Triplicate ECGs at screening and on Day -1 of each treatment period only. Single ECGs at other timepoints (performed at a similar time of day as Day 1 Pre-dose), unless a reading meets the QTc stopping criteria, in which case two further measurements will be taken at the same time point and the average values captured.
5. Triplicate BP and HR assessments at screening and pre-dose on Day 1 of each treatment period only. Single measurements at other timepoints (performed at a similar time of day as Day 1 Pre-dose). HR and BP assessments only performed at the 24 and 48 hr post dose and early discontinuation/follow-up visit timepoints.
6. Meal (where applicable) to be started and completed within 30 minutes prior to danirixin dosing. Normal and high fat meal will be described in the SRM.
7. When danirixin dosing occurs in the fasted state, subjects will be provided with a light snack and then will fast from all food and drink (except water) from 10 hours prior to dose until 4 hr post-dose on Day 1 in each treatment period at which time lunch will be provided. An evening meal will be provided at approximately 9 h post dose. At all other times during residency in the clinic, meals will be provided at appropriate times.
8. OMP will be taken starting on Day -4 continuing daily through all treatment and washout periods until the day of the Period 3, 48hour PK assessment.
9. The Day -4 Qualification visit only applies to period 1.

3. INTRODUCTION

The inflammation associated with COPD is characterized by a prominent infiltration of neutrophils in lung tissue and the airways. Neutrophils and other inflammatory cells are recruited to the lung in response to various chemotactic factors, including chemokines. Specifically, there is a large body of evidence that the CXCR2 chemokine receptor plays a pivotal role in neutrophil recruitment to the lung. For neutrophils, chemokine binding to the CXCR2 results in chemotaxis and cell activation, ultimately resulting in the release of a number of inflammatory mediators and proteases that are thought to contribute to the progressive fibrosis, airway stenosis, and destruction of the lung parenchyma characteristic of COPD.

Selective antagonism of the interaction between CXCR2 and its ligands is a potential strategy for reducing the inflammation in COPD [Chapman, 2009]. A reduction in tissue and airway neutrophilia is expected to result in downstream effects on mucus hypersecretion, lung inflammation, and tissue destruction that are hypothesized to underlie the development and worsening of respiratory symptoms and decline in lung function that occurs in COPD.

Molecules with CXCR2 antagonist activity have been shown to reduce the influx of neutrophils into the lungs in healthy participants (e.g. ozone or LPS challenge models) and to reduce sputum and tissue neutrophils in the lungs of patients with severe, neutrophilic asthma, COPD and bronchiectasis in association with improvements in measures of disease activity in some, but not all, studies [O'Byrne, 2016; Holz, 2010; Watz, 2016, Lazaar 2011; Nair, 2012; Rennard, 2015]. Overall, the results of the reported clinical studies with CXCR2 antagonists suggest that careful selection of the target patient population is important to achieving clinical benefit.

Danirixin is a selective CXCR2 antagonist being developed as a potential anti-inflammatory agent for the treatment of COPD and other inflammatory diseases and influenza. Danirixin has demonstrated potent antagonism of CXCR2 activity both *in vitro* and *in vivo* in preclinical studies [GlaxoSmithKline Document Number, YM2010/00163/07].

3.1. Study Rationale

Part A of this study will provide an understanding of the PK of 3 test tablet formulations of the HBr salt of danirixin in healthy elderly subjects in fed and fasted conditions in comparison to the current HBr salt tablet formulation. The current formulation is a hemihydrate salt tablet formulation manufactured using roller compaction (RC). The test formulations are manufactured by direct compression (DC) and will investigate the performance of these smaller DC tablets, as well as the inclusion of the excipient hydroxypropyl methylcellulose (HPMC). Formulation selection for Part B will occur following review of the PK data collected in Part A.
Part B of this study will provide an understanding of the PK using the selected formulation from Part A in the fed and fasted state; during gastric acid suppression and in the monohydrate state under fed conditions in a population of healthy elderly subjects. Danirixin is currently administered with food, therefore the investigation of food effect

for the selected formulation could potentially enable dosing without food. Additionally, OMP is being administered with the selected formulation to investigate PK interaction potential as gastric pH has been shown to alter PK exposure and this study will further enable us to investigate OMPs influence in the presence and absence of food. Finally, the monohydrate tablet simulates a hemihydrate to monohydrate tablet in stressed conditions. The outcome of this study will contribute to the selection of the most appropriate formulation/dosing regimen for future studies.

3.2. Background

COPD is a major cause of disability, morbidity, and mortality, resulting in millions of deaths annually worldwide contributing significantly to health care costs [Mathers, 2006; Lopez-Campos, 2016; Vastava, 2015; GOLD, 2016]. The morbidity and mortality of COPD are continuing to increase and worldwide and, by the year 2020, COPD is expected to be the third leading cause of death and fifth leading cause of disability [Mathers, 2006; Lopez-Campos, 2016]. The airflow limitation that characterizes COPD is primarily due to small airways disease and parenchymal destruction associated with an excessive inflammatory response in the lung, mainly caused by cigarette smoking [Celli, 2004]. COPD is characterized by symptoms of chronic and, in many patients, progressive breathlessness (or dyspnea), cough and sputum production. Many COPD patients also suffer from periodic worsening of their COPD symptoms that is beyond the typical day to day variation [Hurst, 2010]. These episodes of worsening symptoms (COPD exacerbations) account for a significant proportion of COPD-related and total health care costs. Despite several available therapies that have been shown to reduce COPD exacerbations and respiratory symptoms, many COPD patients continue to experience a high burden of respiratory symptoms and COPD exacerbations resulting in a continuing unmet medical need [Vestbo, 2016]. Additionally, there is growing recognition that a high percentage of COPD patients with mild airflow limitation as well as smokers with preserved lung function suffer from a high burden of symptoms and COPD exacerbations with a subsequent impact on health status [Woodruff, 2016]. Therapies that effectively further reduce COPD exacerbations and improve respiratory symptoms could have a substantial impact on healthcare utilization and most importantly result in an improvement in COPD patients' quality of life.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the treatment and management of patients with COPD recommend that the management of current respiratory symptoms and subsequent worsening of symptoms resulting in COPD exacerbations should be an important component of COPD patient management [GOLD, 2016].

Danirixin is being evaluated as an addition to standard of care inhaled therapies (i.e. long acting bronchodilators and long acting bronchodilator/corticosteroid combination therapies) and is targeting those COPD patients that continue to have a burden of respiratory symptoms and COPD exacerbations despite management with currently available COPD treatments.

3.3. Benefit/Risk Assessment

More detailed information about the potential benefits and risks of danirixin may be found in the danirixin Investigator's Brochure [GlaxoSmithKline Document Number, YM2010/00163/07].

3.3.1. Risk Assessment

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Testicular effects and male fertility	Clinical exposure limits will be based on the NOAELs for testicular toxicity; other findings described above occurred at non-tolerated doses and/or at systemic exposures well in excess of the maximum oral or maximum predicted intravenous exposure in human subjects or were considered non-adverse and monitorable. Exposure margins derived from the 26 and 39 week toxicology studies in rats and dogs, respectively, with DNX are considered sufficient to support oral and intravenous infusion administration of DNX in single and repeat-dose clinical studies under the proposed dosing regimens. Clear NOAELs for testicular effects were established in the rat at 50 mg/kg/day and at 10 mg/kg/day in the dog after oral administration of DNX. These doses resulted in systemic exposures which are 7.7 and 23.5-fold respectively the exposure for an oral clinical dose of 75 mg BID (AUC0-24 of 8.734 µg.h/mL) and 3 and 9.3-fold respectively for the maximum proposed	Standard safety monitoring will be employed. The potential risk of testicular injury has been conveyed in the informed consent. Pharmacokinetic parameters will be monitored in clinical studies to ensure appropriate safety margins.

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	intravenous infusion clinical dose of 50 mg BID (AUC0-24 of 21.94 µg.h/mL).	
Impairment of host defense.	Host defense has not been studied directly in nonclinical studies. However, data in nonclinical species have not identified an increased risk of infection with danirixin. Nonclinical studies in mice and ferrets with two CXCR2 antagonists in the same chemical class as danirixin have not shown an increase in infections in challenge models (e.g., influenza viral load). Secondary bacterial infections after viral infection have not been directly evaluated in nonclinical studies. The data from clinical studies including healthy participants, COPD and influenza patients thus far show no evidence that participants taking danirixin have an increased infection rate compared with participants taking placebo. Neutropenia has been reported in clinical trials of other CXCR2 antagonists. No instances of neutropenia have been reported in nonclinical studies with danirixin. In	Monitoring of neutrophil count. Stopping criteria: in participants with a confirmed absolute neutrophil count ≤ 0.5 x 10^9/L product will be discontinued and neutrophil count will be monitored until return to normal. Participants may be restarted on study treatment as detailed in Appendix 7. Ongoing assessment of AE/SAEs related to infection. Closely monitor, collect information on and characterize infection events such as pneumonia, and use adjudication as appropriate.

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	healthy volunteer studies and a phase 2a study in patients with Influenza (GSK Study 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Reproductive toxicology (Embryofetal development)	In a rat embryofetal development study, an oral dose of 300 mg/kg/day resulted in fetal skeletal variations in the skull (reductions in ossification). There were no test article-related effects on numbers of corpora lutea, implantations, embryofetal survival, placental morphology, gravid uterine weight, sex ratio, fetal body weight, or fetal morphology (external and visceral).	As danirixin HBr has shown the potential to cause fetal malformations, danirixin or danirixin HBr must not be administered to pregnant women or nursing mothers. Women of childbearing potential should only be included in clinical trials with the use of appropriate precautions against pregnancy.
Study Procedures		
None		
Other		
Not applicable		

3.3.2. Benefit Assessment

There is no direct medical benefit to the subjects from taking part in this study. The information obtained from this study will be important in selection of appropriate formulations and doses/dosing regimens for subsequent studies in patient populations.

3.3.3. Overall Benefit:Risk Conclusion

Appropriate measures have been taken to minimize the risk to subjects in this study through eligibility criteria and consideration of burden relative to study procedures. It is acceptable to conduct this study in healthy elderly participants, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical research facility with access to hospital emergency facilities.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part A: • To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed and fasted states. • To provide safety and tolerability information for oral administration of the different formulations of danirixin HBr tablets in elderly subjects.	• Danirixin PK parameters: AUC(0-inf) and Cmax. • AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters
• To estimate the secondary pharmacokinetic parameters of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed and fasted states.	• Danirixin PK parameters: AUC(0-t), AUC(0-24), tmax, t1/2, tlast and tlag.
Part B: • To estimate the effect of food on the	• Danirixin PK parameters:

Objectives	Endpoints
single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects.	AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the effect of OMP on the single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects in various fed and fasted states.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulation of the HBr tablet (MONO), in healthy elderly subjects in the fed state.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To provide safety and tolerability information for oral administration of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters

5. STUDY DESIGN

5.1. Overall Design

This is a Phase I, two part (Part A and Part B each part contains 2 Groups), randomized, open-label, single dose, cross-over study conducted with healthy elderly participants. Part A will support the selection of the formulation and Part B will address the PPI effect, food effect and PK of the monohydrate.

Part A

In Part A, approximately 16 healthy elderly participants will be enrolled such that approximately 13 subjects complete dosing and critical assessments for all planned treatment periods. The 16 participants will be randomized and designated to go into one of two (2) groups, Group 1 and Group 2. Group 1 will be administered danirixin in the fed state in all treatment periods. Group 2 will be administered danirixin in the fasted

state in all treatment periods. Participants will undergo a screening period ~30 days prior to the first dose of study treatment, followed by 4 treatment periods with at least a 5 day washout period between each treatment and a follow-up period of 3-10 days following the last dose of danirixin.

Eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the last dose of danirixin, participants will return to the clinic for the final follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. A study design schematic for Part A is presented in Table 1.

Part B

In Part B, approximately 24 healthy elderly participants will be enrolled such that approximately 20 subjects (10 subjects per group) complete dosing and critical assessments for all planned treatment periods in Group 1 and 2.

In Part B Group 2 eligible participants will take omeprazole (OMP), 40 mg from Day -4 relative to the treatment period 1, Day 1 first dosing of danirixin through all periods and washouts until the final treatment period 3 PK assessment (48hr). Participants will be provided with a participant diary to document daily recordings of OMP dosing occurring outside of the unit.

For Part B Group 2, once screened, eligible participants will be instructed to return to the clinic on Day -4 relative to the first dose of danirixin on Day 1 for a qualification visit. During this visit, clinical safety assessments will be performed as specified in the Section 2 Schedule of Activities of the protocol. Once assessments are complete, eligible participants will be administered a single of dose of OMP in the clinic. Participants will be discharged with OMP and will take OMP on Day -3 and Day -2 at home. OMP be administered in the clinic on Day -1, Day 1, Day 2 and Day 3 of each treatment period. OMP will be taken on an outpatient daily bases on all other days through each period until the Period 3 post dose 48h PK assessment.

For Group 1 and 2 eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the last dose of danirixin participants will return to the clinic for the final follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. Study design schematics are presented in Table 2 and Table 3 for Part B Group 1 and 2, respectively.

5.2. Number of Participants

In Part A, approximately 16 participants will be randomized such that approximately 13 evaluable participants complete the study. Part A will have two (2) groups of participants, Group 1 and Group 2. There will be approximately 8 participants in each group.

In Part B, approximately 24 participants (12 participants per group) will be randomized such that approximately 10 evaluable participants complete each group.

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the final follow-up visit for the part for which they were enrolled.

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

5.4. Scientific Rationale for Study Design

This study will use a single dose, open label, cross-over design. This is a well-established design to evaluate the relative bioavailability of new formulations of an investigational drug.

5.5. Dose Justification

The oral dose strength of 50 mg danirixin HBr will be administered as a single dose in all the treatment periods in the present study. This is a clinically relevant danirixin dose level

and was also the dose used in Clinical Study 201037 [GlaxoSmithKline Document Number, 2015N248339_00].

In Group 2 of Part B, subjects will take an oral dose of 40 mg OMP QD in the morning for four days prior to the initial danirixin dosing day until 48 hrs after the final danirixin dosing day. On the danirixin dosing days, the OMP will be taken in the morning with the dose of danirixin. This omeprazole dose strength and regimen is the same as that administered during Clinical Study 201037 [GlaxoSmithKline Document Number, 2015N248339_00]. The co-administration of 40 mg OMP with danirixin 50 mg in the present study is not expected to influence the pharmacokinetics of OMP. The selection of the OMP dose and dosing frequency is justified based on efficacy and safety data from the package insert. The 40 mg q24h dose of OMP was selected as it is a therapeutic dose that is expected to achieve maximal acid suppression and identify an interaction if one exists. The onset of effect occurs within 1 hr of administration with maximum effect of a single dose occurring within 2 hrs. Following repeated once daily doses, the inhibitory effect of OMP on acid secretion increases, reaching a plateau after four days [Sachs, 1995; Stedman, 2000].

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. Participant must be 65 to 80 years of age inclusive, at the Screening Visit.

Type of Participant and Disease Characteristics

2. Participants who are healthy, as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring or a subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included if the investigator and the GSK Medical Monitor agree that the finding is unlikely to introduce risk factors and will not interfere with the study procedures and objectives. Additionally, laboratory assessments that are specifically listed in the inclusion or exclusion criteria and are outside of the reference range can be repeated once during the screening period.

Weight

3. Body weight ≥50 kg and body mass index (BMI) within the range 19 - 34 kg/m2 (inclusive).

Sex

4. Male or female

   Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

   (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 60 hours after the last dose of study treatment.

Informed Consent

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

Diagnostic Assessments and Other Criteria

6. Aspartate aminotransferase (AST), ALT, alkaline phosphatase and bilirubin ≤ 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
7. Resting BP of ≤ 160/90 mm Hg, irrespective of anti-hypertensive medication status for the subject.
8. Able and willing to consume the Food and Drug Administration (FDA) defined high fat meal [Food and Drug Administration, 2013] within 30 minutes in each of the four treatment periods where study treatment is administered in a fed state.

6.2. Exclusion Criteria

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

Medical Conditions

1. Significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
2. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
3. Breast cancer within the past 10 years
4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)

5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
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. QTc >450 msec
   NOTES:
   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
   - For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

Prior/Concomitant Therapy

8. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the last study assessment, unless in the opinion of the investigator and GSK Medical Monitor, the medication will not interfere with the study procedures or compromise subject safety. Some examples of exceptions (permitted medications) are:
   a. Stable dose of anti-hypertensive medication for at least 3 months prior to the screening visit.
   b. Stable dose of lipid-lowering medications (statins or fibrates) for at least 3 months prior to the screening visit.

This list is not meant to be all inclusive.

9. Use of proton pump inhibitors and histamine receptor 2 antagonists
   Other short acting antacid medications (such as TUMS, Maalox, Mylanta, etc) can be used between periods but must be stopped 24 hours prior to dosing

Prior/Concurrent Clinical Study Experience

10. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months
11. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current

study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

12. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
13. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study

Diagnostic assessments

14. Female Subjects: Positive serum beta-human chorionic gonadotropin (β-hCG) test at screening.
15. Presence of Hepatitis B surface antigen (HBsAg) and/or Positive Hepatitis C antibody test result at screening.

    NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
16. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment
17. Positive pre-study drug/alcohol screen
18. Positive human immunodeficiency virus (HIV) antibody test
19. Regular use of known drugs of abuse

Other Exclusions

20. Regular alcohol consumption within 6 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
21. Consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study treatment until collection of the final blood sample.
22. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 90 days prior to screening.
23. Sensitivity to heparin or heparin-induced thrombocytopenia
24. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of Seville oranges, grapefruit or grapefruit juice, and/or pummelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study treatment until completion of all study procedures in each study period after the final dose. Specific dosing instructions will be provided in the Study Reference Manual (SRM) and will be provided to all study participants by the site staff at each visit.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each treatment period, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic or clinical laboratory sample during each treatment period.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and clinical laboratory sample during each session.
- Use of tobacco- or nicotine-containing products is prohibited, as detailed in the exclusion criteria (Section 6.2).

- When dosing occurs in the fasted state, subjects will be provided with a light snack and then will fast from all food and drink (except water) from midnight on the evening of Day -1 until 4 h post-dose on Day 1 at which time a meal will be provided. An evening meal will be provided at approximately 9 h post dose.

- At all other times during residency in the clinic, meals and snacks will be provided at appropriate times.

- When dosing occurs in the fed state, subjects will be given a high-fat or low-fat diet before study treatment administration.

6.3.3. Activity

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

6.4. Screen Failures

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

demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if, in the opinion of the investigator, the reason for screen failure is temporary and it can be reasonably expected to resolve. Any rescreens must take place within the planned screening period so as to not cause any undue prolongation of the planned study completion.

Any re-screened participant must meet all the protocol specific inclusion/exclusion requirements at the re-screen visit. All screening procedures must be repeated for subjects that are re-screened. If a subject screen fails prior to randomization, he/she can be re-screened **once** if the site staff feels the subject meets eligibility criteria.

Rescreened participants will be assigned a unique screening number for each time they are screened and will receive a participant number when enrolled.

7. TREATMENTS

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

7.1. Treatments Administered

GSK will provide the danirixin study treatment. The study site will be responsible to provide the omeprazole for Part 2, Group 2.

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt) *Reference*	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Danirixin (GSK1325756H, the hydrobromide monohydrate salt)	PRILOSEC (omeprazole)
Dosage formulation:	Immediate release tablet	Immediate release tablet	Immediate release tablet	Delayed-Release capsule
Unit dose strength(s)/Dosage level(s):	50mg	50mg	50mg	40mg
Manufacturing process	Roller Compaction (RC)	Direct Compression (DC)	Direct Compression (DC)	NA
Tablet Size	600mg	475 and 600mg	600mg	NA
Presence of excipient, HPMC	No	Only in 600mg	TBC based on outcome of part A	NA
Route of Administration	Oral	Oral	Oral	Oral
Dosing instructions:	With food and 240 mL (8 oz) water, unless explicitly defined by protocol	With food and 240 mL (8 oz) water, unless explicitly defined by protocol	With food and 240 mL (8 oz) water	Per label
Packaging and Labelling	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement.	Over the counter product

Manufacturer	GSK	GSK	GSK	Over the counter product

7.2. Dose Modification

There will be no dose modifications.

7.3. Method of Treatment Assignment

In Part A, participants will be randomised to a treatment sequence including treatments A-D or AO - DO [Table 4]. Participants randomised to a treatment sequence including treatments A-D will comprise Group 1 and participants randomised to a treatment sequence including treatments AO-DO will comprise Group 2. In Part B, Group 1, participants will be randomised to a treatment sequence including treatments E-H [Table 5], and those in Part B, Group 2 will be randomised to a treatment sequence including treatments I-K [Table 6]. This will be done in accordance with the randomization schedule generated by the study statistician, prior to the start of the study, using validated internal software. Study treatment will be dispensed to participants at the study visits summarized in the Section 2.

7.4. Blinding

This is an open-label study.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required. Danirixin tablets will be provided in multi-dose bottles and packaged with a desiccant. The monohydrate formulation will require storage in a humidity chamber, details will be provided in the study reference manual.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the [Study Reference Manual].

- Under normal conditions of handling and administration, study treatment 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.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.
- Participants self-administer OMP at home, compliance with OMP will be assessed through the participant diary that the participant will complete. Additionally, the participant will be queried at the site visit and documented in the source documents and CRF. A record of the number of OMP tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the CRF.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of informed consent 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

Permitted Medications and Non-Drug Therapies

The following medications have been pre-approved for concomitant use:

- A stable dose of anti-hypertensive medication for at least 3 months prior to the screening visit is permitted
- A stable dose of lipid-lowering medications (statins or fibrates) for at least 3 months prior to the screening visit is permitted.

- Other short acting antacid medications (such as TUMS, Maalox, Mylanta, etc) can be used between periods but must be stopped 24 hours prior to dosing
- Standard doses of vitamins
- A stable dose of thyroid replacement therapy medications
- A stable dose of topical or oral hormone replacement therapy medications
- Occasional use of acetaminophen for patient complaints of discomfort (e.g. headache, achiness) during clinic visits at the investigator's discretion with consideration of proximity to dosing.
- Emergency equipment and drugs will be available within the clinical unit. In the unlikely event that they are required, their use will be documented.

Prohibited Medications and Non-Drug Therapies

Subjects must be advised that no medication should be discontinued without the approval of their primary or treating physician.

Subjects must abstain from the use of prescription or non-prescription drugs, including:

- proton pump inhibitors
- histamine receptor 2 antagonists
- antacid medications (except as indicated above)
- greater than recommended use of vitamins
- herbal and dietary supplements (including St John's Wort)
- oral or injectable CYP3A4 or BRCP (breast cancer resistance protein) substrates with a narrow therapeutic index (CYP3A4 substrates include, but are not limited to, alfenatil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline; BCRP substrates include, but are not limited to, topotecan.)

within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the last study assessment, unless in the opinion of the investigator and GSK Medical Monitor, the medication will not interfere with the study procedures or compromise subject safety.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after the completion of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

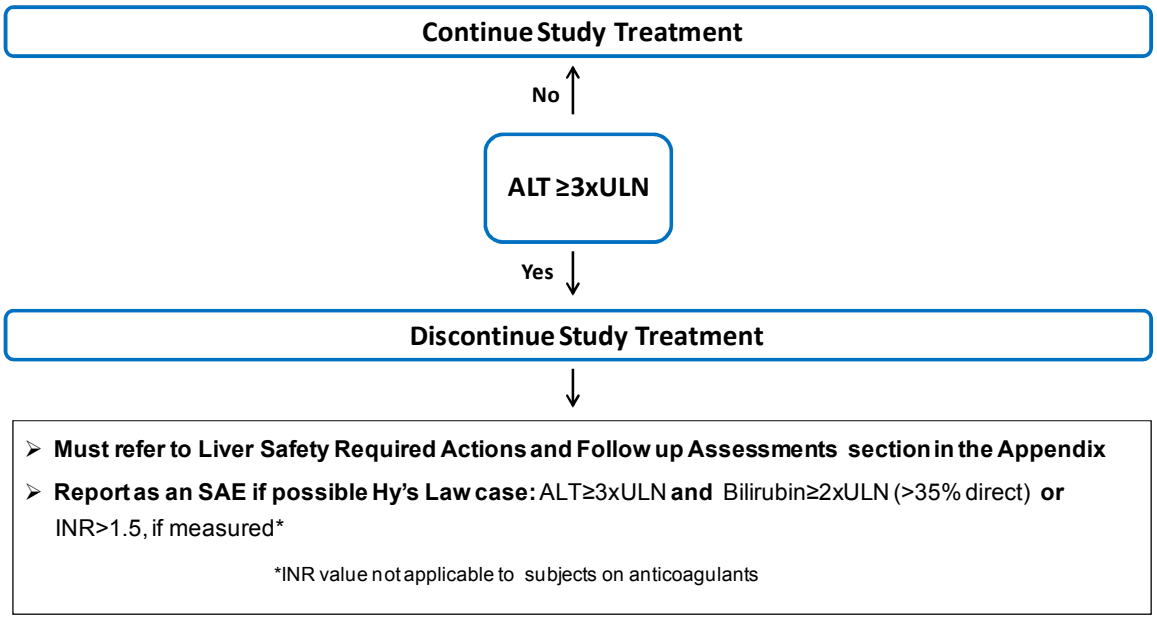
8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm below or if the investigator believes that it is in the best interest of the participant.

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

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

A subject that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.

- QTc or QTcB or QTcF > 500 msec,
- Change from baseline: QTc >60 msec

See the Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Neutrophil Stopping Criteria

A participant with a peripheral blood neutrophil count ≤ 0.5 x 10^9/L that is confirmed on repeat testing will be instructed to suspend dosing. The neutrophil count should be monitored daily until it returns to within the baseline value, as detailed in Appendix 7.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the Section 2 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the Section 2.

The following points must be noted:

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

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including PK and safety assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team members (e.g. medical monitor and GCSP) and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study.

9.1. Efficacy

This study is a single dose PK study and therefore there is no efficacy endpoint.

9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Appendix 4).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 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 in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 60 hours after the last dose of study treatment.
- 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 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

For this study, any dose of study treatment ≥ 4 tablets in a day will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

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

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.

9.4. Safety Assessments

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

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (auscultation and palpation of the abdomen including examination of the liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Heart Rate and Blood Pressure will be assessed at 24 and 48 hours post dose and at the early termination/final follow-up visit only.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute) at time points specified in Section 2. The average of the 3 blood pressure readings will be recorded on the CRF.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

9.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section [8.1.2] for QTc withdrawal criteria and additional QTc readings that may be necessary.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 days after the last dose of study

treatment 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 Section 2.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of whole blood concentrations of danirixin (performed under the control of GSK Platform Technology and Science Department of In Vitro In Vivo Translation Third Party Resourcing (PTS-IVIVT/TPR) as specified in the Section 2. Instructions for the collection and handling of biological samples will be provided by the sponsor in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of danirixin. Each whole blood sample will be used to prepare 4 dried blood spots which will be analysed for danirixin concentrations. Samples collected for analyses of danirixin whole blood may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

No formal hypothesis will be tested. For each pharmacokinetic endpoint, point estimates and corresponding 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

The following comparisons of interest will be constructed:

Part	Question	Comparison
Part A Group 1	Formulation fed	475mg DC tablet formulation versus 600mg RC formulation (reference)
		600mg DC tablet formulation versus reference
		600mg DC tablet with 5% HPMC versus reference
Part A Group 2	Formulation fasted	475mg DC tablet formulation versus 600mg RC formulation (reference)
		600mg DC tablet formulation versus reference
		600mg DC tablet with 5% HPMC versus reference
Part A Group 1 & 2	Food effect	600mg RC formulation fed versus fasted
		475mg DC tablet formulation fed versus fasted
		600mg DC tablet formulation fed versus fasted
		600mg DC tablet with 5% HPMC fed versus fasted
Part B Group 1	Food effect No OMP	High fat meal (heavy) versus Fasted
		Normal meal (light) versus Fasted
		High fat meal (heavy) versus Normal meal (light)
Part B Group 2	Food effect With OMP	High fat meal (heavy) versus Fasted
		Normal meal (light) versus Fasted
		High fat meal (heavy) versus Normal meal (light)
Part B Group 1 & 2	Drug interaction	Fasted with OMP versus Fasted without OMP
		Normal meal (light) with OMP versus Normal meal (light) without OMP
		High fat meal (heavy) with OMP versus High fat meal (heavy) without OMP
Part B Group 1	Pharm Dev	Monohydrate with high fat meal versus High fat meal (heavy)

10.1. Sample Size Determination

The sample size is primarily based on feasibility. Approximately 60 participants will be enrolled in the study to obtain approximately 8 randomized participants (6 completers) in each group in Part A and approximately 12 randomized subjects (10 completers) in each group in Part B.

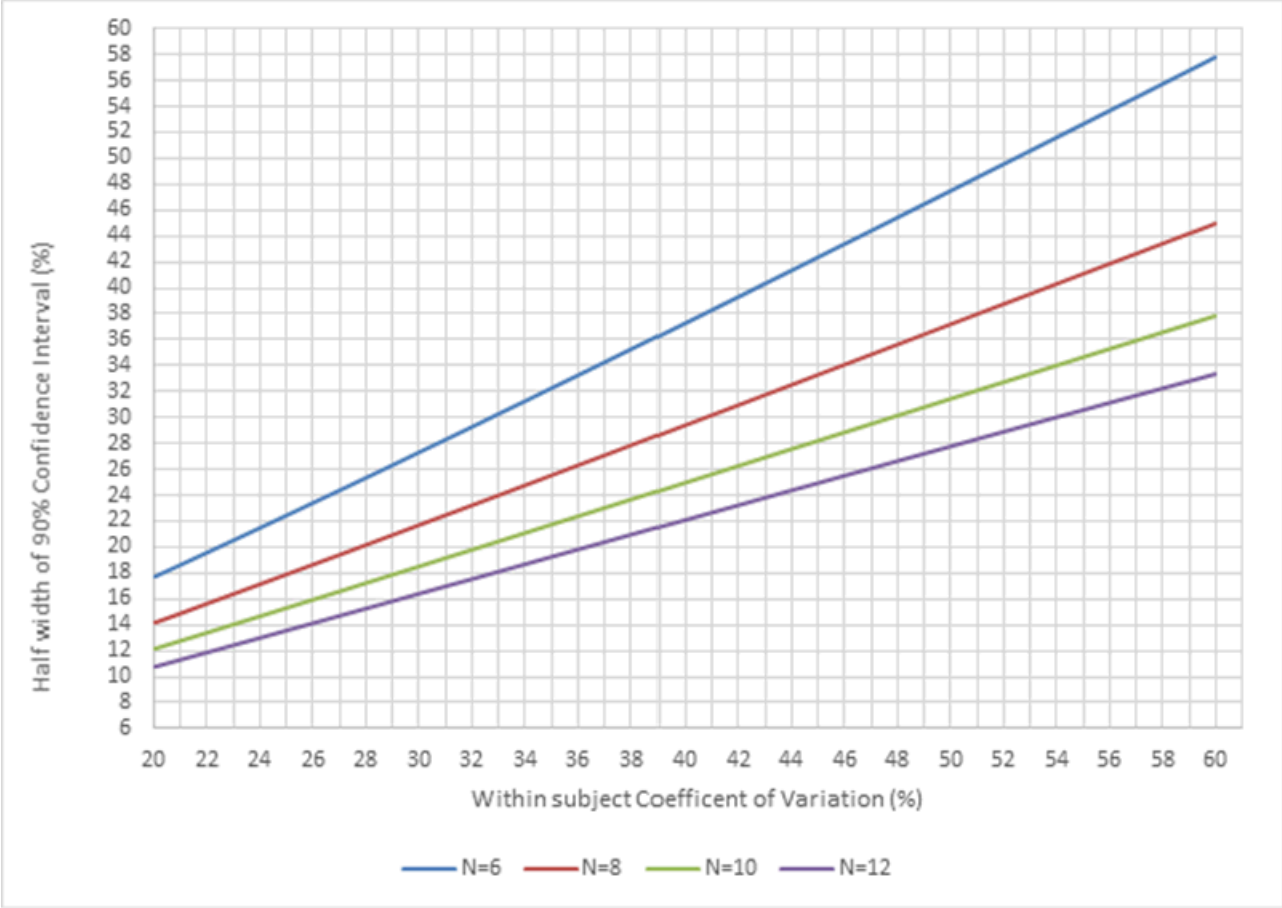
The within-subject variability for AUC(0-inf), AUC(0-t) and Cmax of danirixin [GSK Study 201037, GlaxoSmithKline Document Number 2015N248339_00] was estimated to be 37.3%, 39.3% and 44.7%, respectively. Based upon the largest within-subject coefficient of variation (44.7% for Cmax of danirixin) and a sample size of 6 subjects completing each group in part A of the study, it is estimated that the half-width of the 90% confidence interval for the ratio of geometric means for the comparison of interest should be no more than 42% of the point estimates. Assuming an observed ratio of one, the corresponding 90% confidence interval for the ratio of geometric means would be 0.70 to 1.42.

A PK interim analysis is planned at the completion of Part A to select the formulation for evaluation in Part B.

10.1.1. Sample Size Sensitivity

The figure below shows the half width of the 90% CI for a range of within-subject coefficient of variations for various sample sizes.

Figure 1 Plot of half width of 90% CI by within-subject coefficient of variations



10.1.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants	All participants who receive at least one dose of study medication. This population will be used for the study population and safety analyses.
PK	All participants for whom a pharmacokinetic sample was obtained and analyzed. This will be the population used for all the pharmacokinetic displays.

10.3. Statistical Analyses

Final analyses will be performed after the completion of the study and final dataset authorization.
Data will be listed and summarized separately for each part of the study according to GlaxoSmithKline reporting standards where applicable.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

10.3.1. Pharmacokinetic Analyses

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to GlaxoSmithKline current working practices. . Calculations will be based on the actual sampling times recorded during the study. From the blood concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed blood concentration (Cmax), time to Cmax (tmax), area under the blood concentration-time curve [AUC(0-t), AUC(0-inf), AUC(0-24)], lag time before observation of first blood concentration (tlag), time of last observed blood concentration (tlast), and apparent terminal phase half-life (t1/2).

Pharmacokinetic data will be listed and presented in graphical form and will be summarized descriptively. Complete details will be documented in the Reporting and Analysis Plan (RAP).

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters (AUC and Cmax) and the associated 90% CIs will be provided for treatment comparisons (test:reference). The PK parameters will be log-transformed prior to analysis and treatment comparisons will be expressed as ratios on the original scale.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-24)	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BCG	Bacillus Calmette-Guerin
BID	Twice a Day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CPK	Creatine Phosphokinase
Cmax,	Maximum Observed Concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
DC	Direct Compression
DNX	Danirixin
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety Pharmacovigilance
GLS	Geometric Least Squares
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK1325756	Danirixin
HBcAb	Hepatitis B core antibody
HBr	Hydrobromide
HBsAg	Hepatitis B surface antigen
HBsAg	Hepatitis B Surface Antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
ICF	Informed Consent Form

IEC	Independent Ethics Committees
IRB	Institutional Review Boards
Kg	Kilogram
LDH	Lactate Dehydrogenase LDH
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
Mg	Milligram
MSDS	Material Safety Data Sheet
NOAEL	No-Observed-Adverse-Effect-Level
OMP	Omeprazole
PPI	Proton Pump Inhibitors
PK	Pharmacokinetic
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RC	Roller Compaction
SAE	Serious Adverse Event
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2,	Terminal phase half-life
TB	tuberculosis
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
tmax,	Time of occurrence of Cmax
TST	tuberculin skin test
ULN	Upper Limit of Normal
WBC	While Blood Cells
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Not Applicable

Trademarks not owned by the GlaxoSmithKline group of companies
Not Applicable

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting	Calcium	Alkaline phosphatase,	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Breathalizer alcohol screen and a urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and			

Laboratory Assessments	Parameters
	benzodiazepines. • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology : HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody The results of each test must be entered into the CRF.

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (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).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

- This study will be registered and study information from this protocol will be posted on publicly available clinical trial registers before enrolment of study participants begins.
- The results summary of this study will be posted to the GSK Clinical Study Register and other publicly available clinical trial registers within 8 months of the primary study completion date.
- A manuscript reporting the study results will be submitted to a peer reviewed journal within 18 months of the last participant's last visit.

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Appendix 3.

Study and Site Closure

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

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

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

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

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

Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE

reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (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.

Reporting of SAEs 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 (e.g., InForm). • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • 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 or SAE coordinator by telephone. • Contacts for SAE reporting can be found in the study procedures manual.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8.

Table 8 Highly Effective Contraceptive Methods

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

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 60 hours after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

- Pregnancy testing, with a sensitivity of 5 mIU/mL will be performed using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will not routinely attempt to collect pregnancy information on any male participant's female partner(s) who becomes pregnant while the male participant is participating in this study; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism. This applies only to male participants who receive double-blind study treatment.
- If pregnancy information for a male participant's female partner(s) is voluntarily reported, after obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK

as described in Appendix 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.

12.6. 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>• 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 subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained up to 72 hours after 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 >1.5:

• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.7. Appendix 7: Neutrophil Safety and Study Treatment Restart

<table>
<tr><td colspan="2">Neutrophil Stopping Criteria: Absolute neutrophil count (ANC) ≤ 0.5 x 10^9 /L</td></tr>
<tr><td colspan="2">Required Actions and Follow up Assessments</td></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete an SAE data collection tool if the event also meets the criteria for an SAE
• Monitor the participant until neutrophil count stabilizes or returns to within baseline (see MONITORING below)
• Do not restart participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (see RESTART below)
MONITORING:
• Treatment of any suspected infections[1]
• Repeat CBC within 24 hrs
• Monitor CBC daily until neutrophil count resolves, stabilizes or returns to within baseline</td><td>• Record the appearance or worsening of any clinical symptoms on the AE report form[1]
• Obtain blood sample for pharmacokinetic (PK) analysis within 12 hours after last dose[2]
• Record use of concomitant medications on the concomitant medications report form</td></tr>
<tr><td colspan="2">RESTART</td></tr>
<tr><td>• Restart of study medication must be approved by the GSK Medical Monitor
• Restart may be attempted ONLY if all three criteria are met:
  • The neutrophil count is ≥ 1.5 x 10^9/L for at least 48 hours
  • At least 7 days have elapsed since the suspension of study treatment
  • No sign or symptom of associated infection has been identified</td><td>• Check the CBC within 24-48 hours after re-starting study medication, monitor twice weekly for two weeks, and monthly thereafter.
• If the ANC drops below 1.0 x 10^9/L on restart, the participant should be permanently discontinued from study treatment and withdrawn from the study.</td></tr>
</table>

1. New or worsening symptoms believed to be related to neutropenia such as (but not limited to): sudden onset of fever or malaise, stomatitis, odynophagia, periodontal infection, skin abscesses, signs or symptoms of sinusitis and otitis, symptoms of pneumonia (eg, cough, dyspnea), perirectal pain and irritation, hypotension or signs of septic shock.
2. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment 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.

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

TITLE PAGE

Protocol Title: A Two Part, Randomized, Open-label, Cross over Study in Healthy Elderly Participants to Evaluate the Relative Bioavailability of Hydrobromide Salt Tablet Formulations of Danirixin in the Fed and Fasted States, and to Evaluate the Effect of Food and Gastric Acid Secretion Suppression on Danirixin Pharmacokinetics Following Administration of Hydrobromide Salt Tablets.

Protocol Number: 207573

Short Title: GSK1325756 Relative Bioavailability Study in Healthy Elderly Participants

Compound Number: GSK1325756

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): IND:108168

Approval Date: 21-DEC-2017

SPONSOR SIGNATORY:

PPD

21-Dec 2017

Aili L.Lazaar, MD PPD
Director Discovery Medicine, Respiratory Therapy Area Unit

Date

PPD

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1. SYNOPSIS

Protocol Title:

A Two Part, Randomized, Open-label, Cross over Study in Healthy Elderly Participants to Evaluate the Relative Bioavailability of Hydrobromide Salt Tablet Formulations of Danirixin in the Fed and Fasted States, and to Evaluate the Effect of Food and Gastric Acid Secretion Suppression on Danirixin Pharmacokinetics Following Administration of Hydrobromide Salt Tablets.

Short Title:

GSK1325756 Relative Bioavailability Study in Healthy Elderly Participants

Rationale:

Part A of this study will provide an understanding of the PK of 3 test tablet formulations of the HBr salt of danirixin in healthy elderly participants in fed conditions in comparison to the current HBr salt tablet formulation. The current formulation is a hemihydrate salt tablet formulation manufactured using roller compaction (RC). The test formulations are manufactured by direct compression (DC) and will investigate the performance of these DC tablets, as well as the inclusion of the excipient hydroxypropyl methylcellulose (HPMC). Formulation selection for Part B will occur following review of the PK data collected in Part A.

Part B of this study will provide an understanding of the PK using the selected formulation from Part A in the fed and fasted state; during gastric acid suppression and in the monohydrate state under fed conditions in a population of healthy elderly participants. Danirixin is currently administered with food, therefore the investigation of food effect for the selected formulation could potentially enable dosing without food. Additionally, omeprazole (OMP) is being administered with the selected formulation to investigate a potential PK interaction as gastric pH has been shown to alter PK exposure and this study will further enable us to investigate OMPs influence in the presence and absence of food. Finally, the monohydrate tablet simulates a hemihydrate to monohydrate tablet in stressed conditions.

The outcome of this study will contribute to the selection of the most appropriate formulation/dosing regimen for future studies.

Objectives and Endpoints:

Objectives	Endpoints
Part A: • To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed state.	• Danirixin PK parameters: AUC(0-inf) and Cmax.
• To provide safety and tolerability information for oral administration of the different formulations of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters
• To estimate the secondary pharmacokinetic parameters of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed state.	• Danirixin PK parameters: AUC(0-t), AUC(0-24), tmax, t1/2, tlast and tlag.
Part B:	
• To estimate the effect of food on the single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the effect of OMP on the single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects in various fed and fasted states.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the relative bioavailability of danirixin after single dose	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax,

Objectives	Endpoints
administration of HBr tablet (RC), the reference treatment, relative to the test formulation of the HBr tablet (MONO), in healthy elderly subjects in the fed state.	t1/2, tlast and tlag.
• To provide safety and tolerability information for oral administration of the different formulations of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters

Overall Design:

This is a Phase I, two part (Part A and Part B which contains 2 Strata), randomized, open-label, single dose, cross-over study conducted with healthy elderly participants. Part A will support the selection of the formulation and Part B will address the PPI effect, food effect and PK of the monohydrate.

Part A

In Part A, approximately 16 healthy elderly participants will be enrolled such that approximately 13 subjects complete dosing and critical assessments for all planned treatment periods. Participants will undergo a screening period ~30 days prior to the first dose of study treatment, followed by 4 treatment periods with at least a 5day washout period between each treatment and a follow-up period of 3-10 days following the last dose of danirixin.

Eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the 48 hour clinic visit for the final treatment period, participants will return to the clinic for the follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. A study design schematic for Part A is presented in Table 1.

Table 1 Part A Study Design

Screening Period *Within 30 Days of Day 1*	Treatment Period 1	5- Day Washout	Treatment Period 2	5 Day Washout	Treatment Period 3	5 Day Washout	Treatment Period 4	Follow-Up Visit 3-10 days after last dose of DNX

Part B

In Part B, approximately 24 healthy elderly participants will be enrolled such that approximately 20 subjects (10 subjects per strata) complete dosing and critical assessments for all planned treatment periods in Strata 1 and 2.

In Part B Stratum 2 eligible participants will take omeprazole (OMP), 40 mg from Day -4 to day of final PK assessment (48hr) for treatment period 3. Participants will be provided with a participant diary to document daily recordings of OMP dosing occurring outside of the unit.

Eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the 48 hour clinic visit for the final treatment period, participants will return to the clinic for the follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. Study design schematics are presented in Table 2 and Table 3 for Part B Strata 1 and 2, respectively.

Table 2 Part B Stratum 1 Study Design

Screening Period *Within 30 Days of Day* 1	Treatment Period 1	5- Day Washout	Treatment Period 2	5 Day Washout	Treatment Period 3	5 Day Washout	Treatment Period 4	Follow-Up Visit 3-10 days after last dose of DNX

Table 3 Part B Strata 2 Study Design

Screening Period Within *30 Days of Day* 1	Day -4	Treatment Period 1	5- Day Washout	Treatment Period 2	5 Day Washout	Treatment Period 3	Follow-Up Visit 3 - 10 days after last dose of DNX
OMP taken daily ending with final assessments for Treatment period 3							

Number of Participants:

In Part A, 16 participants will be randomized such that approximately 13 evaluable participants complete the study.

In Part B, a total of 24 participants (12 participants per strata) will be randomized per stratum such that approximately 10 evaluable participants complete each strata.

Table 4 Part A Treatment Descriptions

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
A	1 x 50 mg danirixin HBr tablet (600 mg RC formulation) reference formulation; fed state high fat meal (heavy)	single dose
B	1 x 50 mg danirixin HBr tablet (475mg DC formulation); fed state high fat meal (heavy)	single dose
C	1 x 50 mg danirixin HBr tablet (600 mg DC formulation); fed state high fat meal (heavy)	single dose
D	1 x 50 mg danirixin HBr tablet (600 mg DC tablet formulation with 5% HPMC); fed state high fat meal (heavy)	single dose

Table 5 Part B Stratum 1 Treatment Descriptions (without OMP)

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
E	1 x danirixin Selected formulation; fasted	single dose
F	1 x danirixin Selected formulation; fed state normal meal (light)	single dose
G	1 x danirixin selected formulation; fed state high fat meal (heavy)	single dose
H	1 x 50 mg danirixin monohydrate formulation; fed state high fat meal (heavy)	single dose

Table 6 Part B Stratum 2 Treatment Descriptions (with OMP)

Treatment Arm	Description	Danirixin Dosing Regimen (or Frequency)
I	1 x danirixin selected formulation; fasted with 40mg OMP	single dose
J	1 x danirixin selected formulation; fed state normal meal (light) with 40mg OMP	single dose
K	1 x danirixin selected formulation; fed state high fat meal (heavy) with 40mg OMP	single dose

2. SCHEDULE OF ACTIVITIES (SOA) PART A AND PART B STRATUM 1

Periods 1-4

Procedure	Screening (up to 30 days prior to Day 1) [1]	Study Day (Treatment Periods 1-4) [2]															Follow-up (3 to 10 days post-last dose)
		Day -1	1														
			Pre-dose	0h	0.5h	1h	1.5h	2h	3h	4h	6h	8h	10h	12h	24h	48h	
Informed Consent	X																
Inclusion and Exclusion Criteria	X	X															
Demographics	X																
Full Physical Exam including Height and Weight	X																
Brief Physical Exam			X														X
Medical History (includes substance usage)	X	X															
Pregnancy Test, (WOCBP)[3]	X	X															X
FSH and estradiol (if needed)	X																
TB Screen	X																

Procedure	**Screening (up to 30 days prior to Day 1)** [1]	**Study Day (Treatment Periods 1-4)** [2]														**Follow-up (3 to 10 days post-last dose)**
		Day -1	**1**													
			Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
HIV, Hep B and Hep C Screen	X																
Urine Drug/Alcohol Screen	X	X															
Urine Cotinine Screen	X	X															
Admission to Unit		X															
Laboratory Assessments (include liver chemistries)	X	X														X	X
12-lead ECG	X[4]		X[4]					X[4]									X
Vital Signs	X[5]		X[5]					X[5]							X[5]		X
Randomization			X														
Meal			X[6,7]														
Danirixin Administration				X													
Pharmacokinetic Sampling			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Screening (up to 30 days prior to Day 1)** [1]	**Study Day (Treatment Periods 1-4)** [2]														**Follow-up (3 to 10 days post-last dose)**
		Day -1	**1**													
			Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
SAE Review	←==========→															
AE Review		X	←==========→													
Concomitant Medication Review		X	←==========→													
Discharge															X	

1. Screening must be performed within 30 days prior to receiving the dose of Danirixin on Day 1 of period 1.
2. Treatment periods 1-4 will include a minimum 5 wash-out from day of last dose in between each treatment
3. Serum pregnancy test will be performed at the screening visit and a urine pregnancy test at all other time points specified.
4. Triplicate ECGs at screening and pre-dose on Day 1 only. Single ECGs at other timepoints (performed at a similar time of day as Day 1 Pre-dose), unless a reading meets the QTc stopping criteria, in which case two further measurements will be taken at the same time point and the average values captured.
5. Triplicate vital signs at screening and pre-dose on Day 1 only. Single vital signs at other timepoints (performed at a similar time of day as Day 1 Pre-dose).
6. Meal to be started and completed within 30 minutes of danirixin dosing. Meal to consist of 900-1000 calories and be composed of proper caloric content of protein/fat/carbohydrates per FDA guidance and subjects will be required to consume at least 90% of meal.
7. When danirixin dosing occurs in the fasted state, subjects will be provided with a light snack and then will fast from all food and drink (except water) from 10 hours pre-dose until 4 h post-dose on Day 1 in each treatment period at which time lunch will be provided. An evening meal will be provided at approximately 9 h post dose. At all other times during residency in the clinic, meals will be provided at appropriate times.

Part B – Stratum 2

Periods 1-3

Procedure	Study Day (Treatment Periods -1-3) [2]																	Follow-up (3 to 10 days post-last dose)
	Screening [1] (Up to 30 days prior to Day 1)	Day -4 to -2	Day -1	1														
				Pre-dose	0h	0.5h	1h	1.5h	2h	3h	4h	6h	8h	10h	12h	24h	48h	
Informed Consent	X																	
Inclusion and Exclusion	X		X															
Demographics	X																	
Full Physical Exam including Height and Weight	X																	
Brief Physical Exam				X														X
Medical History (includes substance usage)	X		X															
Pregnancy Test, (WOCBP)[3]	X		X															X
FSH and estradiol (if needed)	X																	
TB Screen	X																	

Procedure	**Study Day (Treatment Periods -1-3)** [2]																	**Follow-up (3 to 10 days post-last dose)**
	Screening [1] **(Up to 30 days prior to Day 1)**	**Day -4 to -2**	**Day -1**	**1**														
				Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
HIV, Hep B and Hep C Screen	X																	
Drug/Alcohol Screen	X		X															
Urine Cotinine Screen	X		X															
Admission to Unit			X															
Laboratory Assessments (include liver chemistries)	X		X													X		X
12-lead ECG	X[4]			X[4]					X[4]									X
Vital Signs	X[5]			X[5]					X[5]							X[5]	X[5]	X
Randomization				X														
Meal				X[6,7]														
Danirixin Administration					X													
Omeprazole Administration [8]	X	X	X		X											x	x	
Diary Card completion for Omeprazole Dosing	X	X	X															
Pharmacokinetic Sampling				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Study Day (Treatment Periods -1-3)** [2]															**Follow-up (3 to 10 days post-last dose)**
	Screening [1] **(Up to 30 days prior to Day 1)**	**Day -4 to -2**	**Day -1**	**1**												
				Pre-dose	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**12h**	**24h**	**48h**	
SAE Review	←==========→																	
AE Review			X	←==========→														
Concomitant Medication Review			X	←==========→														
Discharge																X		

1. Treatment periods 1-3 will include a minimum 5 wash-out from day of last dose in between each treatment
2. Serum pregnancy test will be performed at the screening visit and a urine pregnancy test at all other time points specified.
3. Triplicate ECGs at screening and pre-dose on Day 1 only. Single ECGs at other timepoints (performed at a similar time of day as Day 1 Pre-dose), unless a reading meets the QTc stopping criteria, in which case two further measurements will be taken at the same time point and the average values captured.
4. Triplicate vital signs at screening and pre-dose on Day 1 only. Single vital signs at other timepoints (performed at a similar time of day as Day 1 Pre-dose).
5. Meal to be started and completed within 30 minutes of danirixin dosing. Normal and high fat meal will be described in the SRM.
6. When danirixin dosing occurs in the fasted state, subjects will be provided with a light snack and then will fast from all food and drink (except water) from 10 hours pre-dose until 4 h post-dose on Day 1 in each treatment period at which time lunch will be provided. An evening meal will be provided at approximately 9 h post dose. At all other times during residency in the clinic, meals will be provided at appropriate times.
7. OMP will be taken starting on Day -4 continuing daily through the day of the 48hour PK assessment for period 3

3. INTRODUCTION

The inflammation associated with COPD is characterized by a prominent infiltration of neutrophils in lung tissue and the airways. Neutrophils and other inflammatory cells are recruited to the lung in response to various chemotactic factors, including chemokines. Specifically, there is a large body of evidence that the CXCR2 chemokine receptor plays a pivotal role in neutrophil recruitment to the lung. For neutrophils, chemokine binding to the CXCR2 results in chemotaxis and cell activation, ultimately resulting in the release of a number of inflammatory mediators and proteases that are thought to contribute to the progressive fibrosis, airway stenosis, and destruction of the lung parenchyma characteristic of COPD.

Selective antagonism of the interaction between CXCR2 and its ligands is a potential strategy for reducing the inflammation in COPD [Chapman, 2009]. A reduction in tissue and airway neutrophilia is expected to result in downstream effects on mucus hypersecretion, lung inflammation, and tissue destruction that are hypothesized to underlie the development and worsening of respiratory symptoms and decline in lung function that occurs in COPD.

Molecules with CXCR2 antagonist activity have been shown to reduce the influx of neutrophils into the lungs in healthy participants (e.g. ozone or LPS challenge models) and to reduce sputum and tissue neutrophils in the lungs of patients with severe, neutrophilic asthma, COPD and bronchiectasis in association with improvements in measures of disease activity in some, but not all, studies [O'Byrne, 2016; Holz, 2010; Watz, 2016, Lazaar 2011; Nair, 2012; Rennard, 2015]. Overall, the results of the reported clinical studies with CXCR2 antagonists suggest that careful selection of the target patient population is important to achieving clinical benefit.

Danirixin is a selective CXCR2 antagonist being developed as a potential anti-inflammatory agent for the treatment of COPD and other inflammatory diseases and influenza. Danirixin has demonstrated potent antagonism of CXCR2 activity both *in vitro* and *in vivo* in preclinical studies [GlaxoSmithKline Document Number, YM2010/00163/07].

3.1. Study Rationale

Part A of this study will provide an understanding of the PK of 3 test tablet formulations of the HBr salt of danirixin in healthy elderly subjects in fed conditions in comparison to the current HBr salt tablet formulation. The current formulation is a hemihydrate salt tablet formulation manufactured using roller compaction (RC). The test formulations are manufactured by direct compression (DC) and will investigate the performance of these smaller DC tablets, as well as the inclusion of the excipient hydroxypropyl methylcellulose (HPMC). Formulation selection for Part B will occur following review of the PK data collected in Part A.
Part B of this study will provide an understanding of the PK using the selected formulation from Part A in the fed and fasted state; during gastric acid suppression and in the monohydrate state under fed conditions in a population of healthy elderly subjects. Danirixin is currently administered with food, therefore the investigation of food effect

for the selected formulation could potentially enable dosing without food. Additionally, OMP is being administered with the selected formulation to investigate PK interaction potential as gastric pH has been shown to alter PK exposure and this study will further enable us to investigate OMPs influence in the presence and absence of food. Finally, the monohydrate tablet simulates a hemihydrate to monohydrate tablet in stressed conditions. The outcome of this study will contribute to the selection of the most appropriate formulation/dosing regimen for future studies.

3.2. Background

COPD is a major cause of disability, morbidity, and mortality, resulting in millions of deaths annually worldwide contributing significantly to health care costs [Mathers, 2006; Lopez-Campos, 2016; Vastava, 2015; GOLD, 2016]. The morbidity and mortality of COPD are continuing to increase and worldwide and, by the year 2020, COPD is expected to be the third leading cause of death and fifth leading cause of disability [Mathers, 2006; Lopez-Campos, 2016]. The airflow limitation that characterizes COPD is primarily due to small airways disease and parenchymal destruction associated with an excessive inflammatory response in the lung, mainly caused by cigarette smoking [Celli, 2004]. COPD is characterized by symptoms of chronic and, in many patients, progressive breathlessness (or dyspnea), cough and sputum production. Many COPD patients also suffer from periodic worsening of their COPD symptoms that is beyond the typical day to day variation [Hurst, 2010]. These episodes of worsening symptoms (COPD exacerbations) account for a significant proportion of COPD-related and total health care costs. Despite several available therapies that have been shown to reduce COPD exacerbations and respiratory symptoms, many COPD patients continue to experience a high burden of respiratory symptoms and COPD exacerbations resulting in a continuing unmet medical need [Vestbo, 2016]. Additionally, there is growing recognition that a high percentage of COPD patients with mild airflow limitation as well as smokers with preserved lung function suffer from a high burden of symptoms and COPD exacerbations with a subsequent impact on health status [Woodruff, 2016]. Therapies that effectively further reduce COPD exacerbations and improve respiratory symptoms could have a substantial impact on healthcare utilization and most importantly result in an improvement in COPD patients' quality of life.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the treatment and management of patients with COPD recommend that the management of current respiratory symptoms and subsequent worsening of symptoms resulting in COPD exacerbations should be an important component of COPD patient management [GOLD, 2016].

Danirixin is being evaluated as an addition to standard of care inhaled therapies (i.e. long acting bronchodilators and long acting bronchodilator/corticosteroid combination therapies) and is targeting those COPD patients that continue to have a burden of respiratory symptoms and COPD exacerbations despite management with currently available COPD treatments.

3.3. Benefit/Risk Assessment

More detailed information about the potential benefits and risks of danirixin may be found in the danirixin Investigator's Brochure [GlaxoSmithKline Document Number, YM2010/00163/07].

3.3.1. Risk Assessment

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Testicular effects and male fertility	Clinical exposure limits will be based on the NOAELs for testicular toxicity; other findings described above occurred at non-tolerated doses and/or at systemic exposures well in excess of the maximum oral or maximum predicted intravenous exposure in human subjects or were considered non-adverse and monitorable. Exposure margins derived from the 26 and 39 week toxicology studies in rats and dogs, respectively, with DNX are considered sufficient to support oral and intravenous infusion administration of DNX in single and repeat-dose clinical studies under the proposed dosing regimens. Clear NOAELs for testicular effects were established in the rat at 50 mg/kg/day and at 10 mg/kg/day in the dog after oral administration of DNX. These doses resulted in systemic exposures which are 7.7 and 23.5-fold respectively the exposure for an oral clinical dose of 75 mg BID (AUC0-24 of 8.734 µg.h/mL) and 3 and 9.3-fold respectively for the maximum proposed	Standard safety monitoring will be employed. The potential risk of testicular injury has been conveyed in the informed consent. Pharmacokinetic parameters will be monitored in clinical studies to ensure appropriate safety margins.

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	intravenous infusion clinical dose of 50 mg BID (AUC0-24 of 21.94 µg.h/mL).	
Impairment of host defense.	Host defense has not been studied directly in nonclinical studies. However, data in nonclinical species have not identified an increased risk of infection with danirixin. Nonclinical studies in mice and ferrets with two CXCR2 antagonists in the same chemical class as danirixin have not shown an increase in infections in challenge models (e.g., influenza viral load). Secondary bacterial infections after viral infection have not been directly evaluated in nonclinical studies. The data from clinical studies including healthy participants, COPD and influenza patients thus far show no evidence that participants taking danirixin have an increased infection rate compared with participants taking placebo. Neutropenia has been reported in clinical trials of other CXCR2 antagonists. No instances of neutropenia have been reported in nonclinical studies with danirixin. In	Monitoring of neutrophil count. Stopping criteria: in participants with a confirmed absolute neutrophil count ≤ 0.5 x 109/L product will be discontinued and neutrophil count will be monitored until return to normal. Participants may be restarted on study treatment as detailed in Appendix 7. Ongoing assessment of AE/SAEs related to infection. Closely monitor, collect information on and characterize infection events such as pneumonia, and use adjudication as appropriate.

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	healthy volunteer studies and a phase 2a study in patients with Influenza (GSK Study 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Reproductive toxicology (Embryofetal development)	In a rat embryofetal development study, an oral dose of 300 mg/kg/day resulted in fetal skeletal variations in the skull (reductions in ossification). There were no test article-related effects on numbers of corpora lutea, implantations, embryofetal survival, placental morphology, gravid uterine weight, sex ratio, fetal body weight, or fetal morphology (external and visceral).	As danirixin HBr has shown the potential to cause fetal malformations, danirixin or danirixin HBr must not be administered to pregnant women or nursing mothers. Women of childbearing potential should only be included in clinical trials with the use of appropriate precautions against pregnancy.
Study Procedures		
None		
Other		
Not applicable		

3.3.2. Benefit Assessment

There is no direct medical benefit to the subjects from taking part in this study. The information obtained from this study will be important in selection of appropriate formulations and doses/dosing regimens for subsequent studies in patient populations.

3.3.3. Overall Benefit:Risk Conclusion

Appropriate measures have been taken to minimize the risk to subjects in this study through eligibility criteria and consideration of burden relative to study procedures. It is acceptable to conduct this study in healthy elderly participants, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical research facility with access to hospital emergency facilities.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part A: • To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed state.	• Danirixin PK parameters: AUC(0-inf) and Cmax.
• To provide safety and tolerability information for oral administration of the different formulations of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters
• To estimate the secondary pharmacokinetic parameters of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulations of the HBr tablet (DC 475, DC 600 and HPMC 600), in healthy elderly subjects in the fed state.	• Danirixin PK parameters: AUC(0-t), AUC(0-24), tmax, t1/2, tlast and tlag.
Part B: • To estimate the effect of food on the	• Danirixin PK parameters:

Objectives	Endpoints
single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects.	AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the effect of OMP on the single dose pharmacokinetics of the danirixin HBr tablet formulation selected from Part A in healthy elderly subjects in various fed and fasted states.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To estimate the relative bioavailability of danirixin after single dose administration of HBr tablet (RC), the reference treatment, relative to the test formulation of the HBr tablet (MONO), in healthy elderly subjects in the fed state.	• Danirixin PK parameters: AUC(0-inf), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2, tlast and tlag.
• To provide safety and tolerability information for oral administration of the different formulations of danirixin HBr tablets in elderly subjects.	• AEs/SAEs, vital signs, ECGs, and clinical laboratory parameters

5. STUDY DESIGN

5.1. Overall Design

This is a Phase I, two part (Part A and Part B which contains 2 Strata), randomized, open-label, single dose, cross-over study conducted with healthy elderly participants. Part A will support the selection of the formulation and Part B will address the PPI effect, food effect and PK of the monohydrate.

Part A

In Part A, approximately 16 healthy elderly participants will be enrolled such that approximately 13 subjects complete dosing and critical assessments for all planned treatment periods. Participants will undergo a screening period ~30 days prior to the first dose of study treatment, followed by 4 treatment periods with at least a 5 day washout

period between each treatment and a follow-up period of 3-10 days following the last dose of danirixin.

Eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the 48 hour clinic visit for the final treatment period, participants will return to the clinic for the follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. A study design schematic for Part A is presented in Table 1.

Part B

In Part B, approximately 24 healthy elderly participants will be enrolled such that approximately 20 subjects (10 subjects per strata) complete dosing and critical assessments for all planned treatment periods in Strata 1 and 2.

In Part B Stratum 2 eligible participants will take omeprazole (OMP), 40 mg from Day -4 to day of final PK assessment (48hr) for treatment period 3. Participants will be provided with a participant diary to document daily recordings of OMP dosing occurring outside of the unit.

Eligible participants will be admitted to the clinical facilities on Day -1 of each treatment period.

On Day 1 of each treatment period, following completion of the required pre-dose measurements and procedures, the investigator or authorized study unit personnel will administer a single oral dose of 50 mg danirixin to each participant in the unit. Following dosing, participants will undergo clinical safety assessments and serial PK assessments at timepoints specified in the Section 2. Participants will be discharged from the unit approximately 24 hours following dosing at the Investigator's discretion.

Participants will return back to the unit on an outpatient basis approximately 48 hours post dose for the 48 hour post dose assessments and be discharged once the assessments are complete at the investigator's discretion. Three to ten days following the 48 hour clinic visit for the final treatment period, participants will return to the clinic for the follow-up visit. Refer to Section 2 for study assessments and timepoints.

A minimum washout period of 5 days is required between dosing in each treatment period. Study design schematics are presented in Table 2 and Table 3 for Part B Strata 1 and 2, respectively.

5.2. Number of Participants

In Part A, 16 participants will be randomized such that approximately 13 evaluable participants complete the study.

In Part B, a total of 24 participants (12 participants per strata) will be randomized per stratum such that approximately 10 evaluable participants complete each strata.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including follow-up visit for the part for which they were enrolled.

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

5.4. Scientific Rationale for Study Design

This study will use a single dose, open label, cross-over design. This is a well-established design to evaluate the relative bioavailability of new formulations of an investigational drug.

5.5. Dose Justification

The oral dose strength of 50 mg danirixin HBr will be administered as a single dose in all the treatment periods in the present study. This is a clinically relevant danirixin dose level and was also the dose used in Clinical Study 201037 [GlaxoSmithKline Document Number, 2015N248339_00].

In stratum 2 of Part B, subjects will take an oral dose of 40 mg OMP QD in the morning for four days prior to the initial danirixin dosing day until 48 hrs after the final danirixin dosing day. On the danirixin dosing days, the OMP will be taken in the morning with the dose of danirixin. This omeprazole dose strength and regimen is the same as that administered during Clinical Study 201037 [GlaxoSmithKline Document Number, 2015N248339_00]. The co-administration of 40 mg OMP with danirixin 50 mg in the present study is not expected to influence the pharmacokinetics of OMP. The selection of the OMP dose and dosing frequency is justified based on efficacy and safety data from the package insert. The 40 mg q24h dose of OMP was selected as it is a therapeutic dose that is expected to achieve maximal acid suppression and identify an interaction if one exists. The onset of effect occurs within 1 hr of administration with maximum effect of a single dose occurring within 2 hrs. Following repeated once daily doses, the inhibitory effect of OMP on acid secretion increases, reaching a plateau after four days [Sachs, 1995; Stedman, 2000].

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. Participant must be 65 to 80 years of age inclusive, at the Screening Visit.

Type of Participant and Disease Characteristics

2. Participants who are healthy, as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring or a subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included if the investigator and the GSK Medical Monitor agree that the finding is unlikely to introduce risk factors and will not interfere with the study procedures and objectives. Additionally, laboratory assessments that are specifically listed in the inclusion or exclusion criteria and are outside of the reference range can be repeated once during the screening period.

Weight

3. Body weight ≥50 kg and body mass index (BMI) within the range 19 - 34 kg/m2 (inclusive).

Sex

4. Male or female

Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

(i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

OR

(ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 60 hours after the last dose of study treatment.

Informed Consent

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

Diagnostic Assessments and Other Criteria

6. Aspartate aminotransferase (AST), ALT, alkaline phosphatase and bilirubin ≤ 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

7. Resting BP of ≤ 160/90 mm Hg, irrespective of anti-hypertensive medication status for the subject.

8. Able to consume the Food and Drug Administration (FDA) defined high fat meal [Food and Drug Administration, 2013] within 30 minutes in each of the four treatment periods where study treatment is administered in a fed state.

6.2. Exclusion Criteria.

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

Medical Conditions

1. Significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
2. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration <5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) QuantiFERON®-TB Gold test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.
3. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
4. Breast cancer within the past 10 years
5. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
8. QTc >450 msec
   NOTES:
   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
   - For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

Prior/Concomitant Therapy

9. Use of prescription or non-prescription drugs, including proton pump inhibitors, histamine receptor 2 antagonists, systemic antacid medications (unless these can be held during the study), vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the last study assessment , unless in the opinion of the investigator and GSK Medical Monitor, the medication will not interfere with the study procedures or compromise subject safety. Some examples of exceptions (permitted medications) are:
   a. Stable dose of anti-hypertensive medication for at least 3 months prior to the screening visit.
   b. Stable dose of lipid-lowering medications (statins or fibrates) for at least 3 months prior to the screening visit.
   c. Antacids up to 24 hours prior to dosing

   This list is not meant to be all inclusive.

Prior/Concurrent Clinical Study Experience

10. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months
11. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
12. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
13. Participation in a previous clinical trial with danirixin within 1 year prior to the first

dosing day in the current study

Diagnostic assessments

14. Female Subjects: Positive urine beta-human chorionic gonadotropin (β-hCG) test at screening.
15. Presence of Hepatitis B surface antigen (HBsAg) at screening Positive Hepatitis C antibody test result at screening.

    NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
16. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

    NOTE: Test is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
17. For potent immunosuppressive agents, presence of the Hepatitis B core antibody (HBcAb) should also lead to exclusion from the study even if HBsAg is negative
18. Positive pre-study drug/alcohol screen
19. Positive human immunodeficiency virus (HIV) antibody test
20. Regular use of known drugs of abuse

Other Exclusions

21. Regular alcohol consumption within 6 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
22. Consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study treatment until collection of the final blood sample.
23. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 90 days prior to screening.
24. Sensitivity to heparin or heparin-induced thrombocytopenia
25. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of Seville oranges, grapefruit or grapefruit juice, and/or pummelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before

the start of study treatment until completion of all study procedures in each study period after the final dose. Specific dosing instructions will be provided in the Study Reference Manual (SRM) and will be provided to all study participants by the site staff at each visit.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each treatment period, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic or clinical laboratory sample during each treatment period.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and clinical laboratory sample during each session.
- Use of tobacco- or nicotine-containing products is prohibited, as detailed in the exclusion criteria (Section 6.2).

- When dosing occurs in the fasted state, subjects will be provided with a light snack and then will fast from all food and drink (except water) from midnight on the evening of Day -1 until 4 h post-dose on Day 1 at which time a meal will be provided. An evening meal will be provided at approximately 9 h post dose.

- At all other times during residency in the clinic, meals and snacks will be provided at appropriate times.

- When dosing occurs in the fed state, subjects will be given a high-fat or low-fat diet before study treatment administration.

6.3.3. Activity

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

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if, in the opinion of the investigator, the reason for screen failure is

temporary and it can be reasonably expected to resolve. Any rescreens must take place within the planned screening period so as to not cause any undue prolongation of the planned study completion.

Any re-screened participant must meet all the protocol specific inclusion/exclusion requirements at the re-screen visit. All screening procedures must be repeated for subjects that are re-screened. If a subject screen fails prior to randomization, he/she can be re-screened **once** if the site staff feels the subject meets eligibility criteria.

Rescreened participants will be assigned a unique screening number for each time they are screened and will receive a participant number when enrolled.

7. TREATMENTS

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

7.1. Treatments Administered

GSK will provide the danirixin study treatment. The study site will be responsible to provide the omeprazole for Part 2, stratum 2.

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt) *Reference*	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Danirixin (GSK1325756H, the hydrobromide monohydrate salt)	PRILOSEC (omeprazole)
Dosage formulation:	Immediate release tablet	Immediate release tablet	Immediate release tablet	Delayed-Release capsule
Unit dose strength(s)/Dosage level(s):	50mg	50mg	50mg	40mg
Manfacturing process	Roller Compaction (RC)	Direct Compression (DC)	Direct Compression (DC)	NA
Tablet Size	600mg	475 and 600mg	600mg	NA
Route of Administration	Oral	Oral	Oral	Oral
Dosing instructions:	With food and 240 mL (8 oz) water, unless explicitly defined by protocol	With food and 240 mL (8 oz) water, unless explicitly defined by protocol	With food and 240 mL (8 oz) water	Per label
Packaging and Labelling	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement.	Over the counter product
Manufacturer	GSK	GSK	GSK	Over the counter product

7.2. Dose Modification

There will be no dose modifications.

7.3. Method of Treatment Assignment

In Part 1, participants will be randomised to a treatment sequence including treatments A-D [Table 4]. In Part 2, participants will be stratified by OMP use. Those stratified to stratum 1 will be randomised to a treatment sequence including treatments E-H [Table 5], and those in stratum 2 will be randomised to a treatment sequence including treatments I-K [Table 6]. This will be done in accordance with the randomization schedule generated by the study statistician, prior to the start of the study, using validated internal software. Study treatment will be dispensed to participants at the study visits summarized in the Section 2.

Returned study treatment should not be re-dispensed to any participant.

7.4. Blinding

This is an open-label study.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required. Danirixin tablets will be provided in multi-dose bottles and packaged with a desiccant. The monohydrate formulation will require storage in a humidity chamber, details will be provided in the study reference manual.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the [Study Reference Manual].
    - Under normal conditions of handling and administration, study treatment 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.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.
- Participants self-administer OMP at home, compliance with OMP will be assessed through the participant diary that the participant will complete. Additionally, the participant will be queried at the site visit and documented in the source documents and CRF. A record of the number of OMP tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the CRF.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of informed consent 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

Permitted Medications and Non-Drug Therapies

The following medications have been pre-approved for concomitant use:

- A stable dose of anti-hypertensive medication for at least 3 months prior to the screening visit is permitted
- A stable dose of lipid-lowering medications (statins or fibrates) for at least 3 months prior to the screening visit is permitted.
- Antacids are allowed up to 24 hours prior to start of dosing
- Standard doses of vitamins
- A stable dose of thyroid replacement therapy medications
- A stable dose of topical or oral hormone replacement therapy medications

- Occasional use of acetaminophen for patient complaints of discomfort (e.g. headache, achiness) during clinic visits at the investigator's discretion with consideration of proximity to dosing.

- Emergency equipment and drugs will be available within the clinical unit. In the unlikely event that they are required, their use will be documented.

Prohibited Medications and Non-Drug Therapies

Subjects must be advised that no medication should be discontinued without the approval of their primary or treating physician.

Subjects must abstain from the use of prescription or non-prescription drugs, including:

- proton pump inhibitors
- histamine receptor 2 antagonists
- antacid medications (except as indicated above)
- Greater than recommended use of vitamins
- herbal and dietary supplements (including St John's Wort)
- oral or injectable CYP3A4 or BRCP (breast cancer resistance protein) substrates with a narrow therapeutic index (CYP3A4 substrates include, but are not limited to, alfenatil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline; BCRP substrates include, but are not limited to, topotecan.)

within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the last study assessment, unless in the opinion of the investigator and GSK Medical Monitor, the medication will not interfere with the study procedures or compromise subject safety.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after the completion of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

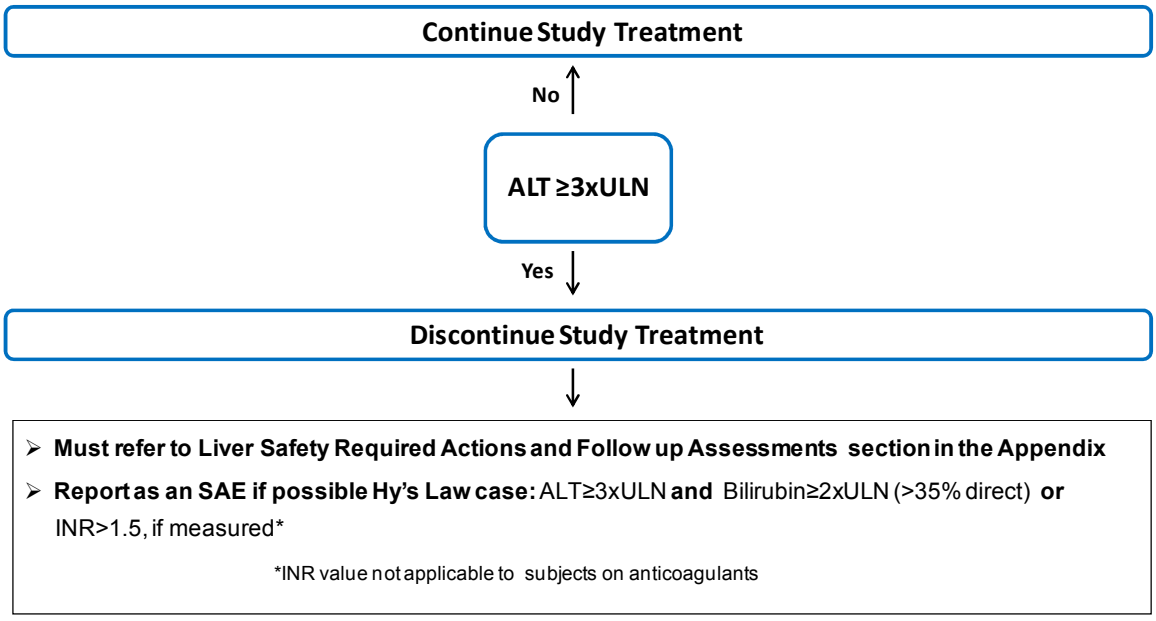
8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm below or if the investigator believes that it is in the best interest of the participant.

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

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

A subject that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.

- QTc, QTcB, QTcF > 500 msec,
- Change from baseline: QTc >60 msec

See the Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Neutrophil Stopping Criteria

A participant with a peripheral blood neutrophil count ≤ 0.5 x 10^9/L that is confirmed on repeat testing will be instructed to suspend dosing. The neutrophil count should be monitored daily until it returns to within the baseline value, as detailed in Appendix 7.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the Section 2 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the Section 2.

The following points must be noted:

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

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including PK and safety assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team members (e.g. medical monitor and GCSP) and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study.

9.1. Efficacy

This study is a single dose PK study and therefore there is no efficacy endpoint.

9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Appendix 4).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

- All SAEs will be recorded and reported to the sponsor or designee within 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 in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 60 hours after the last dose of study treatment.
- 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 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

For this study, any dose of study treatment ≥ 4 tablets in a day will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

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

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.

9.4. Safety Assessments

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

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

9.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section [8.1.2] for QTc withdrawal criteria and additional QTc readings that may be necessary.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 days after the last dose of study treatment 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 Section 2.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of whole blood concentrations of danirixin (performed under the control of GSK Platform Technology and Science Department of In Vitro In Vivo Translation Third Party Resourcing (PTS-IVIVT/TPR) as specified in the Section 2. Instructions for the collection and handling of biological samples will be provided by the sponsor in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of danirixin. Each whole blood sample will be used to prepare 4 dried blood spots which will be analysed for danirixin concentrations. Samples collected for analyses of danirixin whole blood may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

No formal hypothesis will be tested. For each pharmacokinetic endpoint, point estimates and corresponding 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ (reference).

The following comparisons of interest will be constructed:

Part	Question	Comparison
Part A	Formulation	475mg DC tablet formulation versus 600mg RC formulation (reference)
		600mg DC tablet formulation versus reference
		600mg DC tablet with 5% HPMC versus reference
Part B Stratum 1	Food effect No OMP	High fat meal (heavy) versus Fasted
		Normal meal (light) versus Fasted
		High fat meal (heavy) versus Normal meal (light)
Part B Stratum 2	Food effect With OMP	High fat meal (heavy) versus Fasted
		Normal meal (light) versus Fasted
		High fat meal (heavy) versus Normal meal (light)
Part B Strata 1 & 2	Drug interaction	Fasted with OMP versus Fasted without OMP
		Normal meal (light) with OMP versus Normal meal (light) without OMP
		High fat meal (heavy) with OMP versus High fat meal (heavy) without OMP
Part B Stratum 1	Pharm Dev	Monohydrate with high fat meal versus High fat meal (heavy)

10.1. Sample Size Determination

The sample size is primarily based on feasibility. Approximately 60 subjects will be enrolled in the study to obtain approximately 16 randomized subjects (13 completers) in Part A and 12 randomized subjects (10 completers) in each strata of Part B.

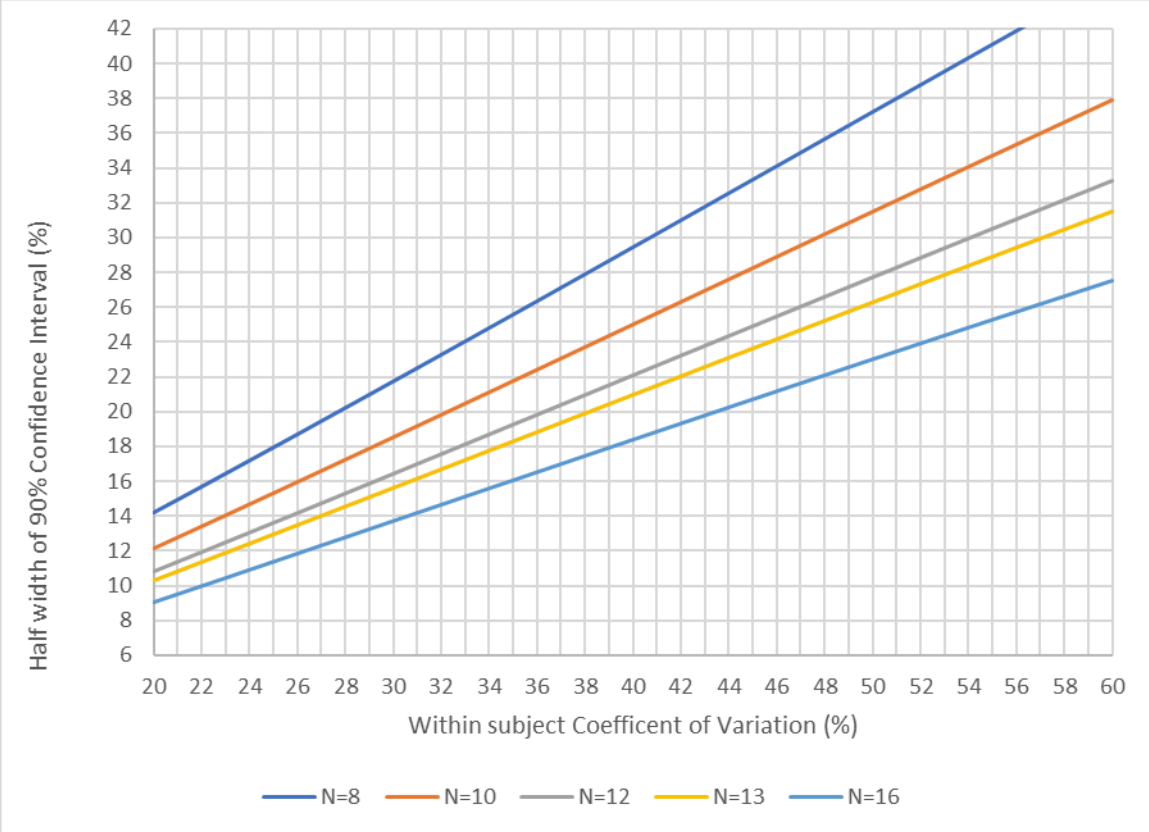
The within-subject variability for AUC(0-inf), AUC(0-t) and Cmax of danirixin [GSK Study 201037, GlaxoSmithKline Document Number 2015N248339_00] was estimated to be 37.3%, 39.3% and 44.7%, respectively. Based upon the largest within-subject coefficient of variation (44.7% for Cmax of danirixin) and a sample size of 13 subjects completing part A of the study, it is estimated that the half-width of the 90% confidence interval for the ratio of geometric means for the comparison of interest should be no more than 23% of the point estimates. Assuming an observed ratio of one, the corresponding 90% confidence interval for the ratio of geometric means would be 0.81 to 1.23.

An interim analysis is planned at the completion of Part A to select the formulation for evaluation in Part B.

10.1.1. Sample Size Sensitivity

The figure below shows the half width of the 90% CI for a range of within-subject coefficient of variations for various sample sizes.

Figure 1 Plot of half width of 90% CI by within-subject coefficient of variations



10.1.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants	All participants who receive at least one dose of study medication. This population will be used for the study population and safety analyses.
PK	All participants for whom a pharmacokinetic sample was obtained and analyzed. This will be the population used for all the pharmacokinetic displays.

10.3. Statistical Analyses

Final analyses will be performed after the completion of the study and final dataset authorization.

Data will be listed and summarized separately for each part of the study according to GlaxoSmithKline reporting standards where applicable.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

10.3.1. Pharmacokinetic Analyses

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to GlaxoSmithKline current working practices. . Calculations will be based on the actual sampling times recorded during the study. From the blood concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed blood concentration (Cmax), time to Cmax (tmax), area under the blood concentration-time curve [AUC(0-t), AUC(0-inf), AUC(0-24)], lag time before observation of first blood concentration (tlag), time of last observed blood concentration (tlast), and apparent terminal phase half-life (t1/2).

Pharmacokinetic data will be listed and presented in graphical form and will be summarized descriptively. Complete details will be documented in the Reporting and Analysis Plan (RAP).

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters (AUC and Cmax) and the associated 90% CIs will be provided for treatment comparisons (test:reference). The PK parameters will be log-transformed prior to analysis and treatment comparisons will be expressed as ratios on the original scale.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-24)	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BCG	Bacillus Calmette-Guerin
BID	Twice a Day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CPK	Creatine Phosphokinase
Cmax,	Maximum Observed Concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
DC	Direct Compression
DNX	Danirixin
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety Pharmacovigilance
GLS	Geometric Least Squares
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK1325756	Danirixin
HBcAb	Hepatitis B core antibody
HBr	Hydrobromide
HBsAg	Hepatitis B surface antigen
HBsAg	Hepatitis B Surface Antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
ICF	Informed Consent Form

IEC	Independent Ethics Committees
IRB	Institutional Review Boards
Kg	Kilogram
LDH	Lactate Dehydrogenase LDH
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
Mg	Milligram
MSDS	Material Safety Data Sheet
NOAEL	No-Observed-Adverse-Effect-Level
OMP	Omeprazole
PK	Pharmacokinetic
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RC	Roller Compaction
SAE	Serious Adverse Event
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2,	Terminal phase half-life
TB	tuberculosis
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
tmax,	Time of occurrence of Cmax
TST	tuberculin skin test
ULN	Upper Limit of Normal
WBC	While Blood Cells
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting	Calcium	Alkaline phosphatase,	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine/breathalizer alcohol screen and a urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and			

Laboratory Assessments	Parameters
	benzodiazepines. • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology : HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody The results of each test must be entered into the CRF.

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (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).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

- This study will be registered and study information from this protocol will be posted on publicly available clinical trial registers before enrolment of study participants begins.
- The results summary of this study will be posted to the GSK Clinical Study Register and other publicly available clinical trial registers within 8 months of the primary study completion date.
- A manuscript reporting the study results will be submitted to a peer reviewed journal within 18 months of the last participant's last visit.

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Appendix 3.

Study and Site Closure

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

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

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

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

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

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

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 (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE

reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (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.

Reporting of SAEs 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 (e.g., InForm). • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • 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 or SAE coordinator by telephone. • Contacts for SAE reporting can be found in the study procedures manual.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8.

Table 8 Highly Effective Contraceptive Methods

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

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 60 hours after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Additional pregnancy testing should be performed at monthly intervals during the treatment period and at 60 hours after the last dose of study treatment and as required locally

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 5 mIU/mL will be performed using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will not routinely attempt to collect pregnancy information on any male participant's female partner(s) who becomes pregnant while the male participant is participating in this study; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism. This applies only to male participants who receive double-blind study treatment.
- If pregnancy information for a male participant's female partner(s) is voluntarily reported, after obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 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.

12.6. 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>• 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 subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained up to 72 hours after 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 >1.5:
• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.7. Appendix 7: Neutrophil Safety and Study Treatment Restart

<table>
<tr><td colspan="2">Neutrophil Stopping Criteria: Absolute neutrophil count (ANC) ≤ 0.5 x 10^9 /L</td></tr>
<tr><td colspan="2">Required Actions and Follow up Assessments</td></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete an SAE data collection tool if the event also meets the criteria for an SAE
• Monitor the participant until neutrophil count stabilizes or returns to within baseline (see MONITORING below)
• Do not restart participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (see RESTART below)
MONITORING:
• Treatment of any suspected infections[1]
• Repeat CBC within 24 hrs
• Monitor CBC daily until neutrophil count resolves, stabilizes or returns to within baseline</td><td>• Record the appearance or worsening of any clinical symptoms on the AE report form[1]
• Obtain blood sample for pharmacokinetic (PK) analysis within 12 hours after last dose[2]
• Record use of concomitant medications on the concomitant medications report form</td></tr>
<tr><td colspan="2">RESTART</td></tr>
<tr><td>• Restart of study medication must be approved by the GSK Medical Monitor
• Restart may be attempted ONLY if all three criteria are met:
  • The neutrophil count is ≥ 1.5 x 10^9/L for at least 48 hours
  • At least 7 days have elapsed since the suspension of study treatment
  • No sign or symptom of associated infection has been identified</td><td>• Check the CBC within 24-48 hours after re-starting study medication, monitor twice weekly for two weeks, and monthly thereafter.
• If the ANC drops below 1.0 x 10^9/L on restart, the participant should be permanently discontinued from study treatment and withdrawn from the study.</td></tr>
</table>

1. New or worsening symptoms believed to be related to neutropenia such as (but not limited to): sudden onset of fever or malaise, stomatitis, odynophagia, periodontal infection, skin abscesses, signs or symptoms of sinusitis and otitis, symptoms of pneumonia (eg, cough, dyspnea), perirectal pain and irritation, hypotension or signs of septic shock.
2. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment 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.