TITLE PAGE

Protocol Title: Randomised, Double-Blind (Sponsor Open), Placebo-Controlled, Multi-centre, Dose Ranging Study to Evaluate the Efficacy and Safety of Danirixin Tablets Administered Twice Daily Compared with Placebo for 24 Weeks in Adult Participants with Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number: 205724 Amendment 1

Short Title: Danirixin Dose Ranging Study in Participants with COPD

Compound Number: GSK1325756

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

31-Oct-2017

PPD

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Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	31-Oct-2017
Original Protocol	28-Nov-2016

Amendment 1: 31-Oct-2017

Overall Rationale for the Amendment: This amendment adds a second, optional, detailed pharmacokinetic profiling at Visit 10 in a subset of participants to allow for a better understanding of danirixin pharmacokinetics. This amendment also removes the Participant Exit Interview from the exploratory endpoints. Additionally, this amendment provides additional information and clarification for the following: spirometry assessments, exclusion for cancers other than lung cancer, permitted use of supplemental oxygen, permitted uses of chronic steroids, participant numbering requirement for re-screening, additional text to explain the timing of the planned interim analysis and updates to the analysis populations.

Section # and Name	**Description of Change**	**Brief Rationale**
Table 1 – Schedule of Activities	Added Pulse Oximetry to Eligibility Assessments	To provide clarification for the eligibility assessment
Table 1 – Schedule of Activities	Added additional, detailed PK profiling in a subset or participants at Visit 10 (additional text was added to footnote n)	To provide an additional PK profile to improve the understanding of danirixin PK
Table 1 – Schedule of Activities	Removed Participant Exit Interview and associated footnote from Schedule of Activities	A completed analysis of Exit Interviews conducted as part of the danirixin phase IIa study (study 200163) did not demonstrate sufficient evidence that the complexity and cost of including Exit Interview was justified as very limited additional information beyond that obtained with other scheduled participant questionnaires was obtained. Study Team decided to remove as an exploratory endpoint.
Section 3.1 – Study Rationale	Exit Interview removed	See above for detailed explanation for removal of the Exit Interview
Section 4 – Objectives and Endpoints	Added additional text to clarify assessment of the E-RS:COPD endpoint	To provide clarification of primary endpoint analysis
Section 4 – Objectives and Endpoints	Exit Interview removed as an exploratory endpoint	See above for detailed explanation of rationale for removal of Exit Interview as an exploratory endpoint
Section 5.1 – Overall Study Design	Provided additional explanatory text to describe interim analyses.	Provides clarification for purpose and timing of interim analyses
Section 6.1 – Inclusion Criteria	Corrected typographical error in inclusion criterion 4	To correct typographical error

Section # and Name	**Description of Change**	**Brief Rationale**
Section 6.2 – Exclusion Criteria	Provided additional explanatory text for exclusion criterion 1	Provided explanatory text to clarify assessment of history of tuberculosis and other cancers
Section 6.2 – Exclusion Criteria	Added new exclusion criterion 26 to clarify prohibited oxygen use (also describes allowed oxygen use)	Provided text to clarify oxygen use study participants
Section 6.4 – Screen Failure	Revised text to indicate that if a participant is rescreened they must be assigned a new participant number at the time of rescreening	This change was made to be consistent with the current GSK SOP requirements for rescreening a clinical trial participant
Section 6.5 – Run In Failures	Additional text added to describe what to do if a COPD exacerbation occurs between Visit 2 and Visit 3	Provide clarification on what to do if a COPD exacerbation occurs between Visit 2 and Visit 3
Section 7.7 – Concomitant Therapy	Provided additional text to define chronic use of systemic corticosteroids	Provided definition of chronic use of systemic corticosteroids to clarify conditions of prohibited use from the screening visit until after completion of the follow up visit
Section 7.7 – Concomitant Therapy	Provided additional text to clarify use of oxygen	Added text clarifies the permitted uses of intermittent oxygen.
Section 9.1.8 – Exit Interview	This subsection was removed since the Exit Interview was removed as an exploratory endpoint.	See above for detailed explanation
Section 9.1.9	Clinically Important Deterioration (CID)	This section renumbered to Section 9.1.8 with removal of the Exit Interview Assessment.
Section 9.2.8.3	Corrected spelling of Form and Medical in 2nd bullet of this section.	Correction of typographical error
Section 9.4.6 –	This section added to provide in the protocol more detail for	Adds spirometry testing detail to the protocol some of which was

Section # and Name	**Description of Change**	**Brief Rationale**
Spirometry Testing	the spirometry testing	previously in the Study Reference Manual (SRM). The SRM will be update to avoid duplicate information. For spirometry testing, investigators should use the information in the protocol and the SRM.
Section 10.4 – Populations for Analysis	Modified Intent to Treat (mITT) population definition added to Populations for Analysis; Intent to Treat (ITT) and Safety Populations removed from Populations for Analysis	To perform analysis based on actual treatment instead of randomised treatment. This is a dose-ranging study and therefore the primary interest is on outcomes based on actual treatment.
Section 10.4 – Populations for Analysis	Definition of the PK Population changed to include all participants in the mITT population	PK population will be based on actual treatment instead of randomized treatment.
Section 10.5.1.1 – Primary Analysis	Revised text to indicate primary endpoint will use the mITT population,	See above for explanation
Section 10.5.1.2	Text revised to indicate that analyses for secondary efficacy endpoints will use the mITT population, unless otherwise noted	Revised text explains that mITT population will be used for the analyses of secondary efficacy endpoints, unless otherwise noted
Section 10.5.2	Text revised to indicate that all safety endpoints will be performed on the mITT population	Revised text explains which population will be used for analysis of all safety endpoints
Section 10.5.4	Additional text was added to provide additional information for the conduct of interim analyses.	To provide additional detail to describe the conduct of interim analyses.
Section 10.5.4.2	Corrected spelling of parameter.	Correction of typographical error
Section 10.5.4.2	Last paragraph of this section was amended.	Futility Interim Analysis will contain outputs for the primary endpoint and

Section # and Name	**Description of Change**	**Brief Rationale**
		some key secondary endpoints – details will be provided in the RAP
Section 10.5.4.3 – Strategic Planning Analyses	Revised text provides additional information for when the Strategic Planning interim analysis will be conducted	Additional text better defines the timing of the Strategic Planning interim analysis
Section 10.5.4.4	This section added to provide additional text to describe interim analyses	Additional text to describe interim analyses
Section 11 – References	Added Miller MR et al (2005) reference	Reference added to support additional spirometry text in Section 9.4.6
Section 12.1 – Appendix 1	ITT abbreviation removed; mITT abbreviation added	Changes reflect changes to Populations for Analysis changes made to section 10.5.1.2
Section 12.3 – Appendix 3	Publication Policy text revised to indicate that interim analyses may be disclosed externally	Provide text to explain that results of interim analyses may be disclosed externally
Section 12.3 – Appendix 3	Additional text added to Committees Structure section to indicate that results of interim analyses may be shared within GSK.	To provide additional explanation for sharing of results of interim analyses.
Section 12. 3 – Appendix 3	Typographical error corrected in third bullet of Dissemination of Clinical Study Data subsection	Correction of typographical error

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1. SYNOPSIS

Protocol Title: Randomised, Double-Blind (Sponsor Open), Placebo-Controlled, Multi-centre, Dose Ranging Study to Evaluate the Efficacy and Safety of Danirixin Tablets Administered Twice Daily Compared with Placebo for 24 Weeks in Adult Participants with Chronic Obstructive Pulmonary Disease (COPD)

Short Title: Danirixin Dose Ranging Study in Participants with COPD

Rationale: The primary aims of this study are to evaluate the clinical activity and safety of 5 doses of danirixin compared with placebo in participants with COPD. The study is intended to support subsequent decisions regarding the progression of danirixin in the COPD indication, including the selection of doses and appropriate endpoints for use in pivotal studies**.**

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To characterize the dose response of danirixin compared with placebo on the incidence and severity of respiratory symptoms in participants with COPD	• Change from baseline in respiratory symptoms measured by the Evaluating Respiratory Symptoms in COPD (E-RS:COPD) daily diary at month 6: total score and subscales (i.e. breathlessness, cough and sputum, and chest symptoms
• To compare the safety of danirixin with placebo in participants with COPD	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG)
Key Secondary	
• To characterize the dose response of danirixin compared with placebo on the annual rate of moderate/severe COPD exacerbations in participants with COPD	• Annual rate of Healthcare Resource Utilization (HCRU)-defined COPD exacerbations
• To further characterize the clinical activity of danirixin compared to placebo in participants with COPD	• Time to first HCRU-defined COPD exacerbation • Change from baseline for the St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)

Overall Design: This is a double-blind (Sponsor Open), placebo-controlled, parallel group study that will evaluate the dose response of danirixin compared with placebo on respiratory symptoms, COPD exacerbations, healthcare-related quality of life and physical activity. The safety of danirixin compared with placebo is also an important objective of the study. Following the completion of baseline assessments collected over a 7 day period (i.e. EXACT/E-RS:COPD, physical activity, and rescue medication use), participants will be randomized (1:1:1:1:1:1) to receive one of five dose strengths of danirixin or placebo for 24 weeks. Three interim analyses are planned for the study. The first interim analysis will be an analysis of danirixin pharmacokinetics, and will be conducted after approximately 10 participants in each treatment group who are participating in the PK substudy have completed Visit 3. A futility analysis interim based on the E-RS:COPD endpoint and will be conducted after approximately 150 participants have completed 3 months of study treatment. An additional interim analysis will be conducted approximately 12-15 months after the beginning of the study, or when 450 participants have completed 6 months of study treatment, whichever is earlier. This interim analysis will be used to support GSK decisions regarding the further development of danirixin and will include clinical activity assessments and key safety assessments available at the time it is conducted. Additional informal summaries of danirixin exposure and efficacy data may be undertaken during the conduct of the study.

Number of Participants:

Approximately 700 participants will be screened to achieve approximately 600 randomized participants. It is anticipated that approximately 540 participants will complete 24 weeks of treatment and key study assessments (dropout rate estimated to be approximately 10%).

Treatment Groups and Duration:

Participants will be randomized to one of six parallel groups and will receive study treatment twice daily for 24 weeks:

- Placebo
- 5 mg danirixin (as hydrobromide hemihydrate salt)
- 10 mg danirixin (as hydrobromide hemihydrate salt)
- 25 mg danirixin (as hydrobromide hemihydrate salt)
- 35 mg danirixin (as hydrobromide hemihydrate salt)
- 50 mg danirixin (as hydrobromide hemihydrate salt)

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of Activities

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**±0d**	**+ 3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		
Eligibility													
Informed consent	X												
Genetic Sample Informed Consent[b]	X												
Demography	X												
COPD Exacerbation History	X												
Pre-Screening Fibrinogenc	X												
Smoking History[d]		X											
Smoking Status[d]		X	X										
Inclusion and Exclusion criteria		X											
Medical history[e]		X											
Full physical examination including height and weight		X											
Chest x-ray (CXR)[f]		X											

Procedure	**Pre-Screening[a] (Visit 0)**	**Screening[a] (Visit 1)**	**Study Visits**									**Early Withdrawal**	**Follow Up (up to 28 days post last dose)**
			2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**±0d**	**+ 3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		
HIV, Hepatitis B and C screening[g]		X											
Pulse Oximetry		X											
Additional Eligibility and In Study Assessments													
Verify Eligibility[h]			X	X									
Brief Physical				X				X			X	X	X
Urine or serum pregnancy test[i]		X		X		X	X	X	X	X	X	X	
Laboratory assessments (clinical chemistry (includes liver chemistries), hematology, urinalysis)		X		X		X					X	X	X
Additional Liver chemistries only					X		X	X					
12-lead ECG		X		X		X		X			X	X	
Vital signs	X	X		X		X		X			X	X	
Spirometry		X		X				X			X	X	
Randomization				X									
Dispense Study Medication				X		X	X	X	X	X			

Procedure	**Pre-Screening[a]** **(Visit 0)**	**Screening[a]** **(Visit 1)**	**Study Visits**									**Early Withdrawal**	**Follow Up** **(up to 28 days post last dose)**
			2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**±0d**	**+ 3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		
Dispense log pad and provide training			X										
Dispense MDI sensors and provide training			X										
Dispense physical activity monitor and provide training			X										
Study treatment				←==========→									
Study treatment compliance (ediary)				←==========→									
Collect IP					←==========→							X	X
Collect MDI sensors				←==========→								X	X
Collect physical activity monitor				←==========→								X	X
Collect log pad				←==========→								X	X
Adverse Event (AE) review				←==========→								X	X
Serious Adverse Event (SAE) review	←==========→											X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**±0d**	**+ 3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		
Clinical Outcomes Assessments													
COPD Exacerbations			←==========→									X	X
EXACT-PRO[j]			←==========→										
Rescue Medication Use[k]			←==========→										
SGRQ-C				X				X			X	X	
COPD Assessment Test				X				X			X	X	
PROactive Questionnaire[l]				X				X			X		
Physical Activity Monitor[l]			X					X			X		
Participant Global Impression of COPD Severity			X										
Participant Impression of Change in COPD Severity					X	X	X	X	X	X	X	X	
Participant Global Impression of Activity Limitation			X										

Procedure	**Pre-Screening[a]** **(Visit 0)**	**Screening[a]** **(Visit 1)**	**Study Visits**									**Early Withdrawal**	**Follow Up** **(up to 28 days post last dose)**
			2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**±0d**	**+ 3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		
Participant Impression of Change in Activity Limitation					X	X	X	X	X	X	X	X	
Genetic, Pharmacokinetic and Biomarker Blood Collections													
Blood sample for Genetics				X									
Blood sample for pharmacokinetics (PK)[m]				X			X	X			X		
Blood sample for Fibrinogen				X				X			X	X	
Blood sample for CRP				X				X			X	X	
Blood Sample for Exploratory Biomarkers				X				X			X	X	

Procedure	**Pre-Screening[a]** (Visit 0)	**Screening[a]** (Visit 1)	**Study Visits** 2	3	4	5	6	7	8	9	10	**Early Withdrawal**	**Follow Up** (up to 28 days post last dose)
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**±0d**	**+ 3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		

a. Pre-screening and screening visits may be completed on the same day.
b. Agreeing to the genetic sample consent is not required for study participation.
c. A pre-screening plasma fibrinogen measurement is only required for participants with 1 COPD exacerbation in the prior year.
d. Smoking status /history assessed at screening: smoking status rechecked at Visit 2
e. Includes substance usage, past and present medical conditions and family history of premature CV disease.
f. See inclusion/exclusion criteria for CXR screening requirement
g. Hepatitis B (HBsAg) and Hepatitis C (HepC antibody) testing is required. If testing otherwise performed within 3 months prior to the first dose of study treatment, testing at screening is not required. Hepatitis C RNA testing is optional; however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease.
h. Participant's clinical status should be reviewed.
i. Pregnancy testing only required for women of child bearing potential (WOCBP). A positive urine pregnancy test requires confirmation with a serum pregnancy test.
j. E-RS:COPD is a subset of EXACT-PRO and is not a separate assessment.
k. Rescue medication use will be assessed via e-diary and MDI sensor.
l. The Clinic Visit PROactive Physical Activity in COPD tool will be assessed in a subset of approximately 50% of study participants
m. Pre-dose PK samples will be collected in all participants at Visits 3, 6, 7, and 10. In a subset of participants (approx. 50 participants at each dose level) at Visit 3, PK samples will be collected at pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose. In a subset of participants (approx.. 50 participants at each dose level) at Visit 10, PK samples will be collected at pre-dose, 0.5. 1. 2. 4. 6, 8, 10, 12 hours post-dose.

Note: The timing and number of planned study assessments, including safety, pharmacokinetic, and biomarker assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

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 No. YM2010/00163/07].

Clinical pharmacology studies in healthy volunteers demonstrated the pharmacodynamic activity of danirixin (inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils). Danirixin has also been tested in a Phase IIa study in symptomatic participants with mild to moderate COPD at risk for exacerbation (GSK Study No. 200163) [GlaxoSmithKline Document No. 2013N180289_03]. In study 200163, twice daily dosing with danirixin free base (75 mg bid) or placebo given on top of standard of care inhaled maintenance treatments was tested for one year. An interim analysis of clinical endpoints from study 200163 demonstrated that danirixin, compared to placebo, reduced respiratory symptoms as measured with E-RS:COPD [Miller, 2016].

3.1. Study Rationale

This protocol describes a Phase IIb dose-ranging study evaluating the clinical activity and safety of danirixin compared with placebo in participants with COPD that have current respiratory symptoms including cough, increased sputum production, and dyspnoea. Study participants will continue with their standard of care inhaled medications (i.e. long acting bronchodilators with or without inhaled corticosteroids) while receiving study treatment. In this study, 5 doses of danirixin and placebo are being evaluated (danirixin or placebo will be taken orally twice daily).

The primary objectives of the study are to evaluate the dose response of danirixin compared with placebo on respiratory symptoms assessed by the E-RS:COPD patient reported outcome (PRO) tool and assess the safety of danirixin compared with placebo. Key secondary objectives include an evaluation of danirixin compared with placebo on healthcare resource utilization (HRCU) defined COPD exacerbations, health status, physical activity, and rescue medication use. Exploratory objectives will include blood biomarkers to investigate the impact of danirixin on biomarkers of extracellular matrix turnover and remodeling.

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, 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 No. 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	The most sensitive species is the rat. Testicular effects present at doses ≥150 mg/kg/day in the rat include spermatid degeneration, seminiferous tubular degeneration and secondary epididymal changes, including oligo/aspermia and/or epididymal intratubular cellular debris. The no observed adverse effect level (NOAEL) in this study, based on the microscopic findings in the testis, was 50 mg/kg/day for male rats. The systemic exposure margins for the NOAEL for testicular effects in the rat is 7.3-fold for an oral clinical dose of 50 mg BID free base tablet. The testicular effects seen in the rat have also been shown to directly impact on male fertility and the NOAEL for these reproductive effects was 100 mg/kg/day. Refer to IB Section 4.4 for full details No adverse events related to testicular effects have been observed in clinical studies to date.	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 (2-fold NOAEL). PK modelling predicts that in a participant receiving 50 mg BID of the HBr salt, the risk of exposure exceeding the 2-fold margin for AUC(0-24) for the NOAEL of testicular effects is low.

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
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 healthy volunteer studies and a phase 2a study in patients with Influenza (GSK Study	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 9. 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**
	201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in subjects receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy subjects, 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. Male participants with female partners of child-bearing potential must comply with the contraception requirements.
Study Procedures		
None		
Other		
Not applicable		

3.3.2. Benefit Assessment

- All participants will undergo a thorough medical assessment during the study. Participants will have frequent study clinic visits for the evaluation of their disease symptoms. During these visits, participants will have spirometry, ECG, vital signs monitoring, and physical examinations. Monitoring for worsening of their disease will also take place.

- Participants may benefit from the knowledge that they are contributing to the process of developing a new treatment in an area of unmet need, even if not directly beneficial for them

- All participants will continue with changes to their medications, where medically appropriate, to receive established standard of care.

3.3.3. Overall Benefit:Risk Conclusion

Danirixin has demonstrated potent antagonism of CXCR2 activity both in vitro and in vivo in preclinical and clinical studies. Its potency and duration of action supports its potential use as an oral, anti-inflammatory agent in the treatment of COPD with anticipated potential for bringing benefit to a serious condition that affects the lives of millions and contributes to significant morbidity and mortality.

In clinical trials completed to date danirixin has been well-tolerated and most adverse events (AEs) were mild to moderate in intensity. The most commonly observed AEs have been nasopharyngitis, headache and diarrhea following administration of danirixin or placebo. There have been no treatment related clinically significant changes in vital signs and ECG at any dose of danirixin.

Taking into account the measures taken to minimize risks to participants in this study, the potential risks identified in association with danirixin are justified by the anticipated benefits that may be afforded to participants with COPD.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To characterize the dose response of danirixin compared with placebo on the incidence and severity of respiratory symptoms in participants with COPD	• Change from baseline in respiratory symptoms measured by E-RS:COPD daily diary at month 6: total score and subscales (i.e. breathlessness, cough and sputum, and chest symptoms)
• To compare the safety of danirixin with placebo in participants with COPD	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG)

Objectives	Endpoints
Secondary • To characterize the dose response of danirixin compared with placebo on the annual rate of moderate/severe COPD exacerbations in participants with COPD	• Healthcare Resource Utilization (HCRU)-defined COPD exacerbations
• To further characterize the clinical activity of danirixin compared to placebo in participants with COPD	• E-RS:COPD Responder Analysis (including subscales) • Number of Exacerbations of Chronic Pulmonary Disease (EXACT) tool defined events • Time to first EXACT event • EXACT event severity • EXACT event duration for all events • Time to first HCRU-defined COPD exacerbation • Time to first severe HCRU-defined COPD exacerbation • HCRU-defined exacerbation duration • Change from baseline for the St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C) • SGRQ responder analysis • Change for baseline COPD Assessment Test (CAT) total score • CAT responder analysis • Lung function (FEV1, FEV1 % predicted, FVC, FEV1/FVC ratio) • Rescue medication use • Participant experience of physical activity (subset of approximately 50% of participants) measured using PROactive Clinic Visit Tool (C-PPAC)

Objectives	Endpoints
• To characterize the pharmacokinetics of danirixin in participants with COPD	• Danirixin concentration and standard pharmacokinetic parameters for danirixin (e.g. AUC, Cmax, Tmax), using dried blood spot data
Tertiary/Exploratory • To further explore study participants experience with study treatment and overall experience with the study	• Time to first Clinically Important Deterioration (CID) • SGRQ domains
• To characterize the effect of danirixin on lung matrix destruction/remodelling	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes)
• Comparison between dried blood spot and wet whole blood analysis of danirixin concentrations in patients with COPD	• Danirixin concentration and standard pharmacokinetic parameters for danirixin (e.g. AUC, Cmax, Tmax)
• To characterise danirixin exposure-response relationships for various safety parameters,if appropriate	• Danirixin systemic exposure and various efficacy/PD/safety parameters, if appropriate

5. STUDY DESIGN

5.1. Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and successful completion of the EXACT daily diary (all participants), rescue medication use daily diary (all participants) and PROactive baseline measurements (questionnaire and participant experience of physical activity) over study days -7 to 1, participants will be randomized (1:1:1:1:1:1) to receive one of five dose strengths of danirixin (5 mg, 10 mg, 25 mg, 35 mg and 50 mg) or placebo. Study treatment will be administed twice daily for 24 weeks. The PROactive baseline measurements will only be collected for those participants selected for the physical activity monitoring subgroup. Participants who do not properly complete (i.e. are not adherent with the requirements for completing and recording) the required baseline assessments (i.e. EXACT/E-RS:COPD daily diary, physical activity monitoring portion of PROactive, and daily rescue medication use baseline measurements) will not be randomized and will not be eligible for rescreening.

A minimum of three interim analyses are planned for the study. The first interim analysis will be an evaluation of danirixin pharmacokinetics after 10 participants in each treatment group participating in the PK substudy have completed Visit 3.

A futility analysis interim based on the E-RS:COPD endpoint and will be conducted after approximately 150 participants have completed 3 months of study treatment.

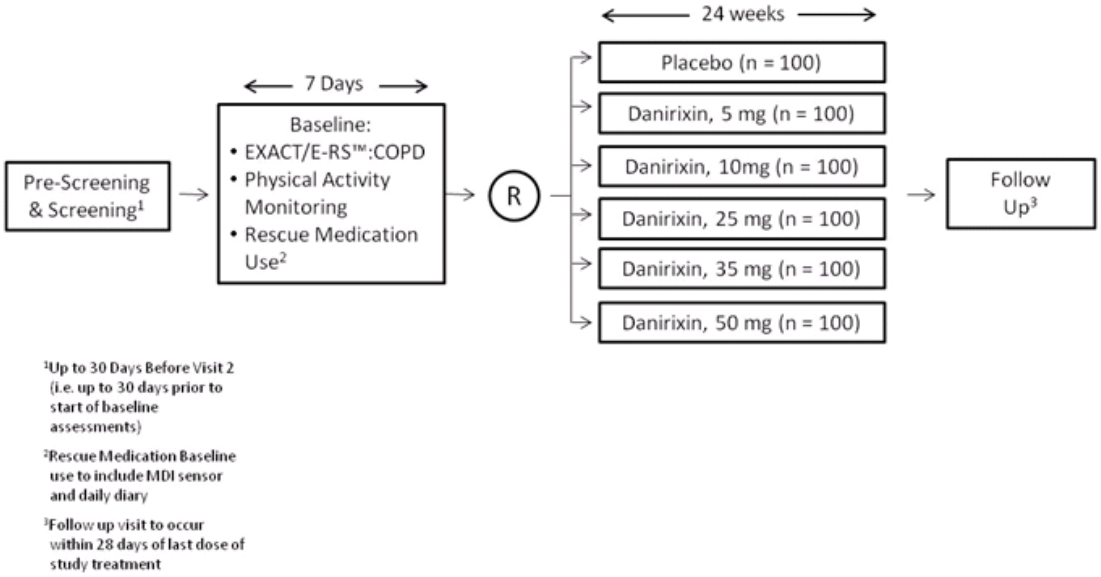
An additional interim analysis will be conducted approximately 12-15 months after the beginning of the study, or when 450 participants have completed 6 months of treatment, whichever is earlier. This interim analysis will be used to support GSK decisions regarding the further development of danirixin, and will include E-RS:COPD dose response modelling, secondary endpoints of HCRU-defined exacerbations and SGRQ total score along with all available safety data. No changes will be made to the study based on the results of this interim analysis.

Additional informal assessments of danirixin exposure and efficacy data may be undertaken during the conduct of the study as data becomes available. No decisions regarding study conduct will be made based on these informal assessments.

Outputs containing unblinded treatment assignments will be created for these interim analyses and will only be made available to a limited number of GSK staff. Full details will be included in the study data dissemination plan.

No Independent Data Monitoring Committee (IDMC) will be utilized for this study. While the study is being conducted, core members of the study team will be unblinded (with the exception of those study team members who will directly interact with study sites, e.g. Operations and Science Leader and Data Quality Leader). There will be ongoing review of safety data and clinical outcomes. Only the study statistician will have access to individual participant treatment assignments, other core team members will review aggregate summaries by study treatments. A study charter will specify which team members will have access to unblinded data while the study is ongoing, the frequency of planned data reviews and the data to be included in the data reviews. The study charter will also state how interim results will be communicated outside the study team. A safety review team will meet approximately every 3 months (or as needed based on emerging data) to review available safety information.

Figure 1 Study Schematic



5.2. Number of Participants

Approximately 700 participants will be screened to achieve approximately 600 randomized participants. It is anticipated that approximately 540 participants will complete 24 weeks of treatment and key study assessment (the dropout rate is estimated to be approximately 10% based on previous experience with studies enrolling similar participants).

For the analysis of study assessments, several analysis populations will be defined. Details of the evaluable participants for each planned analysis population are included in Section 10.4.

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 last study visit and the last scheduled procedure shown in the Schedule of Activities (Table 1).

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 multicenter, randomized, parallel-group design. This is a well-established design to evaluate the efficacy and safety of an investigational drug. Twenty-four weeks should be adequate to demonstrate efficacy based on E-RS:COPD, as well as to collect adequate safety measurements before going into larger phase III trials. Danirixin has already been clinically investigated over one year treatment duration (GSK Study No. 200163, GlaxoSmithKline Document No. 2013N180289_03).

By evaluating a range of doses from 5 mg to 50 mg of danirixin, it will be possible to assess the dose response of danirixin as well as the potential effects of danirixin on biomarker and safety endpoints. The data will provide useful information in determining the therapeutic index of danirixin and in selecting the minimal effective and safe dose to be carried forward in the Phase III COPD program.

PK samples from randomized participants will also be collected in this study. Defining the optimum dose for later stages of development can be made more efficiently by understanding the variability in the pharmacokinetics of a drug. In addition, the study will evaluate the relationship between danirixin blood concentrations and biomarker and safety endpoints.

A placebo arm is included to measure the absolute effect of each dose tested, thereby allowing a robust determination of the dose-response. Inclusion of a placebo arm will also allow a more robust exploration of the therapeutic index of danirixin.

5.5. Dose Justification

Five doses of danirixin (5 mg, 10 mg, 25 mg, 35 mg and 50 mg) are planned for evaluation in this study. The doses to be investigated have been selected based on integrating information available from:

- Dose-exposure-biomarker response using inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils over the dose range of 0-400 mg in healthy volunteer participants
- Evidence of reduced respiratory symptoms in mild to moderate COPD participants in the Phase IIa study (GSK study 200163)

In the early clinical studies, danirixin was administered as a free base tablet, whereas the danirixin formulation to be used in this study will be a hydrobromide salt tablet. The hydrobromide tablet has approximately twice the bioavailability of the free base tablet in healthy elderly participants (GSK Study No. 201037, GlaxoSmithKline Document No. 2015N248339_00). Predicted steady-state exposures and multiples of blood *ex vivo* CXCL1-induced CD11b pharmacology at the proposed danirixin doses are presented in Table 2.

Table 2 Predicted steady state systemic exposure and multiples of blood ex vivo CXCL1-induced pharmacology following twice daily of administration of danirixin

Dose (mg)	Predicted steady-state median (5th, 95th percentile)[a]			Cavg multiple of IC50[b]	Cmin multiple of IC50[b]
	AUC(0-24) steady-state (µg.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
5	1.37 (0.69, 2.78)	57.2 (28.6, 116)	27.8 (6.8, 92.1)	0.7	0.4
10	2.74 (1.34, 5.53)	114 (56.0, 230)	54.8 (13.6, 180)	1.5	0.7
25	6.85 (3.36, 13.8)	285 (140, 576)	137 (34.0, 450)	3.6	1.7
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4
50	13.7 (6.71, 27.6)	571 (280, 1152)	274 (68.0, 900)	7.3	3.5

a. Model derived based on PK data in healthy elderly participants from GSK Study No. 201037 (GlaxoSmithKline Document No. 2015N248339_00).
b. Model predicted population mean IC50=78.5 ng/mL (95% CI: 37.3, 120), sigmoidal Emax model of DNX PK-*ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils in healthy participants.

The predicted multiples of *ex vivo* CXCL1-induced CD11b inhibition achieved at 24 h post steady-state, together with the terminal elimination half-life of danirixin support the twice daily dosing regimen.

Based on the biomarker results described for danirixin and the anticipated higher exposure from the hydrobromide tablet, doses of 5 mg, 10 mg, 25 mg and 35 mg were selected to span the dose range and allow efficient estimation of the dose response curve in this mild/moderate COPD population. Fifty mg twice daily is included as a supra-therapeutic dose but where there is a low possibility of AUC(0-24) exposure exceeding a 2-fold margin for the no observed adverse effect level (NOAEL) for testicular effects.

The risk of exposure exceeding the 2-fold margin for AUC(0-24) for the NOAEL of testicular effects is considered low. Based on PK modeling, the predicted AUC (0-24) for a dose of 50 mg BD is 13.7 ug.hr/mL (6.7, 27.6). This provides 2.5-fold cover over the NOAEL/2 and approximately 5-fold cover over the NOAEL.

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 40 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have COPD (postbronchodilator FEV1/FVC ratio < 0.7 and FEV1 % predicted ≥ 40%) based on American Thoracic Society (ATS)/European Respiratory Society (ERS) current guidelines [Celli, 2004]. Participants with a historical diagnosis of asthma may be included so long as they have a current diagnosis of COPD.

3. History of respiratory symptoms including chronic cough, mucus hypersecretion, and dyspnea on most days for at least the previous 3 months prior to screening.

4. Participants with a documented history of COPD exacerbation(s) in the 12 months prior to study participation (screening) meeting at least one of the following criteria:

    - ≥ 2 COPD exacerbations resulting in prescription for antibiotics and/or oral corticosteroids or hospitalization or extended observation in a hospital emergency room or outpatient center

    - 1 COPD exacerbation resulting in prescription for antibiotics and/or oral corticosteroids or hospitalization or extended observation in a hospital emergency room or outpatient center and a plasma fibrinogen concentration at screening ≥ 3 g/L (300 mg/dL)

5. Smoking history: current and former smokers with a cigarette smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Current smokers are defined as those who are currently smoking cigarettes (i.e. have smoked at least one cigarette daily or most days for the month prior to Visit 1). Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Note: pipe and/or cigar use cannot be used to calculate smoking pack-year history.

6. Participants must have the ability and willingness to use an electronic diary (log pad) on a daily basis.

Weight

7. Body weight ≥ 45 kg

Sex

8. Male or female.

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 60 hours after the last dose of study treatment, corresponding to approximately 6 half-lives (which is the time needed to eliminate any teratogenic study treatment) and to refrain from donating sperm during this period.

   b. 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

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

6.2. Exclusion Criteria

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

Medical Conditions

1. Diagnosis of other clinically relevant lung diseases (other than COPD), e.g. sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer.

   - A participant with a history of tuberculosis may be considered for eligibility if he/she has documented completion of a course of antibiotic therapy (eg, INH) and has no evidence of latent TB infection. A chest x-ray ideally would be available for review by the medical monitor but is not required. All cases of prior TB must be discussed with the medical monitor.

   - For cancers other than lung cancer, participants may be considered for eligibility if the carcinoma has been in remission for at least 5 years. Participants who have had carcinoma *in situ* of the cervix, squamous cell carcinoma or basal cell carcinoma of the skin would not need to be excluded based on the 5 year waiting period if the participant has been considered cured by treatment.

2. Alpha-1-antitrypsin deficiency as the underlying cause of COPD

3. Pulse oximetry < 88% at rest at screening. Participants should be tested while breathing room air. However, participants living at high altitudes (above 5000 feet or 1500 meters above sea level) who are receiving supplemental oxygen can be included provided they are receiving the equivalent of < 4 L/min and screening pulse oximetry is measured while on their usual oxygen settings.
4. Less than 14 days have elapsed from the completion of a course of antibiotics or oral corticosteroids for a recent COPD exacerbation.
5. A peripheral blood neutrophil count < 1.5 x 10^9/L.
6. Diagnosis of pneumonia (chest X-ray or CT confirmed) within the 3 months prior to screening.
7. Chest x-ray (posterior-anterior with lateral) or CT scan reveals evidence of a clinically significant abnormality not believed to be due to the presence of COPD (historic results up to 1 year prior to screening may be used). For sites in Germany: If a chest x-ray (or CT scan) within 1 year prior to screening is not available, approval to conduct a diagnostic chest x-ray will need to be obtained from the Federal Office of Radiation Protection (BfS).
8. History or current evidence of other clinically significant medical condition that is uncontrolled on permitted therapies. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through study participation, or that would affect the safety analysis or other analysis if the disease/condition worsened during the study.
9. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
10. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants who would be at undue risk by participating in the study. An abnormal and clinically significant finding that would preclude a participant from entering the study is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
    a. AF with rapid ventricular rate > 120 bpm
    b. sustained or non-sustained VT
    c. second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
    d. QTcF ≥ 500 msec in participants with QRS < 120 msec and QTcF ≥ 530 msec in participants with QRS ≥ 120 msec
11. Previous lung surgery (e.g. lobectomy, pneumonectomy) or lung volume reduction procedure.

Prior/Concomitant Therapy

12. Current or expected chronic use of macrolide antibiotics during the study period for the prevention of COPD exacerbations. Examples of chronic use include, but are not limited to, daily or two to three times per week use for at least 3 months.

13. 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.) The Investigator should consult with the Medical Monitor if necessary.

14. Current or expected use of phosphodiesterase-4 inhibitors (e.g. roflumilast). Participants currently receiving roflumilast may be included if they are able to discontinue use from 30 days prior to screening through the completion of the follow up visit.

Prior/Concurrent Clinical Study Experience

15. Participation in a previous clinical trial and has received an investigational product within any of the following time periods prior to the first dosing day in the current study: 30 days, 5 half lives, or twice the duration of the biological effect of the investigational product (whichever is longer).
16. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study
17. Exposure to more than four investigational products within 1 year prior to the first dosing day in the current study.

Diagnostic assessments

18. Alanine transferase (ALT) > 2x upper limit of normal (ULN); bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
19. A positive test for HIV antibody.
20. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Other Exclusions

21. Pulmonary rehabilitation: Participants who have taken part in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to screening or participants who plan to enter the acute phase of a pulmonary rehabilitation program during the study. Participants who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
22. A history of allergy or hypersensitivity to any of the ingredients in the study treatment.
23. A known or suspected history of alcohol or drug abuse within the 2 years prior to screening.
24. Inability to read: in the opinion of the Investigator, any participant who is unable to read and/or would not be able to complete study related materials.

25. Affiliation with the study site: study investigators, sub-investigators, study coordinators, employees of a study investigator, sub-investigator or study site, or immediate family member of any of the above that are involved with the study.
26. Oxygen therapy: Chronic treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for > 15 hours a day. Oxygen prn use (i.e.<15 hours per day) is not exclusionary. Oxygen use during an exacerbation is permitted.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

No meal or dietary restrictions are required for participation in this study. Danirixin must be taken with food. Specific dosing instructions will be provided in the Study Reference Manual (SRM) and will be provided to all study participants.

6.3.2. Activity

Participants should abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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 up to two additional times if the investigator judges the participant can meet the eligibility criteria. Any rescreened participant must satisfy all of the protocol specified inclusion/exclusion requirements at the re-screening visit. Rescreened participants should be assigned a new participant number at the time of rescreening.

6.5. Run In Failures

A run in failure is defined as a participant who consents to participate in the clinical study, satisfies all eligibility criteria, but who does not properly complete the required baseline assessments for the daily EXACT diary, daily rescue medication use, and the physical activity monitoring portion of PROactive baseline (if selected to participate in the physical activity subgroup) over 7 days beginning with Visit 2. A participant who is selected to participate in the physical activity subgroup and does not complete the baseline physical activity monitoring portion of PROactive baseline but does complete the daily EXACT diary and daily rescue medication use baseline assessments will still be eligible for participation in the study but will be not be included in the physical activity

subgroup. Participants who are run in failures will not be randomized to any study treatment and are not eligible for rescreening.

A successful EXACT baseline assessment is defined as completion of all 14 questions of the EXACT questionnaire on at least 4 of the 7 days. Successful rescue medication use recording is defined as recording of rescue medication use in the daily diary on at least 4 of the 7 days along with electronic data capture from the MDI sensor device. For participants in the physical activity subgroup a successful baseline determination is defined as recording of physical activity for at least 8 hours per day on at least 3 of the 7 days and completion of the PROactive questionnaire at Visit 3.

During the time period between Visit 2 and Visit 3 if a participant has a moderate or severe COPD exacerbation (one that requires treatment with systemic corticosteroids and/or antibiotics or requires hospitalization), the patient should not be randomized and should be withdrawn. In this case, the participant may be rescreened at a later date if the investigator judges the participant can meet the eligibility criteria. A participant with a mild COPD exacerbation would not need to be withdrawn.

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

Table 3 Treatments Administered

Study Treatment Name:	**Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)**	**Placebo**
Dosage formulation:	White Film coated tablets (oval or round shaped). Refer to Investigator's Brochure for presentation and excipients	White Film coated tablets (oval or round shaped). Refer to Investigator's Brochure for presentation and excipients
Unit dose strength(s)/Dosage level(s):	5, 10, 25, 35 and 50 mg (of free base equivalent)	N/A
Route of Administration	Oral	Oral
Dosing instructions:	One tablet to be taken twice daily with food	One tablet to be taken twice daily with food

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Placebo
Packaging and Labeling	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labeled as required per country requirement.	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labeled as required per country requirement.
Manufacturer	GSK	GSK

7.1.1. Medical Devices

- Subject to availability and any local restrictions on use, MDI sensor devices (manufactured by and purchased from Propeller Health) are being provided by GSK for this study. These devices are fitted onto rescue medication MDI devices to electronically record rescue medication usage. The MDI sensor devices have US FDA 510(k) clearance to market (Class II medical device) and European Union CE marking (Class I medical device).

- Subject to availability and any local restrictions on use, ActiGraph GT9X physical activity monitors (manufactured by and purchased from ActiGraph, LLC) are being provided by GSK for the subset of participants that will be included in the physical activity monitoring subgroup. The device is a tri-axial accelerometer. The participant wears the devices for the period of time that physical activity is being monitored.
- Additional descriptive information and instructions for the eMDI and physical activity monitoring devices are provided in the SRM.
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 9.2).

7.2. Dose Modification

No individual participant dose modifications or adjustments are allowed.

7.3. Method of Treatment Assignment

- This study will use an Interactive Web Response System (IWRS). All participants will be centrally randomized using the IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

- Participant randomization will be stratified by smoking status (i.e. current smoker or former smoker).
- Study treatment will be dispensed to participants at the study visits summarized in the SOA.
- Returned study treatment should not be re-dispensed to any participant.

7.4. Blinding

This will be a double-blind (sponsor open) study. Study participants, all study site staff, and all members of the GSK study team, with the exception of the study statistics and programming team, will be blinded to individual participant treatment assignment. As defined in the study charter and RAP, defined and named members of the GSK study team will have access to unblinded, aggregate summaries of study treatment results.

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

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

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm and document 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.
- 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.
- 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 of records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Precaution will be taken to avoid direct contact with the study treatment. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- 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 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.
- When participants self-administer study treatment(s) at home, compliance with study treatment administration will be assessed through querying the participant during the site visits and documented in the source documents and CRF. In addition, participants will be asked to confirm study administration each day in the daily ediary.
- Study participants who are not compliant with study treatment administration requirements should be re-educated on the importance of treatment compliance. Every effort should be made to keep participants in the study. Participants who continue to be non-compliant after several attempts to re-educate may be discontinued after consultation with the GSK study team.
- A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions 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 enrolment or receives during the study must be recorded along with:

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

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

The following COPD medications are permitted during the study, at the discretion of the GSK Medical Monitor and/or Investigator:

- Inhaled COPD maintenance medications (e.g. long acting bronchodilator medications (i.e. LAMA, LABA) and long-acting bronchodilator combination

therapies (e.g. LAMA/LABA) and long-acting bronchodilator/inhaled steroid combination (ICS) therapies (e.g. LABA/ICS, LAMA/LABA/ICS)

- Short courses of oral corticosteroids and/or antibiotics (including macrolides) are permitted for the acute treatment of exacerbations of COPD and should not exceed 21 days. This use must be recorded as an HCRU exacerbation event.

The following medications are prohibited from the screening visit until after completion of the follow up visit:

- Chronic use of macrolide antibiotics for the prevention of COPD exacerbations. Examples of chronic use include daily or two-three times per week for at least 3 months.
- Oral or injectable CYP3A4 or BCRP substrates with narrow therapeutic index (CYP3A4 substrates include, but are not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline; BCRP substrates include, but are not limited to, topotecan.
- Phosphodiesterase-4 inhibitors (e.g. roflumilast)
- Broad spectrum phosphodiesterase inhibitors (e.g. theophylline)
- Chronic use of systemic corticosteroids, i.e. long term (i.e. greater than 3 weeks), daily use of systemic corticosteroids. Chronic use of intranasal, intraocular and topical (for dermatological conditions) corticosteroids is allowed.

GSK will not supply rescue medication. Participants may continue to use and should obtain rescue medication(s) through via their usual route. The following rescue medications may be used:

- Short acting beta agonists (SABA) (e.g., albuterol/salbutamol)
- Short acting muscarinic antagonists (SAMA) (e.g., ipratropium)
- Short acting combination (SABA/SAMA) bronchodilations, (e.g. Duoneb, Combivent)

The use of rescue medications is allowable at any time during the study. Participants should record in the daily e-diary the number of puffs of rescue medication(s) over each 24 hour period. Data from the MDI sensor device will be electronically captured and transmitted to GSK.

Oxygen for intermittent use or PRN therapy ≤15 hours per day is allowed. Long term oxygen therapy or nocturnal oxygen therapy required for >15 hours is excluded throughout the study.

Annual influenza vaccine is recommended for patients with COPD but is not required for participation in this study. Influenza vaccination is permitted during the study and should be based on applicable local or national guidelines. Pneumococcal vaccine may also be administered, when indicated, based on applicable local or national guidelines.

Additional vaccinations may be administered when indicated. Any vaccination administered during the study should be recorded as a concomitant therapy.

7.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant.

GSK will not provide post-study treatment. There are no plans to provide the study treatment for compassionate use following study completion.

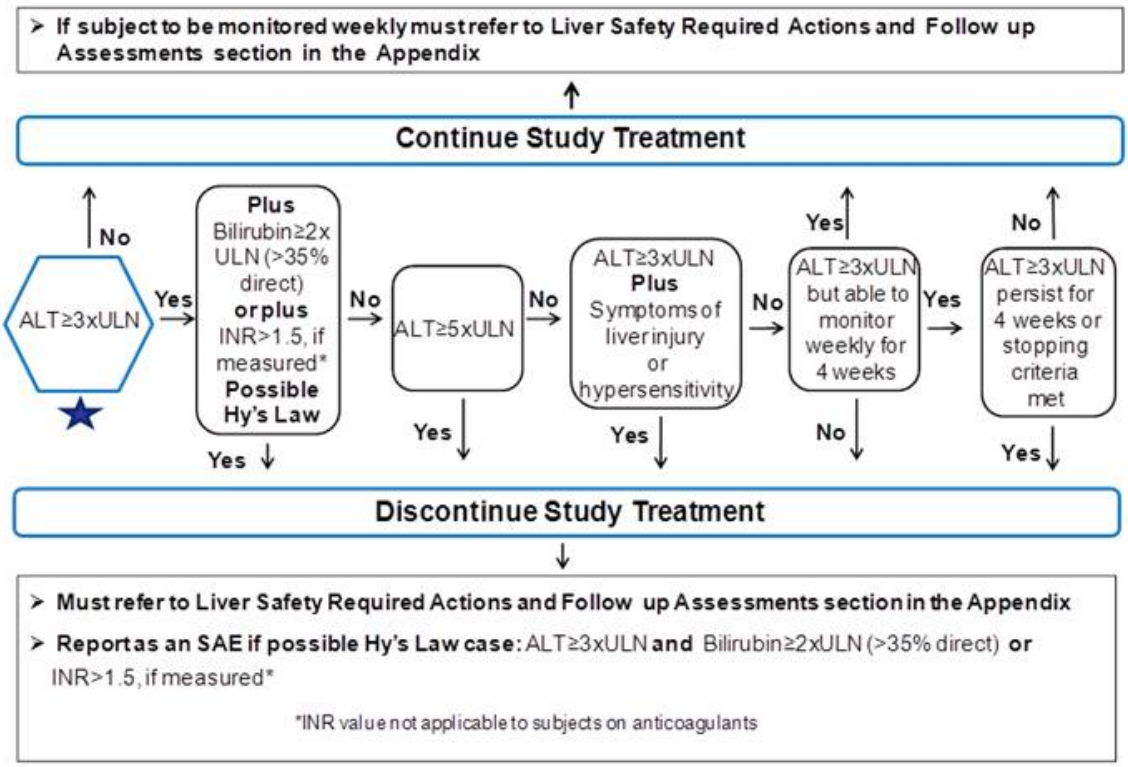
8. DISCONTINUATION CRITERIA

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 [FDA, 2009].

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.



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

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 participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTc > 60 msec

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

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

See the SoA (Table 1) 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 9.

8.1.4. Temporary Discontinuation

Temporary discontinuation of study treatment is allowed for up to 14 days when medically necessary, e.g. for hospitalization for a COPD exacerbation, other medical

condition requiring hospitalization, or reduction in peripheral blood neutrophil counts ≤ 0.5 x 10^9/L. Temporary discontinuation for any other reason should be discussed with the GSK Medical Monitor.

8.1.5. Study Treatment Restart

Study treatment restart after liver chemistry stopping criteria are met by any participant in this study is not allowed. Refer to Appendix 7 for full guidance for required actions and follow-up assessments to undertake if liver stopping criteria are met.

Study treatment restart after neutrophil stopping criteria are met can be considered once the neutrophil count has returned to within baseline and provided that no more than 14 days have elapsed since study medication was halted. The Investigator must obtain approval from the GSK Medical Monitor prior to restarting study treatment. See Appendix 9 for the procedure to be followed for study treatment restart after neutrophil stopping criteria are met.

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

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known

mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

9.1.1. EXACT and E-RS:COPD

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD [Jones, 2011; Leidy, 2010; Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically at bedtime) using an electronic diary. The daily recording of information allows an assessment of underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0 – 100, higher scores indicate more severe symptoms. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The Evaluating Respiratory Symptoms in COPD (E-RS:COPD) tool consists of 11 items from the 14 item EXACT instrument [Leidy, 2014a; Leidy, 2014b]. E-RS:COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough & sputum production, chest tightness and chest congestion. E-RS:COPD has a scoring range of 0 – 40, higher scores indicate more severe symptoms. Three subscales of E-RS are used to describe different symptoms, dyspnea, cough and sputum, and chest symptoms.

E-RS: COPD has recently been recognized as a drug development tool by FDA and EMA [EMA, 2015; FDA, 2016].

9.1.2. COPD Exacerbations

An exacerbation of COPD is defined by a worsening of symptoms.

The following are symptoms used to determine an exacerbation of COPD:

Worsening of two or more of the following major symptoms for at least two consecutive days:

- Dyspnea
- Spontaneous sputum volume
- Sputum purulence

OR

Worsening of any one of the above major symptoms together with any one of the following minor symptoms for at least two consecutive days:

- Sore throat
- Cold (nasal discharge and/or nasal congestion)
- Fever (oral temperature > 37.5 ºC) without other cause
- Increased cough
- Increased wheeze

Participants who experience worsening COPD symptoms for greater than 24 hours should:

- Contact their study investigator and/or research coordinator as soon as possible and report to the study clinic as required
- If the participant is unable to contact their study investigator or research coordinator, they should contact their primary care provider (or other health care provider) and contact their study site as soon as possible
- Continue to record their symptoms and rescue medication use in their daily ediary

- If the participant seeks emergency/acute care for worsening respiratory symptoms he/she should request the caring health care provider to contact the study investigator or research coordinator as soon as possible
- COPD exacerbations will be classified according to severity as follows:
- A COPD exacerbation is defined as a mild exacerbation if it is self-managed by the participant. Mild exacerbations are not associated with the use of antibiotics and/or systemic corticosteroids
- A COPD exacerbation is defined as a moderate exacerbation if it requires a new prescription for antibiotics and/or systemic corticosteroids
- A COPD exacerbation is defined as a severe exacerbation if it requires hospitalization, an emergency room visit, or extended observation in an outpatient centre

Details of an exacerbation should be recorded in the exacerbation page of the eCRF. Exacerbations will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE) as they are considered Disease Related Events (DREs). Only when the event is, in the Investigator's opinion, of greater intensity, or duration than expected for the individual participant, or the Investigator considers that there is a reasonable possibility that the event is related to study treatment should it be reported as an SAE (See Section 9.2). (Pneumonia must be recorded in the AE or SAE section of the eCRF and on the pneumonia page of the eCRF (See Section 9.4.5)).

All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF. If necessary, the PI or other health care personnel may stop the participant's study treatment temporarily in order to treat the COPD exacerbation. The reason for temporarily stopping study treatment and duration should be recorded in the eCRF.

The date of onset and the date of resolution will be recorded in the source documents and the eCRF.

- The date of onset is the first day (of at least 2 consecutive days) or worsening symptoms described above.
- The date of resolution should be based on when the Investigator or participant determines that the COPD symptoms have returned to near pre-exacerbation levels or to a new baseline.

9.1.3. SGRQ-C

The St. George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific tool (SGRQ-C) is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD patient's HRQoL [Meguro, 2007]. As well as producing an overall summary score, scores for the individual domains of symptoms, activity and impacts are also produced. The SGRQ-C has been used in numerous previous studies of COPD participants and has been translated and validated

for use in most major languages. The SGRQ-C is derived from the original SGRQ and produces scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.4. CAT

The COPD Assessment Test is a short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD [Jones, 2009; Jones, 2012]. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (maximum impairment) to 5 (no impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

The CAT consists of 8 items (cough, sputum, chest tightness, breathlessness, going up hills/stairs, activity limitation at home, confidence leaving the home, and sleep and energy). Individual items are scored from 0 to 5 with a total score range from 0 – 40, higher scores indicate worse health status.

9.1.5. PROactive

The PROactive tools, developed under the EU Innovative Medicines Initiative, measure patient experience of Physical Activity in COPD. The tools consist of a patient reported questionnaire combined with output from an activity monitor [Dobbels, 2014; Gimeno-Santos, 2015; Williams, 2012; Rabinovich, 2013; Gimeno-Santos, 2011]. The Clinical Visit PROactive Physical Activity in COPD (C-PPAC) tool is a designed for intermittent use within a clinical study. The 12 item questionnaire has a seven day recall period and participant responses are combined with two activity monitor data outputs covering the same period. The PROactive tools are scored from 0 to 100 with higher scores indicating greater disease impact, two subscales of amount and difficulty can be used to support the total score.

The C-PPAC tool will be implemented in a subset of approx. 50% of participants. Participants will be randomly selected from each study site participating in the physical activity subgroup.

9.1.6. Patient Global Rating of Severity and Global Rating of Change in Disease Severity

Participants will complete the Global Rating of COPD Severity at randomisation and at final study visit or IP Discontinuation Visit. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, very severe).

Participants will complete a Global Rating of Change in COPD (overall disease) question at all Visits subsequent to randomisation including the final Visit (or Early Withdrawal (EW) Visit). Response options will be on a 7 point Likert scale ranging from much better to much worse. Asking at each Visit allows for early detection of response as well as continued response.

9.1.7. Patient Global Rating of Activity Limitation and Global Impression of Change in Activity Limitation

Subjects will complete the Global Rating of Activity Limitation at randomisation and at final visit or EW Visit. This single global question will ask subjects to rate their activity limitation on a four-point scale (not limited, slightly limited, limited, very limited).

Subjects will complete a Global Impression of Change in Activity Limitation question at all Visits subsequent to randomisation including the final Visit (or EW Visit). Response options will be on a 7 point Likert scale ranging from much better to much worse.

9.1.8. Clinically Important Deterioration (CID)

A clinically important deterioration is a composite endpoint defined as at least one of the following events: (1) a decrease of ≥ 100 mL from baseline in trough FEV1, (2) a deterioration in health-related quality of life defined as ≥ a 4-unit increase from baseline in SGRQ total score, or (3) the occurrence of an on-treatment moderate or severe COPD exacerbation [Singh, 2016].

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 treatment (see Section 8).

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

- All SAEs will be collected from Visit 0 (i.e. from the time the informed consent is signed by the participant) until the follow up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of Visit 3 (study treatment randomization visit) 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 AEs and/or SAEs. 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 e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in participants with COPD and can be serious/life threatening:

- COPD exacerbations

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE). These events will be recorded on the DRE page in the participant's CRF within 72 hours after the investigator becomes aware of the event. These DREs will be monitored by the Safety Review Team (SRT) on a routine basis as described in Appendix 3.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

9.2.7. Pregnancy

- Details of all pregnancies in female participants and female partners of male 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.8. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of monitoring inhaled rescue medication use and for evaluating physical activity. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 4.

9.2.8.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 8.

9.2.8.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.8.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- Complete the Medical Device Incident Form for each participant who has a medical device incident with GSK medical devices provided for use during the study period. All of the header information in the form must be completed before sending to GSK. Original documents should be filed in the site study file. A copy of the form must also be sent to the GKS study monitor. Contact details will be included in the SRM. A copy of the form must also be sent to the GSK study monitor. Contact details will be included in the SRM. For incidents fulfilling the definition of an AE or SAE, the appropriate pages of the CRF must be completed. If there is an SAE, the completed CRF pages should be sent together with the Medical Device Incident Form. If the participant is withdrawn due to a medical device incident, ensure the Study Conclusion page is completed.
- The same individual will be the contact for the receipt of medical device reports and SAEs.

9.2.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

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 study treatment can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis as soon as possible 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 SoA (Table 1).

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, pulse, temperature and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. A single measurement of respiratory rate and oral temperature is adequate.

9.4.3. Electrocardiograms

- For participant screening and pre-dose on Day 1, triplicate ECG measurements should be collected. For all subsequent ECG assessments, single measurement are to be collected. 12-lead ECG will be obtained as outlined in the SoA 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.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes.

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 abnormal and clinically significant 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 SoA (Table 1).
- 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 (e.g., SAE or AE), then the results must be recorded in the CRF.

9.4.5. Pneumonia

All suspected pneumonias will require confirmation as defined by the presence or new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms:

- Increased cough
- Increased sputum purulence (colour) or production
- Auscultatory findings of adventitious sounds (e.g. egophony, bronchial breath sounds, rales, etc.)
- Dyspnea or tachypnea
- Fever (oral temperature > 37.5 ^{o}C)
- Elevated white blood cell count (WBC) (> 10 x 10^9/L or > 15% immature forms)
- Hypoxemia (Hb O_2 saturation < 88% or at least 2% lower than baseline value)

All pneumonias must be captured on the AE/SAE page of the eCRF and on the pneumonia page of the eCRF.

The Investigator and site staff should remain vigilant for the possible development of pneumonia in participants as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For all suspected cases of pneumonia, Investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. Any microbiology or virology tests performed to determine etiology should be reported on the pneumonia eCRF page. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

9.4.6. Spirometry Testing

Spirometry assessments will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS/ERS [Miller, 2005]. All participants will have spirometry performed at Visits 1, 3, 7, 10 and where necessary Early Withdrawal. For each spirometry assessment, both pre- and post-bronchodilator measurements will be performed. For each FEV1 and FVC determination, at least 3 acceptable spirometry efforts should be obtained. Acceptable spirometry efforts should have a satisfactory start of the test and end of the test (i.e. a plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons. The largest FEV1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

For each spirometry assessment, the following guidelines should be followed:

- Spirometry procedure conducted between 6:00 AM and 11:00 AM
- Where applicable, after completion of other visit assessments (e.g. participant questionnaires and blood collections)

- Short acting bronchodilators (i.e. rescue medications) should not be used for at least 4 hours prior to the spirometry assessment
- The morning dose of any inhaled maintenance treatment should be withheld until the completion of the spirometry assessment
- Participants should refrain from smoking for at least 1 hour prior to each spirometry assessment
- Participants should abstain from consuming beverages with high levels of caffeine (including tea and coffee) for at least 2 hours prior to each spirometry assessment

Post-Bronchodilator Spirometry Testing

- Following pre-bronchodilator spirometry assessment, post-bronchodilator spirometry is measured. Following measurement of pre-bronchodilator spirometry, post-bronchodilator spirometry is performed 15 ± 5 minutes after 4 puffs of short acting beta-agonist administered using a valved spacer (i.e. 100 µg per puff of salbutamol or albuterol; other short acting bronchodilators may also be sued, e.g. iprotropium bromide, 4 x 40 µg) - according to the ATS/ERS guidelines.

- Similar to pre-bronchodilator spirometry testing, 3 acceptable spirometry efforts should be obtained and the highest FEV1 and FVC from the acceptable efforts should be recorded.

Additional details for the requirements and conduct of spirometry assessments are provided in the SRM.

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 SoA (Table 1). Instructions for the collection, processing, storage and shipping 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 at Visit 3 and 10. Each whole blood sample will be used to prepare 4 dried blood spots which will be analysed for danirixin concentrations and reported as primary data. The remaining whole blood will be retained and approximately 20% of the wet whole blood samples collected in Visit 3 will also be analysed for danirixin concentrations to provide an analytical comparison between dried blood spots and wet whole blood sample results. 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.

- Any remaining whole blood will be stored and may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

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

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

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

See Appendix 6 for Information regarding genetic research. Details on procedures for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

- Collection of samples for biomarker research is also part of this study. The following samples for biomarker research will be collected from all participants in this study as specified in the SoA:
  - peripheral venous blood samples for the preparation of serum and plasma
- Samples will be tested for biomarkers that are indicative of inflammation (i.e. CRP and fibrinogen), extracellular matrix turnover and remodelling to evaluate their association with the observed clinical responses or to help understand the underlying biological responses to danirixin.
- In addition, with the participant's consent, samples will be stored and may be used to investigate additional biomarkers thought to play a role in COPD disease progression or to evaluate their association with observed clinical responses to danirixin
- Samples also may be used for research to develop methods or support identification of prognostic/diagnostic biomarkers associated with clinical outcomes in COPD and related diseases.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Parameters for specific use in Health Economics analysis or Medical Resource Utilization and Health Economics are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

The primary efficacy endpoint is the change from baseline of E-RS:COPD total score at month 6. The primary objective of the study is to study the dose response and select an appropriate dose for future drug development programs.

A model based probability inference approach in Bayesian framework will be used to guide decision-making around dose selection. The posterior probability of the change from baseline of E-RS:COPD for each active dose being less than placebo will be used.

10.2. Sample Size Determination

In order to evaluate the impact of different sample sizes, various simulations were undertaken to understand the following questions around the change in baseline of E-RS:COPD scores at 6 months:

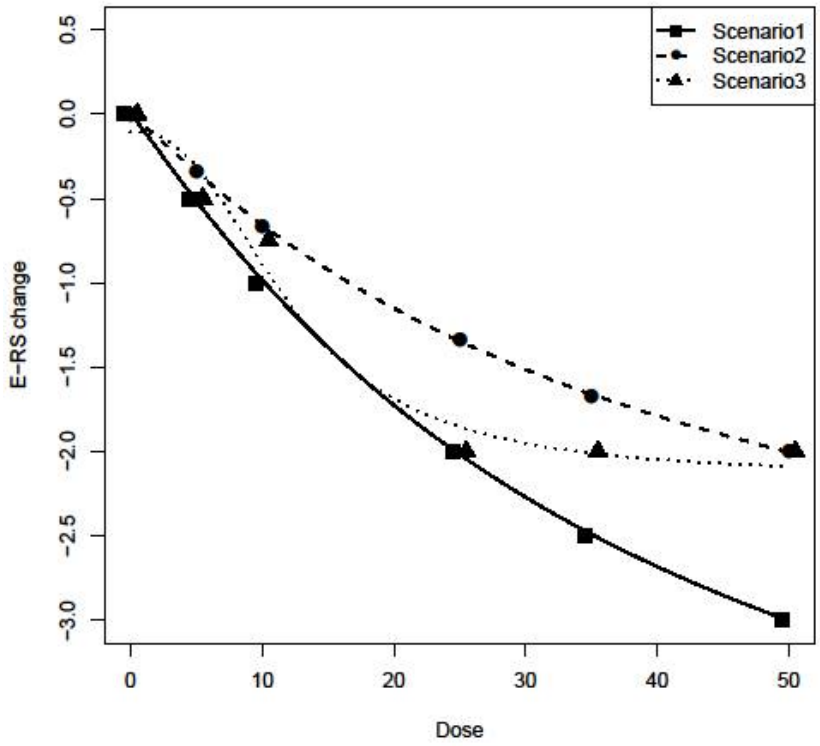
- What is the 90% confidence interval half width for the estimate of the treatment effect of the 5 mg, 25 mg, 35 mg, and 50 mg doses?
- What is the probability that the point estimate of difference from placebo is less than -1.5 for the 5 mg, 25mg, 35mg and 50 mg doses?
- What is the probability that the two-sided 90% confidence interval of the treatment effect excludes 0 for 5 mg, 25 mg, 35 mg and 50 mg doses?
- What is the probability that the two-sided 90% confidence interval of the treatment effect difference from placebo excludes 0 for 5 mg, 25 mg, 35 mg and 50 mg doses?

There are 3 scenarios considered for the simulations, each based on different assumptions of the effect for each of the 6 treatment arms. No model assumptions were made to generate these values. The scenarios are found in Table 4 and Figure 2. The assumed between participant standard deviation is 6.5 which is based on interim data from the 200163 study. For each scenario, 10,000 iterations of simulations were run.

Table 4 Assumptions Used for Sample Size Calculations

	Scenario 1	Scenario 2	Scenario 3
Placebo	0	0	0
5 mg	-0.5	-0.333	-0.5
10 mg	-1	-0.667	-0.75
25 mg	-2	-1.333	-2
35 mg	-2.5	-1.667	-2
50 mg	-3	-2	-2

Figure 2 Simulation scenarios with best fit sigmoidal Emax model



The Emax model will be used for the primary analysis and was the basis for estimation of the simulated data. The more general 4 parameter version of this model is defined as:

$$y(dose) = E_0 + E_{max} [dose^m / (ED_{50}^m + dose^m)]$$

where y( ) represents the E-RS:COPD change from baseline, E_0 is the mean response at dose = 0, E_{max} is the maximum dose effect (at dose = ∞), ED_{50} is the dose that yields a mean response of $E_0 + E_{max} / 2$, and m is the slope parameter allowing for sigmoidal dose response relationships.

Results of the sample size simulations are presented in Figure 3, Figure 4, Figure 5 and Figure 6,with the lowest danirixin dose (5 mg) and the 3 highest doses (25 mg, 35 mg, 50 mg).

Figure 3 Half width of the 90% confidence interval for the 5 mg, 25 mg, 35 mg and 50 mg doses

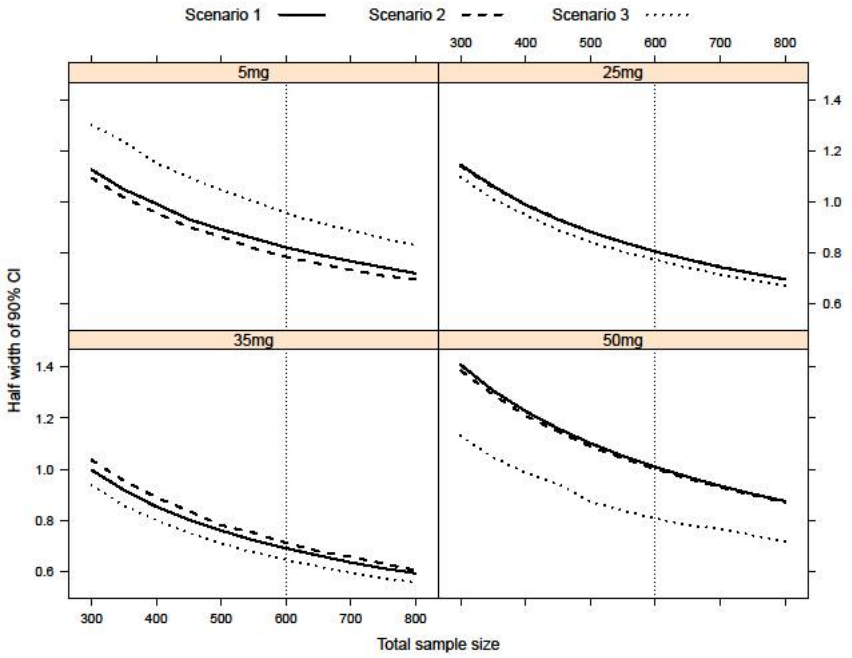


Figure 4 **Proportion of simulations in which the point estimate of difference from placebo is less than -1.5 for doses of 5 mg, 25 mg, 35 mg and 50 mg**

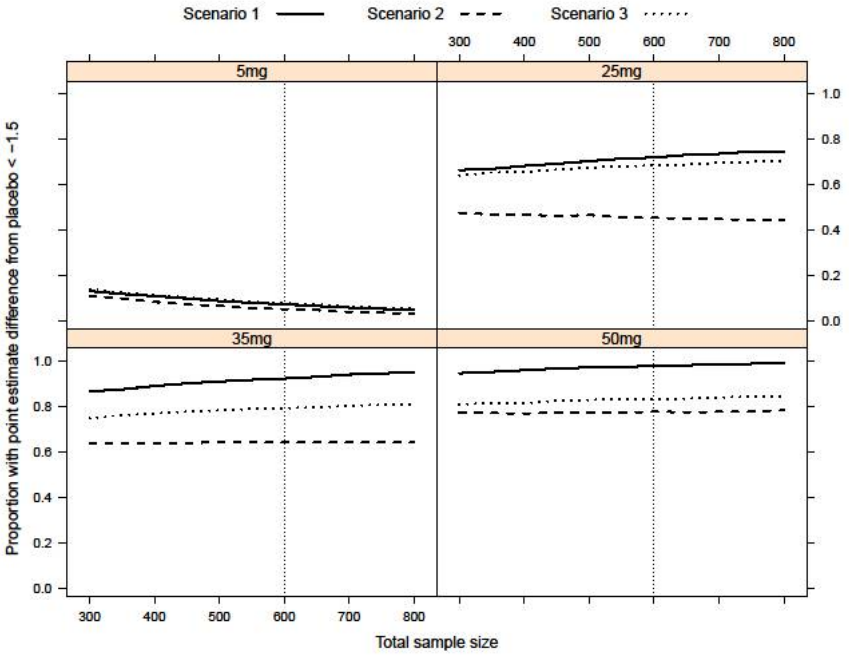


Figure 5 **Proportion of simulations in which the 90% confidence interval exclused 0 for doses of 5 mg, 25 mg, 35 mg and 50 mg**

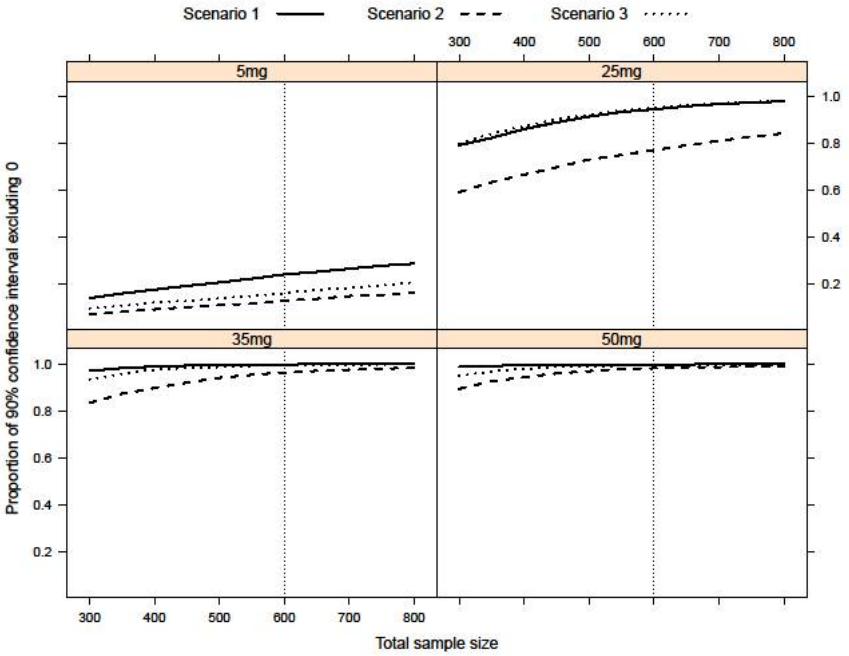
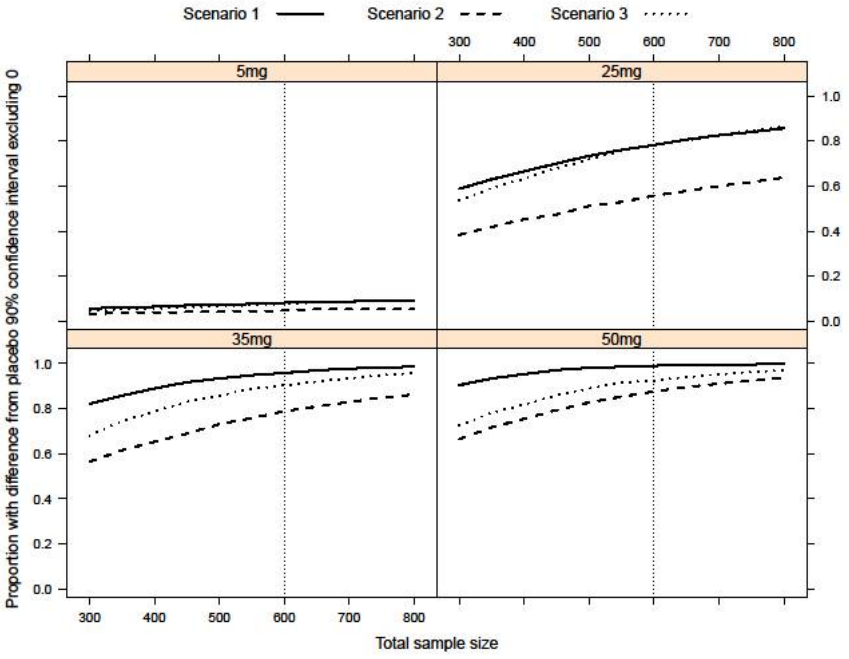


Figure 6 Proportion of simulations in which the 90% confidence interval of difference from placebo excludes 0 for doses of 5 mg, 25 mg, 35 mg and 50 mg



Based on the simulations a sample size of at least n = 600 will allow for adequate precision in estimation of the 35 mg dose as well as sufficient proportion with 90% confidence interval difference from placebo excluding 0 (over 80% for the 35 mg dose under all scenarios) and proportion with 90% confidence interval of dose estimate excluding 0 (over 80% for all higher doses and scenarios except 25 mg under scenario 2).

10.2.1. Sample Size Re-estimation

At the time of the interim analysis for futility, sample size re-estimation may be considered by the study team if the assumptions driving the sample size calculations are shown to be incorrect (e.g., variability is higher than expected). No more than 100 additional participants will be considered.

10.3. Randomization

Participants will be randomized equally (1:1:1:1:1:1) to the six treatment arms of placebo, 5 mg, 10 mg, 25 mg, 35 mg and 50 mg danirixin. Randomization will be stratified by smoking status (current vs. former).

10.4. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants	This population will comprise all participants screened and for whom a record exists on the study database and will be used for the tabulation and listing of reasons for withdrawal before randomization and listings of AEs and SAEs for nonrandomized participants.
Modified Intent To Treat (mITT)	This population will comprise all participants randomized to treatment and who received at least one dose of study medication. Randomized subjects will be assumed to have received study medication unless definitive evidence to the contrary exists. A true Intent-to-treat analysis would use the randomized treatment, but this population will be 'modified' in that all data summaries and analyses for this population will be based on the actual treatment received, if it is different to the randomized treatment. This will constitute the primary population for all analyses of efficacy and safety. If any subject received more than one treatment during a treatment period, their data will be reported according to the treatment they received for the longest period of time.
PK	This population will comprise all participants in the mITT population for whom a pharmacokinetic sample was obtained and analyzed while on treatment with DNX.

10.5. Statistical Analyses

Analysis methods for key endpoints are described below. Unless otherwise stated, all statistical testing will be two-sided and all confidence intervals or Bayesian credible intervals will be 90% two-sided.

Further details on all analyses will be described in the reporting and analysis plan (RAP).

10.5.1. Efficacy Analyses

10.5.1.1. Primary Analysis

The primary endpoint is 6 month change from baseline using the mITT population.

Baseline values of E-RS: COPD will be defined as the daily average of scores for the 7 days prior to randomization. Days with missing values will not count towards the average. A minimum of 4 days will be needed and participants without sufficient days will not be randomized.

Individual monthly E-RS:COPD means will be defined as the average E-RS:COPD scores during the following study days:

- Month 1: days 1-28
- Month 2: days 29-56
- Month 3: days 57-84
- Month 4: days 85-112
- Month 5: days 113-140
- Month 6: days 141-168

Days with missing values will not factor into the calculations. Participants will require a minimum number of 10 observations within a month, otherwise the monthly mean will be considered missing for that patient.

The primary analysis will be Emax (4 parameter) modeling of the dose-response curve for the primary efficacy endpoint of month 6 change from baseline. Smoking status will be included as a covariate in this model, allowing the asymptote values of the dose-response relation for smokers to differ from those of the non-smokers. This model formulation will require estimation of at most six parameters. Simpler models nested within this general formulation will be also considered, comprising formulations of the mean dose-response relation allowing for a fixed difference between smokers and non-smokers (parallel curves model), no difference between smokers and non-smokers and the Emax model restriction m=1. Model fitness will be measured using standard goodness of fit analysis. This analysis will allow for an assessment of the extent to which the variability of the trial data will be captured using the proposed model and what dose-response specification allows the best interpretation of the data.

The dose-response model will be fitted to the data using Bayesian techniques using the function uniform prior (FUP). The rationale for this choice of inference is that the FUP shrinks the dose-response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relation compared to maximum likelihood.

Standard Bayesian diagnostic plots will be produced to aid in the interpretation of results. Based on the selected model, 90% two sided Bayesian credible interval for all treatment arms, all pairwise differences between each danirixin dose and placebo, as well as between active danirixin doses, will be generated.

Other models of dose response such as quadratic and log linear will be considered as alternative analysis option if the Emax model does not fit the data well. Similar analysis with the final model using the endpoint includes months 1-6 and months 3-6 will be fit. A longitudinal mixed effects model will be also be fit with dose as a categorical variable to explore the time trend of E-RS:COPD. Each of the three E-RS:COPD subscales (breathlessness, cough and sputum, and chest symptoms) will be analysed using similar methods for the primary analysis and longitudinal analysis. Details of these sensitivity analyses will be further described in the RAP.

10.5.1.2. Key Secondary Analyses

All analyses for other efficacy endpoints will use the mITT Population, unless otherwise noted. Dose will be treated as a categorical variable and no dose response modelling will be done unless otherwise stated. The treatment comparisons of interest will be between individual danirixin doses and placebo and between different danirixin doses. Smoking status (current vs former) will be included as a covariate in all analyses. All Bayesian analyses will use non-informative priors. Further details will be described in the RAP.

10.5.1.3. HCRU Exacerbations

The number of events associated with HCRU-defined exacerbations will be analyzed using generalised linear models assuming a negative binomial distribution for the underlying exacerbation rate with a log link and an offset to account for the length of time in study for each participant. The exacerbation rates for the danirixin and placebo groups, along with the ratio in exacerbation rates danirixin/placebo, will be estimated and corresponding 95% credible intervals will be produced.

10.5.1.4. Time to First HCRU Exacerbation

Time to first HCRU exacerbation will be defined from the date of randomization. Participants without an exacerbation and participants who withdraw from the study prior to any observed exacerbations will be censored at the time of last contact. Survival will be summarized by treatment groups through Kaplan-Meier curves. Treatment arms will be compared using a stratified log-rank test. Time to first severe HCRU exacerbation will be analysed in a similar manner.

10.5.2. Safety Analyses

All safety endpoints will be tabulated or plotted by treatment group and will be performed on the mITT Population. Further details will be described in the RAP.

10.5.3. PK and PK/PD Analyses

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. For participants in the PK subset non-compartmental PK parameters (e.g. AUC(0-12), Cmax and tmax) will be calculated as data permit. The pharmacokinetic data from this study may be combined with historic DNX pharmacokinetic data for the purposes of population pharmacokinetic modelling which may be reported separately from the main clinical study report. The goal of this analysis is to characterize the population pharmacokinetics of DNX administered orally in subjects with COPD. The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of DNX in this population will be investigated. DNX blood concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model [FDA, 1999]. Further details will be described in the RAP.

Exploratory analysis using scatter plots will be conducted to investigate the relationship between blood exposure to danirixin (PK) and efficacy/PD/safety endpoints as data permit. If appropriate PK/PD modelling will be attempted to describe any relationship including longitudinal efficacy, PD, and/or safety variables versus systemic exposure (or dose) and may be combined with historic data. The results of any PK/PD modelling may be reported separately from the main clinical study report. Further details will be described in the RAP.

10.5.4. Interim Analyses

All interim analyses will be based on unblinded data. The randomization schedules and unblinded datasets will be stored on internal restricted drives. The GSK study team, with the exception of the statistics and programming team, will not have access to an unblinded randomization schedule during the course of the trial. Further details are described in the RAP and study charter.

10.5.4.1. Interim PK Analysis

After approximately 10 participants in the PK subset for each treatment group have completed Visit 3, an interim evaluation of danirixin pharmacokinetic parameters will be undertaken. The purpose of the interim PK analysis is to determine if danirixin exposures are within the expected range.

10.5.4.2. Futility Analysis

An interim analysis will be conducted to allow for the possibility of stopping early for futility. The expected pace of recruitment will be 12 months. Therefore, by the time a sufficient number of participants have been recruited and have accrued 6 months of data, a futility analysis will not be practical. We will therefore consider futility analyses based on the 3 month data using the assumption that the response will be consistent from month 3 onwards. Under this assumption, which is consistent with the Phase IIa study, this is a valid futility approach.

Once approximately 150 participants have completed 3 months of treatment, the 3 parameter Emax model will be fit to the change from baseline of E-RS:COPD. If the posterior predictive probability of difference from placebo being less than 0 is below 30% for all danirixin doses, the study may be stopped for futility.

Based on simulated data, the expected number of participants with completed 6 month data at the time of this analysis will be too small to warrant any analysis (expected number < 10). However, if the recruitment differs greatly from expectations, and enough participants have completed 6 months of treatment, the 6 month change from baseline endpoint may also be explored.

No early stopping for efficacy will be considered. Outputs featuring unblinded treatment assignments will be created for this interim analysis but will not be shared outside of the study team unless the decision is made to halt the study for futility.

10.5.4.3. Strategic Planning Analysis

The study will have an interim analysis for administrative purposes approximately 12-15 months after the beginning of the study, or when 450 participants have completed 6 months of study treatment, whichever is earlier. This analysis will be used to aid in the planning of future studies and for a better understanding of benefit/risk profile of danirixin. This interim analysis will look at the primary endpoint of E-RS:COPD dose response modelling, key secondary endpoints of HCRU exacerbations and SGRQ score, key safety endpoints around hepatotoxicity, neutrophils, pneumonia and other infections and PK data. No changes will be made to this study based on the results of this interim analysis. Outputs featuring unblinded treatment assignments will be created for this interim analysis, reviewed by the study team and potentially shared with selective GSK personnel (to be included in the study results dissemination plan).

Further details of the outputs including key safety outputs that will be produced will be described in the RAP.

10.5.4.4. Additional Interims

Additional informal summaries of danirixin exposure and efficacy data may be undertaken during the conduct of the study.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
BfS	Federal Office of Radiation Protection (Germany)
BID	Twice daily
BRCP	Breast cancer resistance protein
BUN	Blood urea nitrogen
CAT	COPD Assessment Test
CD	Cluster of differentiation
CFR	Code of Federal Regulations (United States)
CI	Confidence Interval
CID	Clinically important deterioration
CIL	Clinical Investigation Leader
Cmax	Maximum observed concentration
CONSORT	Consolidated standards of reporting trials
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Clinical Pharmacokinetics Modelling and Simulation
C-PPAC	Clinic Visit PROactive Physical Activity in COPD Tool
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
CXCR	CXC Chemokine Receptor
CXR	Chest X-Ray
dL	Deciliter
DNA	Deoxyribonucleic acid
DNX	Danirixin
DRE	Disease Related Event
E0	Effect at zero concentration
ECG	Electrocardiogram

eCRF	Electronic Case Report Form
ED50	Dose causing 50% of the maximum achievable response
EMA	European Medicines Agency
Emax	Maximum response achievable
eMDI	Electronic metered dose inhaler
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease-Patient Reported Outcome
E-RS:COPD	Evaluting Respiratory Symptoms in Chronic Obstructive Pulmonary Disease
EW	Early Withdrawal
FDA	Food and Drug Administation (United States)
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FSH	Follicle Stimulation Hormone
FUP	Function Uniform Prior
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HBsAG	Hepatitis B surface antigen
HCRU	Healthcare Resource Utilization
hCG	Human chorionic gonadotrophin
HDPE	High density polyethylene
Hep B	Hepatitis B
Hep C	Hepatitis C
hsCRP	High sensitivity C-reactive protein
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IVIVT	In vitro In vivo Translation
IWRS	Interactive Web Response System
kg	Kilogram
L	Liter
LABA	Long acting β2 receptor agonist
LAMA	Long acting muscarinic receptor antagonist
LH	Leutinizing Hormone
LTOT	Long term oxygen therapy
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin count
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mITT	Modified Intent to treat
mL	Milliliter
MM	Medical monitor
MSDS	Material Safety Data Sheet
msec	Millisecond
NOAEL	No observed adverse effect level
O_2	Oxygen
PK	Pharmacokinetics
PR	PR interval; duration in milliseconds from the beginning of the P wave to onset of ventricular depolarization (R)
PRO	Patient Reported Outcome
PTS	Platform Technology and Science
QRS	QRS interval; duration in milliseconds of the QRS complex

QT	QT interval; duraction in milliseconds between the start of the Q wave and the end of the T wave
QTcF	QT interval corrected for heart rate (Friderica formula)
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SABA	Short-acting β2 Receptor Agonist
SAE	Serious Adverse Event
SAMA	Short-acting Muscarinic Receptor Agonist
SGRQ	St George's Respiratory Questionnaire
SGRQ-C	SGRQ for COPD patients
SRM	Study Reference Manual
SRT	Safety Review Team
SOA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal phase half-life
TB	Tuberculosis
tmax	Time to reach Cmax
TPR	Third Party Resourcing
ULN	Upper limit of normal
µg	Microgram
VT	Ventricular tachycardia
WBC	White blood cells
WOCBP	Women of child bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 Protocol-Required Safety Laboratory Assessments will be performed by the central laboratory, except as noted.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium Chloride Bicarbonate	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 required for screening)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity			

Laboratory Assessments	Parameters
	• pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Plasma fibrinogen (a screening plasma fibrinogen is only needed for participants with 1 COPD exacerbation in the prior year) • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[3] • All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine testing

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 hCG testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease

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

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

Data Protection

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

Committees Structure

- A study charter will be created to describe important governance aspects while the study is being conducted.
- The core GSK study team (this will include the Clinical Investigation Leader (CIL), Medical Monitor (MM), study statistician, GCSP physician, GCSP scientist, and CPMS representative) will have access to unblinded, aggregate summaries for study treatments. Only the study statistician will have access to individual participant treatment assignments. Study team members who interact

with study site staff will remain blinded until the study is completed. Complete details will be included in the study charter. Results of the interim analyses may be shared with and discussed with selective GSK personnel (to be included in the study results dissemination plan).

- The SRT will include the Safety Development Leader, GCSP scientist, MM, CIL and study statistician but will extend to other functions as required. The SRT will provide a proactive, aggregate and holistic evaluation of the safety data of danirixin. Further details are included in the SRT charter.

Publication Policy

- The results of this study, including the results of interim analyses, may be published, presented at scientific meetings or otherwise shared externally (e.g. via a GSK press release or other communication). 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 electronic Case Report Report (eCRF) 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/eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF/eCRF.

- 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/eCRF 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 after from the issue of the final Clinical Study Report (CSR) or 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.

Data Management

- For this study subject data will be entered into GSK-defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.
- Adverse events and concomitant medication terms will be coded using the Medical Dictionary for Regulatory Activities (MeDRA) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, 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.

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.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

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 SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool and fax or email the paper form to GSK and the Medical Monitor.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE
- 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/SAE coordinator by telephone or e-mail.
- Contacts for SAE reporting can be found in the SRM.

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

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 6 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- Refrain from donating sperm for the duration of study and for at least 60 hours after the last dose of study treatment.

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 6.

Table 6 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 will be performed at approximately monthly intervals during the study treatment period, after the last dose of study treatment and as required locally.
- Pregnancy testing, with a high sensitivity test will be performed using the test kit provided by the central laboratory and approved by the sponsor and in accordance with instructions provided in the test kit package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

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

- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 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 discontinue study treatment and be withdrawn from the study.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples may be used for research related to danirixin or COPD and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to danirixin treatment, and COPD (and related diseases). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples may be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples also may be analyzed as part of a multi-study assessment of genetic factors involved in the response to danirixin treatment or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on danirixin (or study treatments of this class) or COPD and related diseases continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • 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 chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, up to 72 h after last dose[5] • 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

discontinue study treatment and continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	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 (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 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 participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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

5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) 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.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

Reference

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.

12.8. Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.1.1 for the list of GSK medical devices to be used in this study).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.9. Appendix 9: 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.

12.10. Appendix 10: Country Specific Requirements

Korea - Investigational Product Label

PPD

12.11. Appendix 11: Protocol Amendment History

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

Amendment 1: 31-Oct-2017

TITLE PAGE

Protocol Title: Randomised, Double-Blind (Sponsor Open), Placebo-Controlled, Multi-centre, Dose Ranging Study to Evaluate the Efficacy and Safety of Danirixin Tablets Administered Twice Daily Compared With Placebo for 24 Weeks in Adult Participants With Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number: 205724

Short Title: Danirixin Dose Ranging Study in Participants with COPD

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 will be provided in the Study Reference Manual

Regulatory Agency Identifying Number(s): IND: 108168; EudraCT: 2016-003675-21

Approval Date: 28-NOV-2016

SPONSOR SIGNATORY:

PPD

28-NOV-2016

Aili L. Lazaar, MD PPD
Clinical Development Director
Respiratory Therapy Area Unit

Date

PPD

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: Randomised, Double-Blind (Sponsor Open), Placebo-Controlled, Multi-centre, Dose Ranging Study to Evaluate the Efficacy and Safety of Danirixin Tablets Administered Twice Daily Compared With Placebo for 24 Weeks in Adult Participants With Chronic Obstructive Pulmonary Disease (COPD)

Short Title: Danirixin Dose Ranging Study in Participants with COPD

Rationale: The primary aims of this study are to evaluate the clinical activity and safety of 5 doses of danirixin compared with placebo in participants with COPD. The study is intended to support subsequent decisions regarding the progression of danirixin in the COPD indication, including the selection of doses and appropriate endpoints for use in pivotal studies**.**

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To characterize the dose response of danirixin compared with placebo on the incidence and severity of respiratory symptoms in participants with COPD	• Change from baseline in respiratory symptoms measured by the Evaluating Respiratory Symptoms in COPD (E-RS:COPD) daily diary: total score and subscales (i.e. breathlessness, cough and sputum, and chest symptoms
• To compare the safety of danirixin with placebo in participants with COPD	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG)
Key Secondary	
• To characterize the dose response of danirixin compared with placebo on the annual rate of moderate/severe COPD exacerbations in participants with COPD	• Annual rate of Healthcare Resource Utilization (HCRU)-defined COPD exacerbations
• To further characterize the clinical activity of danirixin compared to placebo in participants with COPD	• Time to first HCRU-defined COPD exacerbation • Change from baseline for the St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)

Overall Design: This is a double-blind (Sponsor Open), placebo-controlled, parallel group study that will evaluate the dose response of danirixin compared with placebo on respiratory symptoms, COPD exacerbations, healthcare-related quality of life and physical activity. The safety of danirixin compared with placebo is also an important objective of the study. Following the completion of baseline assessments collected over a 7 day period (i.e. EXACT/E-RS:COPD, physical activity, and rescue medication use), participants will be randomized (1:1:1:1:1:1) to receive one of five dose strengths of danirixin or placebo for 24 weeks. Three interim analyses are planned for the study. The first interim analysis will be an analysis of danirixin pharmacokinetics and and will be conducted after approximately 10 participants in each treatment group have completed Visit 3. The second interim analysis will be a futility analysis based on the E-RS:COPD endpoint and will be conduced after approximately 150 participants have completed 3 months of study treatment. The third interim analysis will be conducted after approximately 450 participants have completed 6 months of study treatment. The third interim analysis will be used to support GSK decisions regarding the further development of danirixin. This interim analysis will include all clinical activity assessments and safety assessments available at the time it is conducted.

Number of Participants:

Approximately 700 participants will be screened to achieve approximately 600 randomized participants. It is anticipated that approximately 540 participants will complete 24 weeks of treatment and key study assessments (dropout rate estimated to be approximately 10%).

Treatment Groups and Duration:

Participants will be randomized to one of six parallel groups and will receive study treatment twice daily for 24 weeks:

- Placebo
- 5 mg danirixin (as hydrobromide hemihydrate salt)
- 10 mg danirixin (as hydrobromide hemihydrate salt)
- 25 mg danirixin (as hydrobromide hemihydrate salt)
- 35 mg danirixin (as hydrobromide hemihydrate salt)
- 50 mg danirixin (as hydrobromide hemihydrate salt)

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of Activities

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**+/- 0d**	**+ 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**		
Eligibility													
Informed consent	X												
Genetic Sample Informed Consent[b]	X												
Demography	X												
COPD Exacerbation History	X												
Pre-Screening Fibrinogenc	X												
Smoking History[d]		X											
Smoking Status[d]		X	X										
Inclusion and Exclusion criteria		X											
Medical history[e]		X											
Full physical examination including height and weight		X											
Chest x-ray (CXR)[f]		X											

Procedure	**Pre-Screening[a] (Visit 0)**	**Screening[a] (Visit 1)**	**Study Visits**									**Early Withdrawal**	**Follow Up (up to 28 days post last dose)**
			2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**+/- 0d**	**+ 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**		
HIV, Hepatitis B and C screening[g]		X											
Additional Eligibility and In Study Assessments													
Verify Eligibility[h]			X	X									
Brief Physical				X				X			X	X	X
Urine or serum pregnancy test[i]		X		X		X	X	X	X	X	X	X	
Laboratory assessments (clinical chemistry (includes liver chemistries), hematology, urinalysis)		X		X		X					X	X	X
Additional Liver chemistries only					X		X	X					
12-lead ECG		X		X		X		X			X	X	
Vital signs	X	X		X		X		X			X	X	
Spirometry		X		X				X			X	X	
Randomization				X									
Dispense Study Medication				X		X	X	X	X	X			

Procedure	**Pre-Screening[a] (Visit 0)**	**Screening[a] (Visit 1)**	**Study Visits**									**Early Withdrawal**	**Follow Up (up to 28 days post last dose)**
			2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**+/- 0d**	**+ 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**		
Dispense log pad and provide training			X										
Dispense MDI sensors and provide training			X										
Dispense physical activity monitor and provide training			X										
Study treatment				←==========→									
Study treatment compliance (ediary)				←==========→									
Collect IP						←==========→						X	X
Collect MDI sensors												X	X
Collect physical activity monitor												X	X
Collect log pad												X	X
Adverse Event (AE) review				←==========→								X	X
Serious Adverse Event (SAE) review	←==========→											X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**+/- 0d**	**+ 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**		
Clinical Outcomes Assessments													
COPD Exacerbations			←==========→									X	X
EXACT-PRO[j]			←==========→										
Rescue Medication Use[k]			←==========→										
SGRQ-C				X				X			X	X	
COPD Assessment Test				X				X			X	X	
PROactive Questionnaire[l]				X				X			X		
Physical Activity Monitor[l]			X					X			X		
Participant Global Impression of COPD Severity			X										
Participant Impression of Change in COPD Severity					X	X	X	X	X	X	X	X	
Participant Global Impression of Activity Limitation			X										

Procedure	**Pre-Screening[a] (Visit 0)**	**Screening[a] (Visit 1)**	**Study Visits**									**Early Withdrawal**	**Follow Up (up to 28 days post last dose)**
			2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**+/- 0d**	**+ 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**	**+/- 3d**		
Participant Impression of Change in Activity Limitation					X	X	X	X	X	X	X	X	
Exit Interview[m]											X	X	
Genetic, Pharmacokinetic and Biomarker Blood Collections													
Blood sample for Genetics				X									
Blood sample for pharmacokinetics (PK)[n]				X			X	X			X		
Blood sample for Fibrinogen				X				X			X	X	
Blood sample for CRP				X				X			X	X	
Blood Sample for Exploratory Biomarkers				X				X			X	X	

a. Pre-screening and screening visits may be completed on the same day.
b. Agreeing to the genetic sample consent is not required for study participation.
c. A pre-screening plasma fibrinogen measurement is only required for participants with 1 COPD exacerbation in the prior year.
d. Smoking status /history assessed at screening: smoking status rechecked at Visit 2
e. Includes substance usage, past and present medical conditions and family history of premature CV disease.
f. See inclusion/exclusion criteria for CXR screening requirement
g. Hepatitis B (HBsAg) and Hepatitis C (HepC antibody) testing is required. If testing otherwise performed within 3 months prior to the first dose of study treatment, testing at screening is not required. Hepatitis C RNA testing is optional; however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease.

h. Participant's clinical status should be reviewed.
i. Pregnancy testing only required for women of child bearing potential (WOCBP). A positive urine pregnancy test requires confirmation with a serum pregnancy test.
j. E-RS:COPD is a subset of EXACT-PRO and is not a separate assessment.
k. Rescue medication use will be assessed via e-diary and MDI sensor.
l. The Clinic Visit PROactive Physical Activity in COPD tool will be assessed in a subset of approximately 50% of study participants
m. An Exit Interview will be collected in approximately 15 – 20% of study participants.
n. Pre-dose PK samples will be collected in all participants at Visits 3, 6, 7, and 10. In a subset of participants (approx. 50 participants at each dose level) at Visit 3, PK samples will be collected at pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose.

Note: The timing and number of planned study assessments, including safety, pharmacokinetic, and biomarker assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

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 No. YM2010/00163/07].

Clinical pharmacology studies in healthy volunteers demonstrated the pharmacodynamic activity of danirixin (inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils). Danirixin has also been tested in a Phase IIa study in symptomatic participants with mild to moderate COPD at risk for exacerbation (GSK Study No. 200163) [GlaxoSmithKline Document No. 2013N180289_03]. In study 200163, twice daily dosing with danirixin free base (75 mg bid) or placebo given on top of standard of care inhaled maintenance treatments was tested for one year. An interim analysis of clinical endpoints from study 200163 demonstrated that danirixin, compared to placebo, reduced respiratory symptoms as measured with E-RS:COPD [Miller, 2016].

3.1. Study Rationale

This protocol describes a Phase IIb dose-ranging study evaluating the clinical activity and safety of danirixin compared with placebo in participants with COPD that have current respiratory symptoms including cough, increased sputum production, and dyspnoea. Study participants will continue with their standard of care inhaled medications (i.e. long acting bronchodilators with or without inhaled corticosteroids) while receiving study treatment. In this study, 5 doses of danirixin and placebo are being evaluated (danirixin or placebo will be taken orally twice daily).

The primary objectives of the study are to evaluate the dose response of danirixin compared with placebo on respiratory symptoms assessed by the E-RS:COPD patient reported outcome (PRO) tool and assess the safety of danirixin compared with placebo. Key secondary objectives include an evaluation of danirixin compared with placebo on healthcare resource utilization (HRCU) defined COPD exacerbations, health status, physical activity, and rescue medication use. Exploratory objectives will include a participant exit interview and blood biomarkers to investigate the impact of danirixin on biomarkers of extracellular matrix turnover and remodeling.

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, 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 No. 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	The most sensitive species is the rat. Testicular effects present at doses ≥150 mg/kg/day in the rat include spermatid degeneration, seminiferous tubular degeneration and secondary epididymal changes, including oligo/aspermia and/or epididymal intratubular cellular debris. The no observed adverse effect level (NOAEL) in this study, based on the microscopic findings in the testis, was 50 mg/kg/day for male rats. The systemic exposure margins for the NOAEL for testicular effects in the rat is 7.3-fold for an oral clinical dose of 50 mg BID free base tablet. The testicular effects seen in the rat have also been shown to directly impact on male fertility and the NOAEL for these reproductive effects was 100 mg/kg/day. Refer to IB Section 4.4 for full details No adverse events related to testicular effects have been observed in clinical studies to date.	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 (2-fold NOAEL). PK modelling predicts that in a participant receiving 50 mg BID of the HBr salt, the risk of exposure exceeding the 2-fold margin for AUC(0-24) for the NOAEL of testicular effects is low.

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
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 healthy volunteer studies and a phase 2a study in patients with Influenza (GSK Study	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 9. 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**
	201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in subjects receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy subjects, 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. Male participants with female partners of child-bearing potential must comply with the contraception requirements.
Study Procedures		
None		
Other		
Not applicable		

3.3.2. Benefit Assessment

- All participants will undergo a thorough medical assessment during the study. Participants will have frequent study clinic visits for the evaluation of their disease symptoms. During these visits, participants will have spirometry, ECG, vital signs monitoring, and physical examinations. Monitoring for worsening of their disease will also take place.

- Participants may benefit from the knowledge that they are contributing to the process of developing a new treatment in an area of unmet need, even if not directly beneficial for them

- All participants will continue with changes to their medications, where medically appropriate, to receive established standard of care.

3.3.3. Overall Benefit:Risk Conclusion

Danirixin has demonstrated potent antagonism of CXCR2 activity both in vitro and in vivo in preclinical and clinical studies. Its potency and duration of action supports its potential use as an oral, anti-inflammatory agent in the treatment of COPD with anticipated potential for bringing benefit to a serious condition that affects the lives of millions and contributes to significant morbidity and mortality.

In clinical trials completed to date danirixin has been well-tolerated and most adverse events (AEs) were mild to moderate in intensity The most commonly observed AEs have been nasopharyngitis, headache and diarrhea following administration of danirixin or placebo. There have been no treatment related clinically significant changes in vital signs and ECG at any dose of danirixin.

Taking into account the measures taken to minimize risks to participants in this study, the potential risks identified in association with danirixin are justified by the anticipated benefits that may be afforded to participants with COPD.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To characterize the dose response of danirixin compared with placebo on the incidence and severity of respiratory symptoms in participants with COPD	• Change from baseline in respiratory symptoms measured by E-RS:COPD daily diary: total score and subscales (i.e. breathlessness, cough and sputum, and chest symptoms)
• To compare the safety of danirixin with placebo in participants with COPD	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG)

Objectives	Endpoints
Secondary • To characterize the dose response of danirixin compared with placebo on the annual rate of moderate/severe COPD exacerbations in participants with COPD	• Healthcare Resource Utilization (HCRU)-defined COPD exacerbations
• To further characterize the clinical activity of danirixin compared to placebo in participants with COPD	• E-RS:COPD Responder Analysis (including subscales) • Number of Exacerbations of Chronic Pulmonary Disease (EXACT) tool defined events • Time to first EXACT event • EXACT event severity • EXACT event duration for all events • Time to first HCRU-defined COPD exacerbation • Time to first severe HCRU-defined COPD exacerbation • HCRU-defined exacerbation duration • Change from baseline for the St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C) • SGRQ responder analysis • Change for baseline COPD Assessment Test (CAT) total score • CAT responder analysis • Lung function (FEV1, FEV1 % predicted, FVC, FEV1/FVC ratio) • Rescue medication use • Participant experience of physical activity (subset of approximately 50% of participants) measured using PROactive Clinic Visit Tool (C-PPAC)
• To characterize the	

Objectives	Endpoints
pharmacokinetics of danirixin in participants with COPD	• Danirixin concentration and standard pharmacokinetic parameters for danirixin (e.g. AUC, Cmax, Tmax), using dried blood spot data
Tertiary/Exploratory	
• To further explore study participants experience with study treatment and overall experience with the study	• Time to first Clinically Important Deterioration (CID) • SGRQ domains • Responses to a participant Exit Interview at the end of treatment (in a subset of 15 – 20% of participants)
• To characterize the effect of danirixin on lung matrix destruction/remodelling	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes)
• Comparison between dried blood spot and wet whole blood analysis of danirixin concentrations in patients with COPD	• Danirixin concentration and standard pharmacokinetic parameters for danirixin (e.g. AUC, Cmax, Tmax)
• To characterise danirixin exposure-response relationships for various safety parameters,if appropriate	• Danirixin systemic exposure and various efficacy/PD/safety parameters, if appropriate

5. STUDY DESIGN

5.1. Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and successful completion of the EXACT daily diary (all participants), rescue medication use daily diary (all participants) and PROactive baseline measurements (questionnaire and participant experience of physical activity) over study days -7 to 1, participants will be randomized (1:1:1:1:1:1) to receive one of five dose strengths of danirixin (5 mg, 10 mg, 25 mg, 35 mg and 50 mg) or placebo. Study treatment will be administed twice daily for 24 weeks. The PROactive baseline measurements will only be collected for those participants selected for the physical activity monitoring subgroup. Participants who do not properly complete (i.e. are not adherent with the requirements for completing and recording) the required baseline assessments (i.e. EXACT/E-RS:COPD

daily diary, physical activity monitoring portion of PROactive, and daily rescue medication use baseline measurements) will not be randomized and will not be eligible for rescreening.

Three interim analyses are planned for the study. The first interim analysis will be an evaluation of danirixin pharmacokinetics after 10 participants in each treatment group have completed Visit 3.

The second interim analysis will be a futility analysis based on the E-RS:COPD endpoint and will be conducted after approximately 150 participants have completed 3 months of study treatment.

The third interim analysis will be conducted after approximately 450 participants have completed 6 months of treatment. The second interim will be used to support GSK decisions regarding the further development of danirixin. This interim analysis will include the E-RS:COPD dose response modelling, secondary endpoints of HCRU-defined exacerbations and SGRQ total score along with all available safety data. No changes will be made to the study based on the results of the second interim analysis. Outputs containing unblinded treatment assignments will be created for this interim analysis and will only be made available to a limited number of GSK staff. Full details will be included in the study data dissemination plan.

No Independent Data Monitoring Committee (IDMC) will be utilized for this study. While the study is being conducted, core members of the study team will be unblinded (with the exception of those study team members who will directly interact with study sites, e.g. Operations and Science Leader and Data Quality Leader). There will be ongoing review of safety data and clinical outcomes. Only the study statistician will have access to individual participant treatment assignments, other core team members will review aggregate summaries by study treatments. A study charter will specify which team members will have access to unblinded data while the study is ongoing, the frequency of planned data reviews and the data to be included in the data reviews. The study charter will also state how interim results will be communicated outside the study team. A safety review team will meet approximately every 3 months (or as needed based on emerging data) to review available safety information.

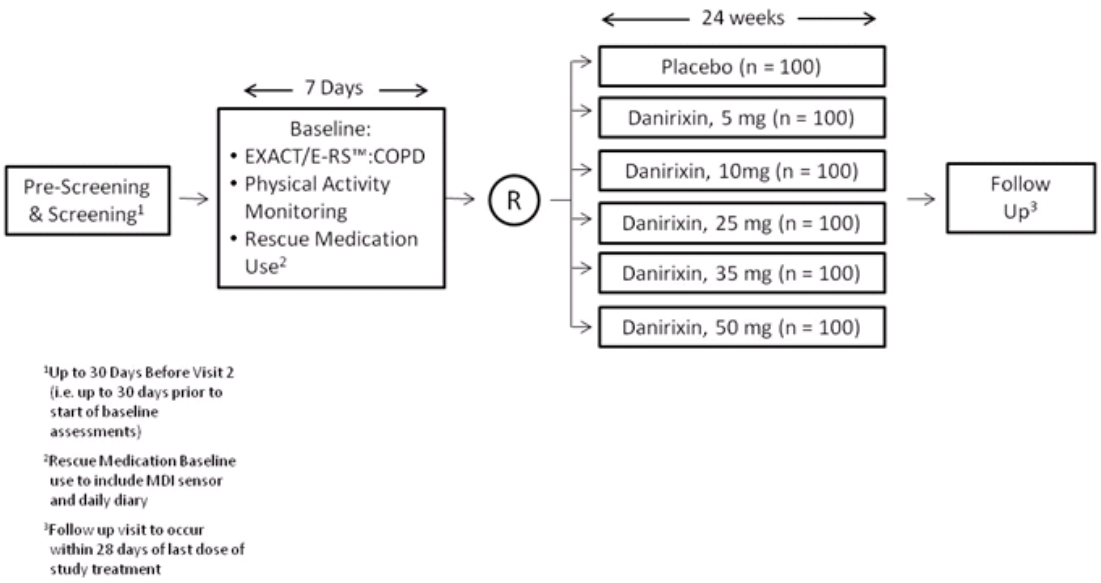


Figure 1 Study Schematic

5.2. Number of Participants

Approximately 700 participants will be screened to achieve approximately 600 randomized participants. It is anticipated that approximately 540 participants will complete 24 weeks of treatment and key study assessment (the dropout rate is estimated to be approximately 10% based on previous experience with studies enrolling similar participants).

For the analysis of study assessments, several analysis populations will be defined. Details of the evaluable participants for each planned analysis population are included in Section 10.4.

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 last study visit and the last scheduled procedure shown in the Schedule of Activities (Table 1).

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 multicenter, randomized, parallel-group design. This is a well-established design to evaluate the efficacy and safety of an investigational drug. Twenty-four weeks should be adequate to demonstrate efficacy based on E-RS:COPD, as well as to collect adequate safety measurements before going into larger phase III trials. Danirixin has already been clinically investigated over one year treatment duration (GSK Study No. 200163, GlaxoSmithKline Document No. 2013N180289_03).

By evaluating a range of doses from 5 mg to 50 mg of danirixin, it will be possible to assess the dose response of danirixin as well as the potential effects of danirixin on biomarker and safety endpoints. The data will provide useful information in determining the therapeutic index of danirixin and in selecting the minimal effective and safe dose to be carried forward in the Phase III COPD program.

PK samples from randomized participants will also be collected in this study. Defining the optimum dose for later stages of development can be made more efficiently by understanding the variability in the pharmacokinetics of a drug. In addition, the study will evaluate the relationship between danirixin blood concentrations and biomarker and safety endpoints.

A placebo arm is included to measure the absolute effect of each dose tested, thereby allowing a robust determination of the dose-response. Inclusion of a placebo arm will also allow a more robust exploration of the therapeutic index of danirixin.

5.5. Dose Justification

Five doses of danirixin (5 mg, 10 mg, 25 mg, 35 mg and 50 mg) are planned for evaluation in this study. The doses to be investigated have been selected based on integrating information available from:

- Dose-exposure-biomarker response using inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils over the dose range of 0-400 mg in healthy volunteer participants
- Evidence of reduced respiratory symptoms in mild to moderate COPD participants in the Phase IIa study (GSK study 200163)

In the early clinical studies, danirixin was administered as a free base tablet, whereas the danirixin formulation to be used in this study will be a hydrobromide salt tablet. The hydrobromide tablet has approximately twice the bioavailability of the free base tablet in healthy elderly participants (GSK Study No. 201037, GlaxoSmithKline Document No. 2015N248339_00). Predicted steady-state exposures and multiples of blood *ex vivo* CXCL1-induced CD11b pharmacology at the proposed danirixin doses are presented in Table 2.

Table 2 Predicted steady state systemic exposure and multiples of blood ex vivo CXCL1-induced pharmacology following twice daily of administration of danirixin

Dose (mg)	Predicted steady-state median (5th, 95th percentile)[a]			Cavg multiple of IC50[b]	Cmin multiple of IC50[b]
	AUC(0-24) steady-state (µg.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
5	1.37 (0.69, 2.78)	57.2 (28.6, 116)	27.8 (6.8, 92.1)	0.7	0.4
10	2.74 (1.34, 5.53)	114 (56.0, 230)	54.8 (13.6, 180)	1.5	0.7
25	6.85 (3.36, 13.8)	285 (140, 576)	137 (34.0, 450)	3.6	1.7
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4
50	13.7 (6.71, 27.6)	571 (280, 1152)	274 (68.0, 900)	7.3	3.5

Model derived based on PK data in healthy elderly participants from GSK Study No. 201037 (GlaxoSmithKline Document No. 2015N248339_00).

Model predicted population mean IC50=78.5 ng/mL (95% CI: 37.3, 120), sigmoidal Emax model of DNX PK-*ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils in healthy participants.

The predicted multiples of *ex vivo* CXCL1-induced CD11b inhibition achieved at 24 h post steady-state, together with the terminal elimination half-life of danirixin support the twice daily dosing regimen.

Based on the biomarker results described for danirixin and the anticipated higher exposure from the hydrobromide tablet, doses of 5 mg, 10 mg, 25 mg and 35 mg were selected to span the dose range and allow efficient estimation of the dose response curve in this mild/moderate COPD population. Fifty mg twice daily is included as a supra-therapeutic dose but where there is a low possibility of AUC(0-24) exposure exceeding a 2-fold margin for the no observed adverse effect level (NOAEL) for testicular effects.

The risk of exposure exceeding the 2-fold margin for AUC(0-24) for the NOAEL of testicular effects is considered low. Based on PK modeling, the predicted AUC (0-24) for a dose of 50 mg BD is 13.7 ug.hr/mL (6.7, 27.6). This provides 2.5-fold cover over the NOAEL/2 and approximately 5-fold cover over the NOAEL.

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 40 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have COPD (postbronchodilator FEV1/FVC ratio < 0.7 and FEV1 % predicted ≥ 40%) based on American Thoracic Society (ATS)/European Respiratory Society (ERS) current guidelines [Celli, 2004]. Participants with a historical diagnosis of asthma may be included so long as they have a current diagnosis of COPD.

3. History of respiratory symptoms including chronic cough, mucus hypersecretion, and dyspnea on most days for at least the previous 3 months prior to screening.

4. Participants with a documented history of COPD exacerbation(s) in the 12 months prior to study participation (screening) meeting at least one of the following criteria:

    - ≥ 2 COPD exacerbations resulting in prescription for antibiotics and/or oral corticosteroids or hospitalization or extended observation in a hospital emergency room or outpatient center

    - 1 COPD exacerbation resulting in prescription for antibiotics and/or oral corticosteroids of hospitalization or extended observation in a hospital emergency room or outpatient center and a plasma fibrinogen concentration at screening ≥ 3 g/L (300 mg/dL)

5. Smoking history: current and former smokers with a cigarette smoking history of ≥ 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Current smokers are defined as those who are currently smoking cigarettes (i.e. have smoked at least one cigarette daily or most days for the month prior to Visit 1). Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Note: pipe and/or cigar use cannot be used to calculate smoking pack-year history.

6. Participants must have the ability and willingness to use an electronic diary (log pad) on a daily basis.

Weight

7. Body weight ≥ 45 kg

Sex

8. Male or female.

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 60 hours after the last dose of study treatment, corresponding to approximately 6 half-lives (which is the time needed to eliminate any teratogenic study treatment) and to refrain from donating sperm during this period.

   b. 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

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

6.2. Exclusion Criteria

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

Medical Conditions

1. Diagnosis of other clinically relevant lung diseases (other than COPD), e.g. sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer.
2. Alpha-1-antitrypsin deficiency as the underlying cause of COPD
3. Pulse oximetry < 88% at rest at screening. Participants should be tested while breathing room air. However, participants living at high altitudes (above 5000 feet or 1500 meters above sea level) who are receiving supplemental oxygen can be included provided they are receiving the equivalent of < 4 L/min and screening pulse oximetry is measured while on their usual oxygen settings.
4. Less than 14 days have elapsed from the completion of a course of antibiotics or oral corticosteroids for a recent COPD exacerbation.
5. A peripheral blood neutrophil count < 1.5 x 10^9/L.
6. Diagnosis of pneumonia (chest X-ray or CT confirmed) within the 3 months prior to screening.

7. Chest x-ray (posterior-anterior with lateral) or CT scan reveals evidence of a clinically significant abnormality not believed to be due to the presence of COPD (historic results up to 1 year prior to screening may be used). For sites in Germany: If a chest x-ray (or CT scan) within 1 year prior to screening is not available, approval to conduct a diagnostic chest x-ray will need to be obtained from the Federal Office of Radiation Protection (BfS).
8. History or current evidence of other clinically significant medical condition that is uncontrolled on permitted therapies. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through study participation, or that would affect the safety analysis or other analysis if the disease/condition worsened during the study.
9. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
10. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants who would be at undue risk by participating in the study. An abnormal and clinically significant finding that would preclude a participant from entering the study is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
    a. AF with rapid ventricular rate > 120 bpm
    b. sustained or non-sustained VT
    c. second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
    d. QTcF ≥ 500 msec in participants with QRS < 120 msec and QTcF ≥ 530 msec in participants with QRS ≥ 120 msec
11. Previous lung surgery (e.g. lobectomy, pneumonectomy) or lung volume reduction procedure.

Prior/Concomitant Therapy

12. Current or expected chronic use of macrolide antibiotics during the study period for the prevention of COPD exacerbations. Examples of chronic use include, but are not limited to, daily or two to three times per week use for at least 3 months.

13. 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.) The Investigator should consult with the Medical Monitor if necessary.

14. Current or expected use of phosphodiesterase-4 inhibitors (e.g. roflumilast). Participants currently receiving roflumilast may be included if they are able to discontinue use from 30 days prior to screening through the completion of the follow up visit.

Prior/Concurrent Clinical Study Experience

15. Participation in a previous clinical trial and has received an investigational product within any of the following time periods prior to the first dosing day in the current study: 30 days, 5 half lives, or twice the duration of the biological effect of the investigational product (whichever is longer).
16. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study
17. Exposure to more than four investigational products within 1 year prior to the first dosing day in the current study.

Diagnostic assessments

18. Alanine transferase (ALT) > 2x upper limit of normal (ULN); bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
19. A positive test for HIV antibody.
20. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Other Exclusions

21. Pulmonary rehabilitation: Participants who have taken part in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to screening or participants who plan to enter the acute phase of a pulmonary rehabilitation program during the study. Participants who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
22. A history of allergy or hypersensitivity to any of the ingredients in the study treatment.
23. A known or suspected history of alcohol or drug abuse within the 2 years prior to screening.
24. Inability to read: in the opinion of the Investigator, any participant who is unable to read and/or would not be able to complete study related materials.
25. Affiliation with the study site: study investigators, sub-investigators, study coordinators, employees of a study investigator, sub-investigator or study site, or immediate family member of any of the above that are involved with the study.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

No meal or dietary restrictions are required for participation in this study. Danirixin must be taken with food. Specific dosing instructions will be provided in the Study Reference Manual (SRM) and will be provided to all study participants.

6.3.2. Activity

Participants should abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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 up to two additional times if the investigator judges the participant can meet the eligibility criteria. Any rescreened participant must satisfy all of the protocol specified inclusion/exclusion requirements at the re-screening visit. Rescreened participants should be assigned the same participant number as for the initial screening.

6.5. Run In Failures

A run in failure is defined as a participant who consents to participate in the clinical study, satisfies all eligibility criteria, but who does not properly complete the required baseline assessments for the daily EXACT diary, daily rescue medication use, and the physical activity monitoring portion of PROactive baseline (if selected to participate in the physical activity subgroup) over 7 days beginning with Visit 2. A participant who is selected to participate in the physical activity subgroup and does not complete the baseline physical activity monitoring portion of PROactive baseline but does complete the daily EXACT diary and daily rescue medication use baseline assessments will still be eligible for participation in the study but will be not be included in the physical activity subgroup. Participants who are run in failures will not be randomized to any study treatment and are not eligible for rescreening.

A successful EXACT baseline assessment is defined as completion of all 14 questions of the EXACT questionnaire on at least 4 of the 7 days. Successful rescue medication use recording is defined as recording of rescue medication use in the daily diary on at least 4 of the 7 days along with electronic data capture from the MDI sensor device. For participants in the physical activity subgroup a successful baseline determination is defined as recording of physical activity for at least 8 hours per day on at least 3 of the 7 days and completion of the PROactive questionnaire at Visit 3.

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

Table 3 Treatments Administered

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Placebo
Dosage formulation:	White Film coated tablets (oval or round shaped). Refer to Investigator's Brochure for presentation and excipients	White Film coated tablets (oval or round shaped). Refer to Investigator's Brochure for presentation and excipients
Unit dose strength(s)/Dosage level(s):	5, 10, 25, 35 and 50 mg (of free base equivalent)	N/A
Route of Administration	Oral	Oral
Dosing instructions:	One tablet to be taken twice daily with food	One tablet to be taken twice daily with food
Packaging and Labeling	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labeled as required per country requirement.	Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labeled as required per country requirement.
Manufacturer	GSK	GSK

7.1.1. Medical Devices

- Subject to availability and any local restrictions on use, MDI sensor devices (manufactured by and purchased from Propeller Health) are being provided by GSK for this study. These devices are fitted onto rescue medication MDI devices to electronically record rescue medication usage. The MDI sensor devices have US FDA 510(k) clearance to market (Class II medical device) and European Union CE marking (Class I medical device).

- Subject to availability and any local restrictions on use, ActiGraph GT9X physical activity monitors (manufactured by and purchased from ActiGraph, LLC) are being provided by GSK for the subset of participants that will be included in the physical activity monitoring subgroup. The device is a tri-axial accelerometer. The participant wears the devices for the period of time that physical activity is being monitored.

- Additional descriptive information and instructions for the eMDI and physical activity monitoring devices are provided in the SRM.
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 9.2).

7.2. Dose Modification

No individual participant dose modifications or adjustments are allowed.

7.3. Method of Treatment Assignment

- This study will use an Interactive Web Response System (IWRS). All participants will be centrally randomized using the IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.
- Participant randomization will be stratified by smoking status (i.e. current smoker or former smoker).
- Study treatment will be dispensed to participants at the study visits summarized in the SOA.
- Returned study treatment should not be re-dispensed to any participant.

7.4. Blinding

This will be a double-blind (sponsor open) study. Study participants, all study site staff, and all members of the GSK study team, with the exception of the study statistician, will be blinded to individual participant treatment assignment. As defined in the study charter, core members of the GSK study team will have access to unblinded, aggregate summaries of study treatment results.

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

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

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm and document 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.
- 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.
- 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 of records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Precaution will be taken to avoid direct contact with the study treatment. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- 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 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.
- When participants self-administer study treatment(s) at home, compliance with study treatment administration will be assessed through querying the participant during the site visits and documented in the source documents and CRF. In addition, participants will be asked to confirm study administration each day in the daily ediary.
- Study participants who are not compliant with study treatment administration requirements should be re-educated on the importance of treatment compliance. Every effort should be made to keep participants in the study. Participants who continue to be non-compliant after several attempts to re-educate may be discontinued after consultation with the GSK study team.

- A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions 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 enrolment or receives during the study must be recorded along with:

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

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

The following COPD medications are permitted during the study, at the discretion of the GSK Medical Monitor and/or Investigator:

- Inhaled COPD maintenance medications (e.g. long acting bronchodilator medications (i.e. LAMA, LABA) and long-acting bronchodilator combination therapies (e.g. LAMA/LABA) and long-acting bronchodilator/inhaled steroid combination (ICS) therapies (e.g. LABA/ICS, LAMA/LABA/ICS)
- Short courses of oral corticosteroids and/or antibiotics (including macrolides) are permitted for the acute treatment of exacerbations of COPD and should not exceed 21 days. This use must be recorded as an HCRU exacerbation event.

The following medications are prohibited from the screening visit until after completion of the follow up visit:

- Chronic use of macrolide antibiotics for the prevention of COPD exacerbations. Examples of chronic use include daily or two-three times per week for at least 3 months.
- Oral or injectable CYP3A4 or BCRP substrates with narrow therapeutic index (CYP3A4 substrates include, but are not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline; BCRP substrates include, but are not limited to, topotecan.
- Phosphodiesterase-4 inhibitors (e.g. roflumilast)
- Broad spectrum phosphodiesterase inhibitors (e.g. theophylline)

GSK will not supply rescue medication. Participants may continue to use and should obtain rescue medication(s) through via their usual route. The following rescue medications may be used:

- Short acting beta agonists (SABA)(e.g., albuterol/salbutamol)
- Short acting muscarinic antagonists (SAMA)(e.g., ipratropium)
- Short acting combination (SABA/SAMA) bronchodilations, (e.g. Duoneb, Combivent)

The use of rescue medications is allowable at any time during the study. Participants should record in the daily e-diary the number of puffs of rescue medication(s) over each 24 hour period. Data from the MDI sensor device will be electronically captured and transmitted to GSK.

Annual influenza vaccine is recommended for patients with COPD but is not required for participation in this study. Influenza vaccination is permitted during the study and should be based on applicable local or national guidelines. Pneumococcal vaccine may also be administered, when indicated, based on applicable local or national guidelines. Additional vaccinations may be administered when indicated. Any vaccination administered during the study should be recorded as a concomitant therapy.

7.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant.

GSK will not provide post-study treatment. There are no plans to provide the study treatment for compassionate use following study completion.

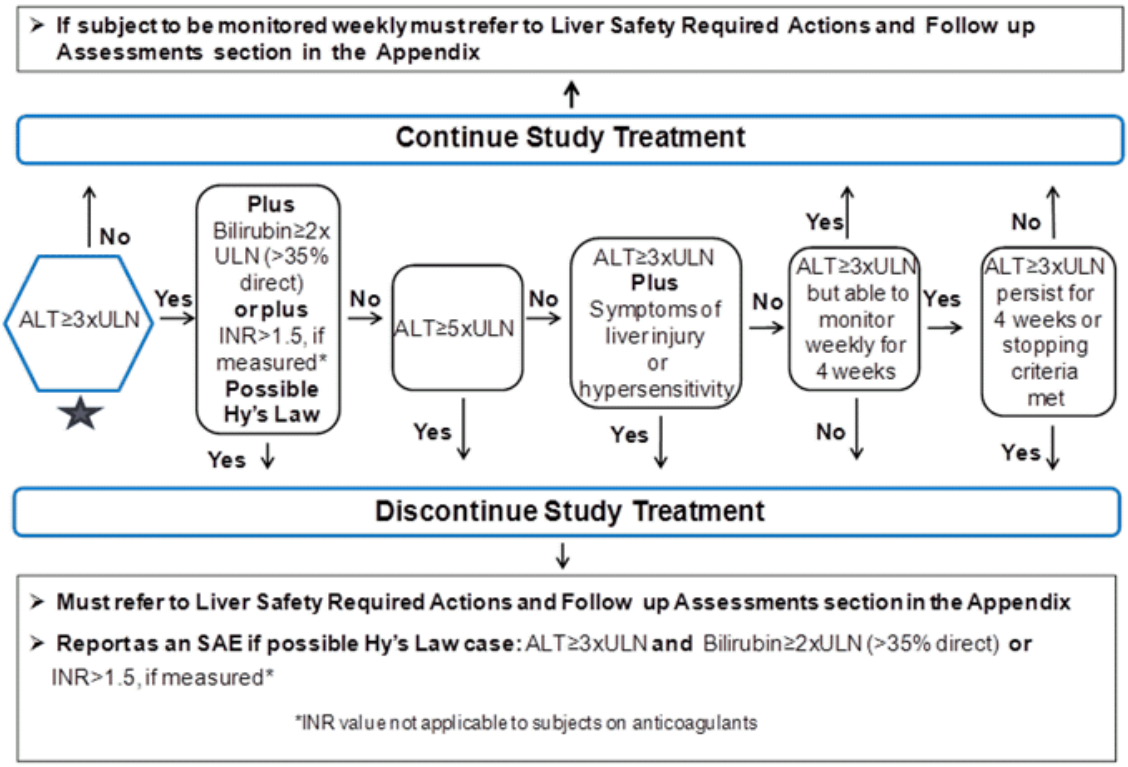
8. DISCONTINUATION CRITERIA

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 [FDA, 2009].

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.



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

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 participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTc > 60 msec

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

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

See the SoA (Table 1) 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 9.

8.1.4. Temporary Discontinuation

Temporary discontinuation of study treatment is allowed for up to 14 days when medically necessary, e.g. for hospitalization for a COPD exacerbation, other medical condition requiring hospitalization, or reduction in peripheral blood neutrophil counts ≤ 0.5 x 10^9/L. Temporary discontinuation for any other reason should be discussed with the GSK Medical Monitor.

8.1.5. Study Treatment Restart

Study treatment restart after liver chemistry stopping criteria are met by any participant in this study is not allowed. Refer to Appendix 7 for full guidance for required actions and follow-up assessments to undertake if liver stopping criteria are met.

Study treatment restart after neutrophil stopping criteria are met can be considered once the neutrophil count has returned to within baseline and provided that no more than 14 days have elapsed since study medication was halted. The Investigator must obtain approval from the GSK Medical Monitor prior to restarting study treatment. See Appendix 9 for the procedure to be followed for study treatment restart after neutrophil stopping criteria are met.

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, behavioural, compliance or administrative reasons.

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

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for

screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

9.1.1. EXACT and E-RS:COPD

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD [Jones, 2011; Leidy, 2010; Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically at bedtime) using an electronic diary. The daily recording of information allows an assessment of underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0 – 100, higher scores indicate more severe symptoms. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The Evaluating Respiratory Symptoms in COPD (E-RS:COPD) tool consists of 11 items from the 14 item EXACT instrument [Leidy, 2014a; Leidy, 2014b]. E-RS:COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough & sputum production, chest tightness and chest congestion. E-RS:COPD has a scoring range of 0 – 40, higher scores indicate more severe symptoms. Three subscales of E-RS are used to describe different symptoms, dyspnea, cough and sputum, and chest symptoms.

E-RS: COPD has recently been recognized as a drug development tool by FDA and EMA [EMA, 2015; FDA, 2016].

9.1.2. COPD Exacerbations

An exacerbation of COPD is defined by a worsening of symptoms.

The following are symptoms used to determine an exacerbation of COPD:

Worsening of two or more of the following major symptoms for at least two consecutive days:

- Dyspnea
- Spontaneous sputum volume

- Sputum purulence

OR

Worsening of any one of the above major symptoms together with any one of the following minor symptoms for at least two consecutive days:

- Sore throat
- Cold (nasal discharge and/or nasal congestion)
- Fever (oral temperature > 37.5 ^{o}C) without other cause
- Increased cough
- Increased wheeze

Participants who experience worsening COPD symptoms for greater than 24 hours should:

- Contact their study investigator and/or research coordinator as soon as possible and report to the study clinic as required
- If the participant is unable to contact their study investigator or research coordinator, they should contact their primary care provider (or other health care provider) and contact their study site as soon as possible
- Continue to record their symptoms and rescue medication use in their daily ediary
- If the participant seeks emergency/acute care for worsening respiratory symptoms he/she should request the caring health care provider to contact the study investigator or research coordinator as soon as possible
- COPD exacerbations will be classified according to severity as follows:
- A COPD exacerbation is defined as a mild exacerbation if it is self-managed by the participant. Mild exacerbations are not associated with the use of antibiotics and/or systemic corticosteroids
- A COPD exacerbation is defined as a moderate exacerbation if it requires a new prescription for antibiotics and/or systemic corticosteroids
- A COPD exacerbation is defined as a severe exacerbation if it requires hospitalization, an emergency room visit, or extended observation in an outpatient centre

Details of an exacerbation should be recorded in the exacerbation page of the eCRF. Exacerbations will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE) as they are considered Disease Related Events (DREs). Only when the event is, in the Investigator's opinion, of greater intensity, or duration than expected for the individual participant, or the Investigator considers that there is a reasonable possibility that the event is related to study treatment should it be reported as an SAE (See Section 9.2).

(Pneumonia must be recorded in the AE or SAE section of the eCRF and on the pneumonia page of the eCRF (See Section 9.4.5)).

All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF. If necessary the PI or other health care personnel may stop the participant's study treatment temporarily in order to treat the COPD exacerbation. The reason for temporarily stopping study treatment and duration should be recorded in the eCRF.

The date of onset and the date of resolution will be recorded in the source documents and the eCRF.

- The date of onset is the first day (of at least 2 consecutive days) or worsening symptoms described above.
- The date of resolution should be based on when the Investigator or participant determines that the COPD symptoms have returned to near pre-exacerbation levels or to a new baseline.

9.1.3. SGRQ-C

The St. George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific tool (SGRQ-C) is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD patient's HRQoL [Meguro, 2007]. As well as producing an overall summary score, scores for the individual domains of symptoms, activity and impacts are also produced. The SGRQ-C has been used in numerous previous studies of COPD participants and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ and produces scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.4. CAT

The COPD Assessment Test is a short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD [Jones, 2009; Jones, 2012]. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (maximum impairment) to 5 (no impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

The CAT consists of 8 items (cough, sputum, chest tightness, breathlessness, going up hills/stairs, activity limitation at home, confidence leaving the home, and sleep and energy). Individual items are scored from 0 to 5 with a total score range from 0 – 40, higher scores indicate worse health status.

9.1.5. PROactive

The PROactive tools, developed under the EU Innovative Medicines Initiative, measure patient experience of Physical Activity in COPD. The tools consist of a patient reported questionnaire combined with output from an activity monitor [Dobbels, 2014; Gimeno-

Santos, 2015; Williams, 2012; Rabinovich, 2013; Gimeno-Santos, 2011]. The Clinical Visit PROactive Physical Activity in COPD (C-PPAC) tool is a designed for intermittent use within a clinical study. The 12 item questionnaire has a seven day recall period and participant responses are combined with two activity monitor data outputs covering the same period. The PROactive tools are scored from 0 to 100 with higher scores indicating greater disease impact, two subscales of amount and difficulty can be used to support the total score.

The C-PPAC tool will be implemented in a subset of approx. 50% of participants. Participants will be randomly selected from each study site participating in the physical activity subgroup.

9.1.6. Patient Global Rating of Severity and Global Rating of Change in Disease Severity

Participants will complete the Global Rating of COPD Severity at randomisation and at final study visit or IP Discontinuation Visit. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, very severe).

Participants will complete a Global Rating of Change in COPD (overall disease) question at all Visits subsequent to randomisation including the final Visit (or Early Withdrawal (EW) Visit). Response options will be on a 7 point Likert scale ranging from much better to much worse. Asking at each Visit allows for early detection of response as well as continued response.

9.1.7. Patient Global Rating of Activity Limitation and Global Impression of Change in Activity Limitation

Subjects will complete the Global Rating of Activity Limitation at randomisation and at final visit or EW Visit. This single global question will ask subjects to rate their activity limitation on a four-point scale (not limited, slightly limited, limited, very limited).

Subjects will complete a Global Impression of Change in Activity Limitation question at all Visits subsequent to randomisation including the final Visit (or EW Visit). Response options will be on a 7 point Likert scale ranging from much better to much worse.

9.1.8. Exit Interview

An exit interview will be administered by trained study staff at visit 10 or the EW Visit. The questions included in the exit interview are designed to more fully understand the participant's experience with the study medication and the study itself. Study staff will be provided with a semi-structured interview guide and data collection sheet and trained on interview administrative techniques. Responses will be audio-recorded for purposes of accurate transcription and analysis. Site training, and transcription and analysis of the exit interview data will be conducted by a specialist research organisation. Full guidance on implementing the exit interview, including guidance on interview organisation, the semi-structured interview script, guidance on conducting the interview and the use of interview probes will be included in the SRM.

A representative subset of participants (approx. 15 – 20% of all participants) will be selected to participate in the exit interview. The total number of interviews conducted will be driven by analysis of blinded transcripts. This analysis will be conducted in batches during the course of the study and interviews will only continue until saturation is confirmed.

9.1.9. Clinically Important Deterioration (CID)

A clinically important deterioration is a composite endpoint defined as at least one of the following events: (1) a decrease of ≥ 100 mL from baseline in trough FEV1, (2) a deterioration in health-related quality of life defined as ≥ a 4-unit increase from baseline in SGRQ total score, or (3) the occurrence of an on-treatment moderate or severe COPD exacerbation [Singh, 2016].

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 treatment (see Section 8).

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

- All SAEs will be collected from Visit 0 (i.e. from the time the informed consent is signed by the participant) until the follow up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of Visit 3 (study treatment randomization visit) 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 AEs and/or SAEs. 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 e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in participants with COPD and can be serious/life threatening:

- COPD exacerbations

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE). These events will be recorded on the DRE page in the participant's CRF within 72 hours after the investigator becomes aware of the event. These DREs will be monitored by the Safety Review Team (SRT) on a routine basis as described in Appendix 3.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

9.2.7. Pregnancy

- Details of all pregnancies in female participants and female partners of male 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.8. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of monitoring inhaled rescue medication use and for evaluating physical activity. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 4.

9.2.8.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 8.

9.2.8.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.8.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- Complete the Medical Device Incident Form for each participant who has a medical device incident with GSK medical devices provided for use during the study period. All of the header information in the form must be completed before sending to GSK. Original documents should be filed in the site study file. A copy of the form must also be sent to the GKS study monitor. Contact details will be included in the SRM. A copy of the form must also be sent to the GSK study monitor. Contact details will be included in the SRM. For incidents fulfilling the definition of an AE or SAE, the appropriate pages of the CRF must be completed. If there is an SAE, the completed CRF pages should be sent together with the Medical Device Incident From. If the participant is withdrawn due to a medial device incident, ensure the Study Conclusion page is completed.
- The same individual will be the contact for the receipt of medical device reports and SAEs.

9.2.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about

certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

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 study treatment can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis as soon as possible 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 SoA (Table 1).

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, pulse, temperature and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. A single measurement of respiratory rate and oral temperature is adequate.

9.4.3. Electrocardiograms

- For participant screening and pre-dose on Day 1, triplicate ECG measurements should be collected. For all subsequent ECG assessments, single measurement are to be collected. 12-lead ECG will be obtained as outlined in the SoA 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.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes.

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 abnormal and clinically significant 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 SoA (Table 1).
- 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 (e.g., SAE or AE), then the results must be recorded in the CRF.

9.4.5. Pneumonia

All suspected pneumonias will require confirmation as defined by the presence or new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms:

- Increased cough
- Increased sputum purulence (colour) or production
- Auscultatory findings of adventitious sounds (e.g. egophony, bronchial breath sounds, rales, etc.)
- Dyspnea or tachypnea
- Fever (oral temperature > 37.5 ^{o}C)
- Elevated white blood cell count (WBC) (> 10 x 10^{9}/L or > 15% immature forms)
- Hypoxemia (Hb O_2 saturation < 88% or at least 2% lower than baseline value)

All pneumonias must be captured on the AE/SAE page of the eCRF and on the pneumonia page of the eCRF.

The Investigator and site staff should remain vigilant for the possible development of pneumonia in participants as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For all suspected cases of pneumonia, Investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. Any microbiology or virology tests performed to determine etiology should be reported on the pneumonia eCRF page. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

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 SoA (Table 1). Instructions for the collection, processing, storage and shipping 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 and reported as primary data. The remaining whole blood will be retained and approximately 20% of the wet whole blood samples collected in Visit 3 will also be analysed for danirixin concentrations to provide an analytical comparison between dried blood spots and wet whole blood sample results. 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.

- Any remaining whole blood will be stored and may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

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

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

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

See Appendix 6 for Information regarding genetic research. Details on procedures for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

- Collection of samples for biomarker research is also part of this study. The following samples for biomarker research will be collected from all participants in this study as specified in the SoA:
  - peripheral venous blood samples for the preparation of serum and plasma
- Samples will be tested for biomarkers that are indicative of inflammation (i.e. CRP and fibrinogen), extracellular matrix turnover and remodelling to evaluate their association with the observed clinical responses or to help understand the underlying biological responses to danirixin.
- In addition, with the participant's consent, samples will be stored and may be used to investigate additional biomarkers thought to play a role in COPD disease progression or to evaluate their association with observed clinical responses to danirixin
- Samples also may be used for research to develop methods or support identification of prognostic/diagnostic biomarkers associated with clinical outcomes in COPD and related diseases.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Parameters for specific use in Health Economics analysis or Medical Resource Utilization and Health Economics are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

The primary efficacy endpoint is the change from baseline of E-RS:COPD total score at month 6. The primary objective of the study is to study the dose response and select an appropriate dose for future drug development programs.

A model based probability inference approach in Bayesian framework will be used to guide decision-making around dose selection. The posterior probability of the change from baseline of E-RS:COPD for each active dose being less than placebo will be used.

10.2. Sample Size Determination

In order to evaluate the impact of different sample sizes, various simulations were undertaken to understand the following questions around the change in baseline of E-RS:COPD scores at 6 months:

- What is the 90% confidence interval half width for the estimate of the treatment effect of the 5 mg, 25 mg, 35 mg, and 50 mg doses?
- What is the probability that the point estimate of difference from placebo is less than -1.5 for the 5 mg, 25mg, 35mg and 50 mg doses?
- What is the probability that the two-sided 90% confidence interval of the treatment effect excludes 0 for 5 mg, 25 mg, 35 mg and 50 mg doses?
- What is the probability that the two-sided 90% confidence interval of the treatment effect difference from placebo excludes 0 for 5 mg, 25 mg, 35 mg and 50 mg doses?

There are 3 scenarios considered for the simulations, each based on different assumptions of the effect for each of the 6 treatment arms. No model assumptions were made to generate these values. The scenarios are found in Table 4 and Figure 2. The assumed between participant standard deviation is 6.5 which is based on interim data from the 200163 study. For each scenario, 10,000 iterations of simulations were run.

Table 4 Assumptions Used for Sample Size Calculations

	Scenario 1	Scenario 2	Scenario 3
Placebo	0	0	0
5 mg	-0.5	-0.333	-0.5
10 mg	-1	-0.667	-0.75
25 mg	-2	-1.333	-2
35 mg	-2.5	-1.667	-2
50 mg	-3	-2	-2

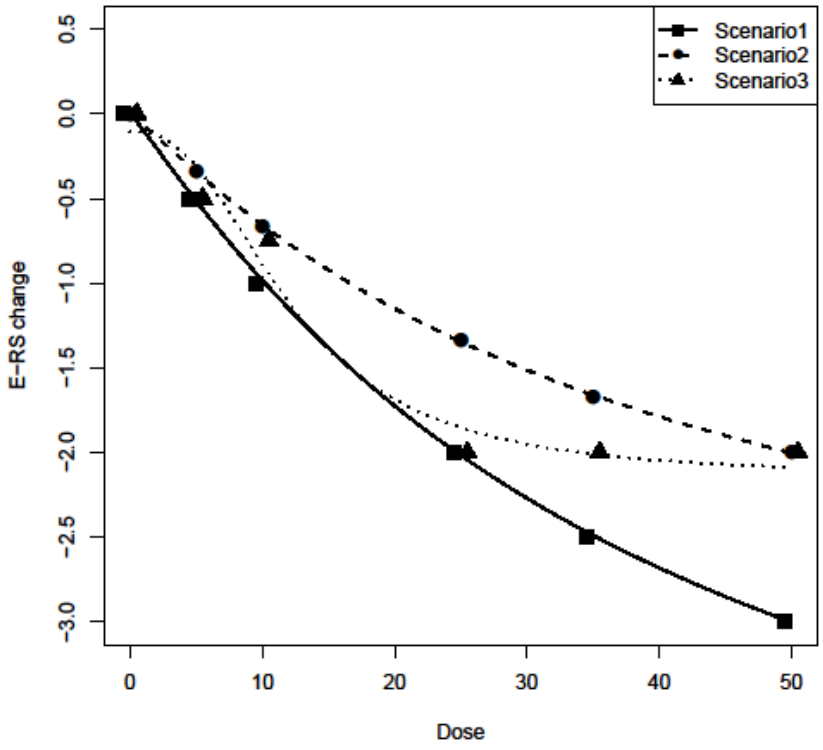


Figure 2 Simulation scenarios with best fit sigmoidal Emax model

The Emax model will be used for the primary analysis and was the basis for estimation of the simulated data. The more general 4 parameter version of this model is defined as:

$$y(dose) = E_0 + E_{max} [dose^m / (ED_{50}^m + dose^m)]$$

where y( ) represents the E-RS:COPD change from baseline, E_0 is the mean response at dose = 0, E_{max} is the maximum dose effect (at dose = ∞), ED_{50} is the dose that yields a mean response of $E_0 + E_{max} / 2$, and m is the slope parameter allowing for sigmoidal dose response relationships.

Results of the sample size simulations are presented in Figure 3, Figure 4, Figure 5 and Figure 6,with the lowest danirixin dose (5 mg) and the 3 highest doses (25 mg, 35 mg, 50 mg).

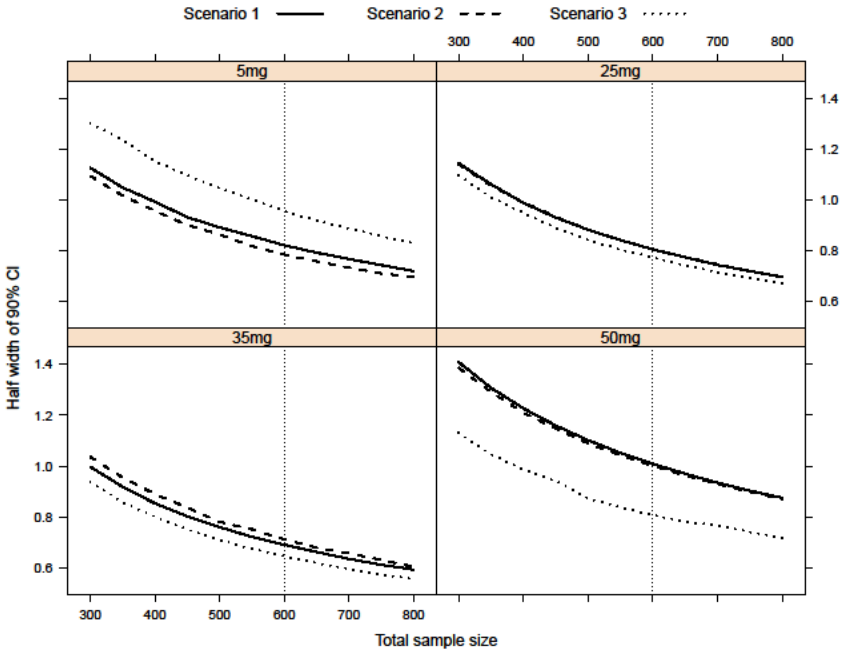


Figure 3 Half width of the 90% confidence interval for the 5 mg, 25 mg, 35 mg and 50 mg doses

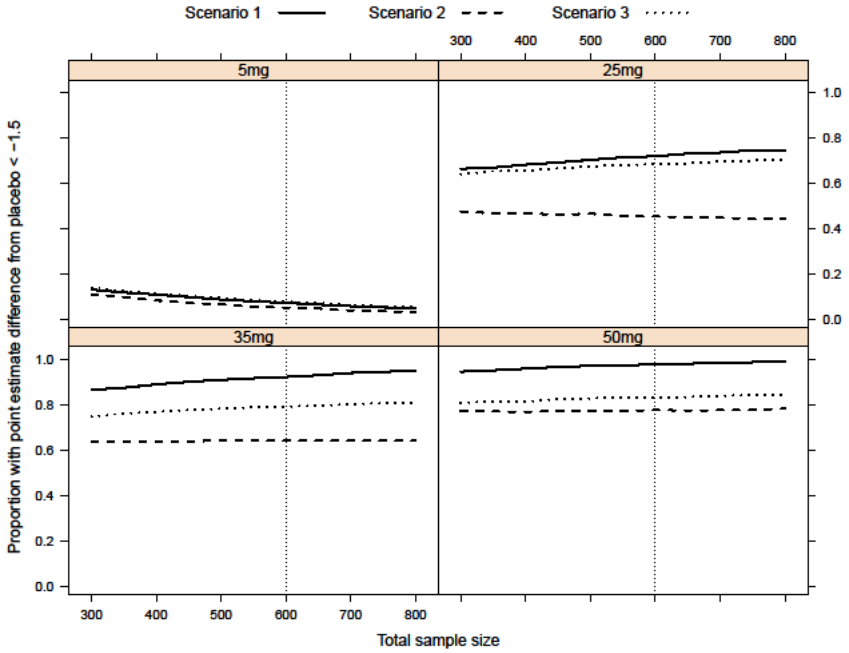


Figure 4 **Proportion of simulations in which the point estimate of difference from placebo is less than -1.5 for doses of 5 mg, 25 mg, 35 mg and 50 mg**

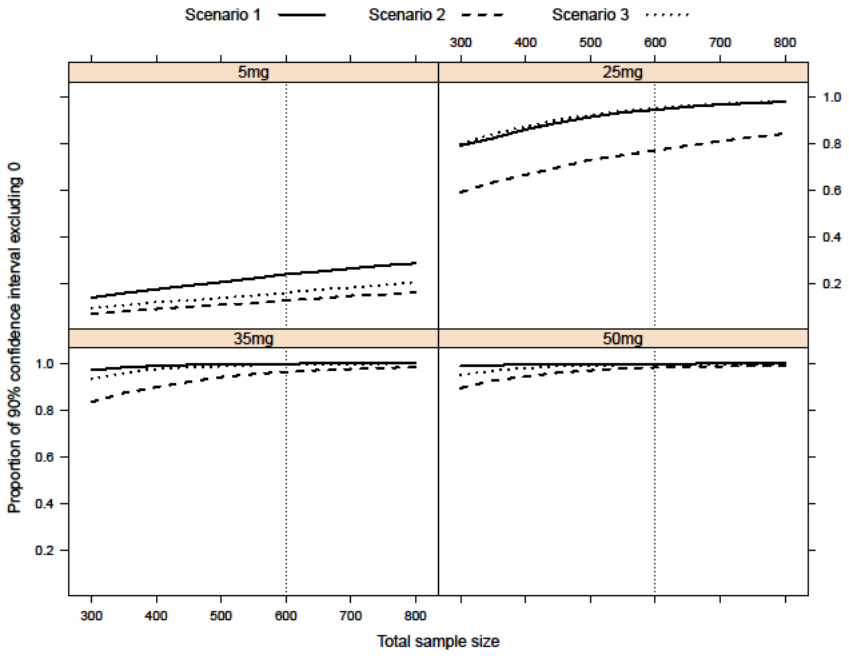


Figure 5 **Proportion of simulations in which the 90% confidence interval exclused 0 for doses of 5 mg, 25 mg, 35 mg and 50 mg**

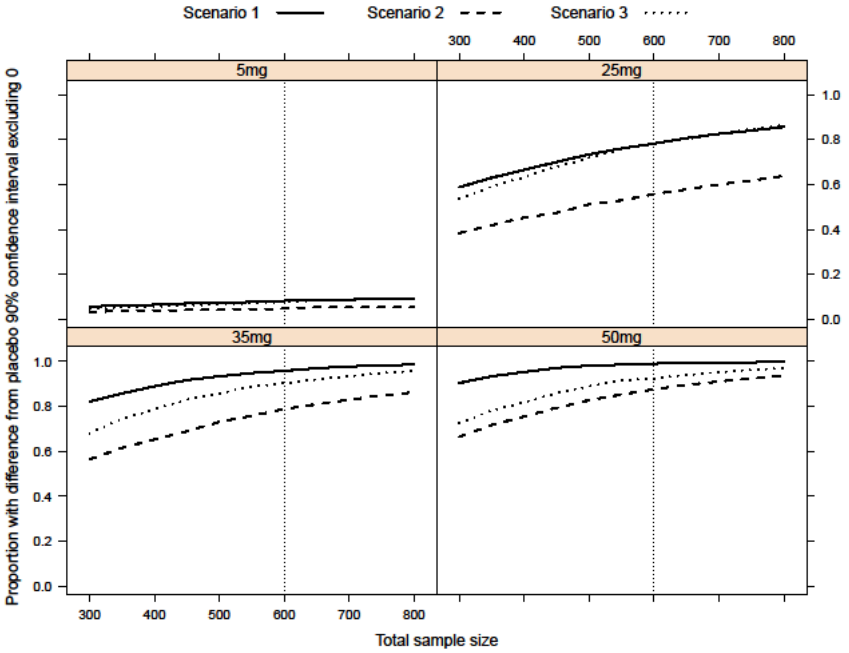


Figure 6 Proportion of simulations in which the 90% confidence interval of difference from placebo excludes 0 for doses of 5 mg, 25 mg, 35 mg and 50 mg

Based on the simulations a sample size of at least n = 600 will allow for adequate precision in estimation of the 35 mg dose as well as sufficient proportion with 90% confidence interval difference from placebo excluding 0 (over 80% for the 35 mg dose under all scenarios) and proportion with 90% confidence interval of dose estimate excluding 0 (over 80% for all higher doses and scenarios except 25 mg under scenario 2).

10.2.1. Sample Size Re-estimation

At the time of the interim analysis for futility, sample size re-estimation may be considered by the study team if the assumptions driving the sample size calculations are shown to be incorrect (e.g., variability is higher than expected). No more than 100 additional participants will be considered.

10.3. Randomization

Participants will be randomized equally (1:1:1:1:1:1) to the six treatment arms of placebo, 5 mg, 10 mg, 25 mg, 35 mg and 50 mg danirixin. Randomization will be stratified by smoking status (current vs. former).

10.4. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants	This population will comprise all participants screened and for whom a record exists on the study database and will be used for the tabulation and listing of reasons for withdrawal before randomization and listings of AEs and SAEs for nonrandomized participants.
Intent To Treat (ITT)	This population will comprise all participants randomized to treatment and who received at least one dose of study medication. This will constitute the primary population for all analyses of efficacy and safety. Outcomes will be reported according to the randomized treatment allocation.
PK	This population will comprise all participants in the ITT population for whom a pharmacokinetic sample was obtained and analyzed.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.5. Statistical Analyses

Analysis methods for key endpoints are described below. Unless otherwise stated, all statistical testing will be two-sided and all confidence intervals or Bayesian credible intervals will be 90% two-sided.

Further details on all analyses will be described in the reporting and analysis plan (RAP).

10.5.1. Efficacy Analyses

10.5.1.1. Primary Analysis

The primary endpoint is 6 month change from baseline using the ITT population.

Baseline values of E-RS:COPD will be defined as the daily average of scores for the 7 days prior to randomization. Days with missing values will not count towards the average. A minimum of 4 days will be needed and participants without sufficient days will not be randomized.

Individual monthly E-RS:COPD means will be defined as the average E-RS:COPD scores during the following study days:

- Month 1: days 1-28
- Month 2: days 29-56
- Month 3: days 57-84

- Month 4: days 85-112
- Month 5: days 113-140
- Month 6: days 141-168

Days with missing values will not factor into the calculations. Participants will require a minimum number of 10 observations within a month, otherwise the monthly mean will be considered missing for that patient.

The primary analysis will be Emax (4 parameter) modeling of the dose-response curve for the primary efficacy endpoint of month 6 change from baseline. Smoking status will be included as a covariate in this model, allowing the asymptote values of the dose-response relation for smokers to differ from those of the non-smokers. This model formulation will require estimation of at most six parameters. Simpler models nested within this general formulation will be also considered, comprising formulations of the mean dose-response relation allowing for a fixed difference between smokers and non-smokers (parallel curves model), no difference between smokers and non-smokers and the Emax model restriction m=1. Model fitness will be measured using standard goodness of fit analysis. This analysis will allow for an assessment of the extent to which the variability of the trial data will be captured using the proposed model and what dose-response specification allows the best interpretation of the data.

The dose-response model will be fitted to the data using Bayesian techniques using the function uniform prior (FUP). The rationale for this choice of inference is that the FUP shrinks the dose-response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relation compared to maximum likelihood.

Standard Bayesian diagnostic plots will be produced to aid in the interpretation of results. Based on the selected model, 90% two sided Bayesian credible interval for all treatment arms, all pairwise differences between each danirixin dose and placebo, as well as between active danirixin doses, will be generated.

Other models of dose response such as quadratic and log linear will be considered as alternative analysis option if the Emax model does not fit the data well. Similar analysis with the final model using the endpoint includes months 1-6 and months 3-6 will be fit. A longitudinal mixed effects model will be also be fit with dose as a categorical variable to explore the time trend of E-RS:COPD. Each of the three E-RS:COPD subscales (breathlessness, cough and sputum, and chest symptoms) will be analysed using similar methods for the primary analysis and longitudinal analysis. Details of these sensitivity analyses will be further described in the RAP.

10.5.1.2. Key Secondary Analyses

All analyses for other efficacy endpoints will use the ITT Population, unless otherwise noted. Dose will be treated as a categorical variable and no dose response modelling will be done unless otherwise stated. The treatment comparisons of interest will be between individual danirixin doses and placebo and between different danirixin doses. Smoking

status (current vs former) will be included as a covariate in all analyses. All Bayesian analyses will use non-informative priors. Further details will be described in the RAP.

10.5.1.3. HCRU Exacerbations

The number of events associated with HCRU-defined exacerbations will be analyzed using generalised linear models assuming a negative binomial distribution for the underlying exacerbation rate with a log link and an offset to account for the length of time in study for each participant. The exacerbation rates for the danirixin and placebo groups, along with the ratio in exacerbation rates danirixin/placebo, will be estimated and corresponding 95% credible intervals will be produced.

10.5.1.4. Time to First HCRU Exacerbation

Time to first HCRU exacerbation will be defined from the date of randomization. Participants without an exacerbation and participants who withdraw from the study prior to any observed exacerbations will be censored at the time of last contact. Survival will be summarized by treatment groups through Kaplan-Meier curves. Treatment arms will be compared using a stratified log-rank test. Time to first severe HCRU exacerbation will be analysed in a similar manner.

10.5.2. Safety Analyses

All safety endpoints will be tabulated or plotted by treatment group and will be performed on the Safety Population. Further details will be described in the RAP.

10.5.3. PK and PK/PD Analyses

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. For participants in the PK subset non-compartmental PK parameters (e.g. AUC(0-12), Cmax and tmax) will be calculated as data permit. The pharmacokinetic data from this study may be combined with historic DNX pharmacokinetic data for the purposes of population pharmacokinetic modelling which may be reported separately from the main clinical study report. The goal of this analysis is to characterize the population pharmacokinetics of DNX administered orally in subjects with COPD. The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of DNX in this population will be investigated. DNX blood concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model [FDA, 1999]. Further details will be described in the RAP.

Exploratory analysis using scatter plots will be conducted to investigate the relationship between blood exposure to danirixin (PK) and efficacy/PD/safety endpoints as data permit. If appropriate PK/PD modelling will be attempted to describe any relationship including longitudinal efficacy, PD, and/or safety variables versus systemic exposure (or dose) and may be combined with historic data. The results of any PK/PD modelling may be reported separately from the main clinical study report. Further details will be described in the RAP.

10.5.4. Interim Analyses

10.5.4.1. Interim PK Analysis

After approximately 10 participants in the PK subset for each treatment group have completed Visit 3, an interim evaluation of danirixin pharmacokinetic parameters will be undertaken. The purpose of the interim PK analysis is to determine if danirixin exposures are within the expected range.

10.5.4.2. Futility Analysis

An interim analysis will be conducted to allow for the possibility of stopping early for futility. The expected pace of recruitment will be 12 months. Therefore, by the time a sufficient number of participants have been recruited and have accrued 6 months of data, a futility analysis will not be practical. We will therefore consider futility analyses based on the 3 month data using the assumption that the response will be consistent from month 3 onwards. Under this assumption, which is consistent with the Phase IIa study, this is a valid futility approach.

Once approximately 150 participants have completed 3 months of treatment, the 3 paramter Emax model will be fit to the change from baseline of E-RS:COPD. If the posterior predictive probability of difference from placebo being less than 0 is below 30% for all danirixin doses, the study may be stopped for futility.

Based on simulated data, the expected number of participants with completed 6 month data at the time of this analysis will be too small to warrant any analysis (expected number < 10). However, if the recruitment differs greatly from expectations, and enough participants have completed 6 months of treatment, the 6 month change from baseline endpoint may also be explored.

No early stopping for efficacy will be considered and only outputs relating to the primary endpoint of E-RS:COPD change from baseline will be created. Outputs featuring unblinded treatment assignments will be created for this interim analysis but will not be shared outside of the study team unless the decision is made to halt the study for futility.

10.5.4.3. Strategic Planning Analysis

When 450 participants have completed 6 months of treatment or prematurely withdrawn from treatment, the study will have an interim analysis for administrative purposes. This analysis will be used to aid in the planning of future studies and for a better understanding of benefit/risk profile of danirixin. This interim analysis will look at the primary endpoint of E-RS: COPD dose response modelling, key secondary endpoints of HCRU exacerbations and SGRQ score, key safety endpoints around hepatotoxicity, neutrophils, pneumonia and other infections and PK data. No changes will be made to this study based on the results of this interim analysis. Outputs featuring unblinded treatment assignments will be created for this interim analysis, reviewed by the study team and potentially shared with selective GSK personnel (to be included in the data dissemination plan).

Further details of the outputs including key safety outputs that will be produced will be described in the RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
BfS	Federal Office of Radiation Protection (Germany)
BID	Twice daily
BRCP	Breast cancer resistance protein
BUN	Blood urea nitrogen
CAT	COPD Assessment Test
CD	Cluster of differentiation
CFR	Code of Federal Regulations (United States)
CI	Confidence Interval
CID	Clinically important deterioration
CIL	Clinical Investigation Leader
Cmax	Maximum observed concentration
CONSORT	Consolidated standards of reporting trials
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Clinical Pharmacokinetics Modelling and Simulation
C-PPAC	Clinic Visit PROactive Physical Activity in COPD Tool
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
CXCR	CXC Chemokine Receptor
CXR	Chest X-Ray
dL	Deciliter
DNA	Deoxyribonucleic acid
DNX	Danirixin
DRE	Disease Related Event
E0	Effect at zero concentration
ECG	Electrocardiogram

eCRF	Electronic Case Report Form
ED50	Dose causing 50% of the maximum achievable response
EMA	European Medicines Agency
Emax	Maximum response achievable
eMDI	Electronic metered dose inhaler
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease-Patient Reported Outcome
E-RS:COPD	Evaluting Respiratory Symptoms in Chronic Obstructive Pulmonary Disease
EW	Early Withdrawal
FDA	Food and Drug Administation (United States)
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FSH	Follicle Stimulation Hormone
FUP	Function Uniform Prior
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HBsAG	Hepatitis B surface antigen
HCRU	Healthcare Resource Utilization
hCG	Human chorionic gonadotrophin
HDPE	High density polyethylene
Hep B	Hepatitis B
Hep C	Hepatitis C
hsCRP	High sensitivity C-reactive protein
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IVIVT	In vitro In vivo Translation
IWRS	Interactive Web Response System
kg	Kilogram
L	Liter
LABA	Long acting β2 receptor agonist
LAMA	Long acting muscarinic receptor antagonist
LH	Leutinizing Hormone
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin count
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MM	Medical monitor
MSDS	Material Safety Data Sheet
msec	Millisecond
NOAEL	No observed adverse effect level
O_2	Oxygen
PK	Pharmacokinetics
PR	PR interval; duration in milliseconds from the beginning of the P wave to onset of ventricular depolarization (R)
PRO	Patient Reported Outcome
PTS	Platform Technology and Science
QRS	QRS interval; duration in milliseconds of the QRS complex

QT	QT interval; duraction in milliseconds between the start of the Q wave and the end of the T wave
QTcF	QT interval corrected for heart rate (Friderica formula)
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SABA	Short-acting β2 Receptor Agonist
SAE	Serious Adverse Event
SAMA	Short-acting Muscarinic Receptor Agonist
SGRQ	St George's Respiratory Questionnaire
SGRQ-C	SGRQ for COPD patients
SRM	Study Reference Manual
SRT	Safety Review Team
SOA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal phase half-life
tmax	Time to reach Cmax
TPR	Third Party Resourcing
ULN	Upper limit of normal
µg	Microgram
VT	Ventricular tachycardia
WBC	White blood cells
WOCBP	Women of child bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 Protocol-Required Safety Laboratory Assessments will be performed by the central laboratory, except as noted.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium Chloride Bicarbonate	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 required for screening)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity			

Laboratory Assessments	Parameters
	• pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Plasma fibrinogen (a screening plasma fibrinogen is only needed for participants with 1 COPD exacerbation in the prior year) • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[3] • All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine testing

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 hCG testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease

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

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

Data Protection

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

Committees Structure

- A study charter will be created to describe important governance aspects while the study is being conducted.
- The core GSK study team (this will include the Clinical Investigation Leader (CIL), Medical Monitor (MM), study statistician, GCSP physician, GCSP scientist, and CPMS representative) will have access to unblinded, aggregate summaries for study treatments. Only the study statistician will have access to individual participant treatment assignments. Study team members who interact

with study site staff will remain blinded until the study is completed. Complete details will be included in the study charter.

- The SRT will include the Safety Development Leader, GCSP scientist, MM, CIL and study statistician but will extend to other functions as requied. The SRT will provide a proactive, aggregate and holistic evaluation of the safety data of danirixin. Further details are included in the SRT charter.

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 partcipant's last visit.

Data Quality Assurance

- All participant data relating to the study will be recorded on electronic Case Report Report (eCRF) 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/eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF/eCRF.
- 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/eCRF 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 after from the issue of the final Clinical Study Report (CSR) or 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.

Data Management

- For this study subject data will be entered into GSK-defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.
- Adverse events and concomitant medication terms will be coded using the Medical Dictionary for Regulatory Activities (MeDRA) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM.

Study and Site Closure

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

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

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

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

12.4. Appendix 4: 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, 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.

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.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

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 SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool and fax or email the paper form to GSK and the Medical Monitor.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE
- 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/SAE coordinator by telephone or e-mail.
- Contacts for SAE reporting can be found in the SRM.

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

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 6 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- Refrain from donating sperm for the duration of study and for at least 60 hours after the last dose of study treatment.

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 6.

Table 6 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 will be performed at approximately monthly intervals during the study treatment period, after the last dose of study treatment and as required locally.
- Pregnancy testing, with a high sensitivity test will be performed using the test kit provided by the central laboratory and approved by the sponsor and in accordance with instructions provided in the test kit package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

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

- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 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 discontinue study treatment and be withdrawn from the study.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples may be used for research related to danirixin or COPD and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to danirixin treatment, and COPD (and related diseases). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples may be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples also may be analyzed as part of a multi-study assessment of genetic factors involved in the response to danirixin treatment or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on danirixin (or study treatments of this class) or COPD and related diseases continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • 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 chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, up to 72 h after last dose[5] • 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

discontinue study treatment and continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	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 (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease[3] complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 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 participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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

5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) 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.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

Reference

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.

12.8. Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.1.1 for the list of GSK medical devices to be used in this study).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.9. Appendix 9: 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.

12.10. Appendix 10: Country Specific Requirements

Korea - Investigational Product Label

PPD