TITLE PAGE

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Protocol Number: 205864 Amendment 3

Short Title: Danirixin Pilot Study for Disease Progression

Compound Number: GSK1325756

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): IND:108168

Approval Date: 18-MAY-2018

SPONSOR SIGNATORY

PPD

18 May 2018

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	18-May-2018
Amendment 2	24-Jul-2017
Amendment 1	17-May-2017
Original Protocol	21-Mar-2017

Amendment 1: 17-MAY-2017

Overall Rationale for the Amendment: This amendment excludes the enrolment of women of childbearing potential and clarifies the testing required for determination of post menopausal status in specific situations.

Section # and Name	Description of Change	Brief Rationale
Table 1 – Schedule of Activities	• Remove pregnancy testing • Added missing check marks • Updated screening period	• Not required as no longer enrolling WOCBP • Error in original protocol • Required to allow for screening lab tests
Section 6.1 Inclusion Criteria	Update to only allow females to participate if they are not women of childbearing potential (WOCBP)	To remove additional burden on female subjects of childbearing potential requiring additional visits for pregnancy testing only.
Section 12.2 – Appendix 2 Clinical Laboratory Tests	Update Table 6 – Protocol-Required Safety Laboratory Assessments to remove pregnancy testing	Removed pregnancy testing based on the exclusion of WOCBP
Section 12.5 – Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information	• Adding clarification on determination of post menopausal state in the absence of 12 months of amenorrhea • Updated wording to be in line with exclusion of WOCBP	• Current wording in template is not clear on testing required • Clarification of wording

Amendment 2: 24-JUL-2017

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 3.3.1 Risk Assessment	Removal of the following text from the mitigation strategy of the reproductive toxicology section: "Male participants with female partners of child-bearing potential must comply with the contraception requirements."	Additional data available demonstrating absence of genotoxic effects
Section 7.1.1 and Section 9.2.8 Medical Devices and Medical Device Incidents	Update to add mobile spirometer (MicroDiary) as a medical device	This device is being used in the study and was inadvertently omitted from the previous versions of the protocol
Section 6.1 and Section 12.5 (Appendix 5) Inclusion Criteria and Contraceptive Guidance and Collection of Pregnancy Information	Removal of requirement for male contraception with partners of WOCBP	Additional data available demonstrating absence of genotoxic effects

Amendment 3: 18-MAY-2018

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Updated Smoking history to reflect that it is captured only at V1 and smoking status is captured at both V1 and V2; also updated Screening visit window to up to 32 days	Correcting error from original version and discussion with investigators
Section 4 Objectives and Endpoints	Updated to match the obectives and endpoints in the synopsis	Correcting error from original version
Section 5.1	Updated screening period from up to 28 days to up to 32 days	Based on discussion with investigators
Section 6 Study Population	Updated to reflect that cohorts in addition to COPDGene may be used to support recruitment. Removed the use of the Random Forest data in patient selection and changed history of lung function decline from 20mL/yr to 15 mL/yr. Changed inclusion criteria from weight >45kg to body mass index ≥ 21.	Based on discussion with investigators
Appendix 5	Removed pregnancy testing requirements	Overisight from previous amendment when WOCBP were excluded. No pregnancy testing needed with this exclusion criteria.

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Short Title: Danirixin Pilot Study for Disease Progression in COPD

Rationale: This is a pilot study to investigate the effect of danirixin hydrobromide (HBr) 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction and a demonstrated history of decline in FEV_1. This study aims to assess whether danirixin has the potential to impact disease progression in participants with COPD and with a demonstrated history of disease progression measured by lung function.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess whether danirixin HBr 35mg tablets impact disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
Secondary	
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events • Vital Signs • ECG • Clinical Laboratory Assessments (hematology, clinical chemistry, urinalysis)
• To further characterize the clinical activity of danirixin HBr 35mg tablets compared with placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use

Overall Design:

This is a Phase 2 study to investigate the potential impact of danirixin HBr 35mg tablets compared with placebo on disease progression in participants with mild to moderate airflow obstruction. The study will also assess the enrichment strategy of enrolling participants identified from the COPDGene study. These participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period.

Number of Participants:

Approximately 130 participants will be screened to enrol 100 participants in this study. It is anticipated that approximately 85 participants will complete the 52 weeks of treatment (assuming a 15% drop out rate).

Treatment Groups and Duration:

Participants will receive either placebo or danirixin 35mg tablets (as hydrobromide hemihydrate salt) twice daily for 52 weeks (12months).

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -32 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Eligibility														
Informed Consent	X													
Genetics Informed Consent[b]	X													
Demography	X													
Inclusion and Exclusion Criteria	X													
Smoking Status[c]	X	X												
Smoking History[c]	X													
Medical History[d]	X													
Full physical	X													
Chest X-ray (historical within 1 year acceptable)	X													
HIV, Hepatitis B and C screening[e]	X													
Additional Eligibility and In Study Assessments														
Verify Eligibility[f]	X	X												
Brief physical		X				X			X			X	X	
Laboratory assessments (clinical chemistry, including liver chemistries), hematology, urinalysis	X	X		X					X			X	X	
Additional Liver chemistries only			X		X	X	X	X		X	X			
12 lead ECG	X	X		X		X			X			X	X	
Vital Signs	X	X		X		X			X			X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -32 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Office spirometry (centralized)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Home spirometry - (weekly)	X	←	—	—	—	—	—	—	—	—	→	X	X	
Randomization		X												
Dispense study medication		X		X	X	X	X	X	X	X	X			
Dispense log pad and provide training	X													
Dispense MDI sensors and provide training	X													
Study Treatment		←	—	—	—	—	—	—	—	—	→			
Study Treatment Compliance (ediary)		←	—	—	—	—	—	—	—	—	→			
Collect IP				←	—	—	—	—	—	—	→			
Collect MDI sensors												X	X	
Collect log pad												X	X	
AE review		←	—	—	—	—	—	—	—	—	→		X	X
SAE review	←	—	—	—	—	—	—	—	—	—	→		X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Outcomes Assessments														
COPD exacerbation review		X	X	X	X	X	X	X	X	X	X	X	X	
Rescue medication Use	←	—	—	—	—	—	—	—	—	—	—	→		
SGRQ-C		X				X			X	X		X	X	
COPD Assessment Test (CAT)		X				X			X	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	X	X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -32 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Genetic, Pharmacokinetic and Biomarker Blood Collections														
Blood sample for Genetics		X												
Blood sample for CRP		X							X			X	X	
Blood sample for exploratory biomarkers		X							X			X	X	

a Informed consent may be signed prior to screening visit in the case that any changes in medications are necessary
b Agreeing to genetic sample consent is not required for study participation
c Smoking status/history assessed at screening; smoking status re-checked at Visit 2
d Includes substance usage, past and present medical conditions and family history of premature CV disease
e 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.
f Participant's clinical status should be reviewed

The timing and number of planned study assessments, including safety and biomarker assessments may be altered during the course of the study based on newly available data to ensure appropriate data collection. Any changes in the timing or addition of time points for any planned study assess 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 Number 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 [GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163]. 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. Analyses 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 pilot study to investigate the effect of danirixin HBr 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction identified from the COPDGene cohort. 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.

Specifically, this study aims to assess whether or not danirixin has the potential to impact disease progression in participants with a demonstrated history of decline in FEV_1 based on 5 year data from COPDGene and support the conduct of a larger Phase III study for disease progression. In addition to lung function and HRQoL, this study will assess moderate/severe COPD exacerbations, health status (CAT), and rescue medication use.

3.2. Background

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

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

Danirixin is being evaluated as an addition to standard of care inhaled therapies (i.e. long acting bronchodilators and long acting bronchodilator/corticosteroid combination

therapies) and is targeting those COPD patients that continue to have a burden of respiratory symptoms and COPD exacerbations despite management with currently available COPD treatments.

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Testicular effects and male fertility	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. PK modelling predicts that in a participant receiving 35 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 10^9/L product will be discontinued and neutrophil count will be monitored until return to normal. Participants may be restarted on study treatment as detailed in Appendix 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 participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

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

3.3.2. Benefit Assessment

- 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 or 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 assess whether danirixin HBr 35mg tablets impacts disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
Secondary • To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation • To further characterize the clinical activity of danirixin HBr 35mg tablets compared to placebo	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers • Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use
Exploratory • To characterize the effect of danirixin on lung matrix destruction/remodelling and inflammation • Further characterize efficacy of danirixin	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes) and inflammation (e.g. CRP) • Global assessment of COPD severity

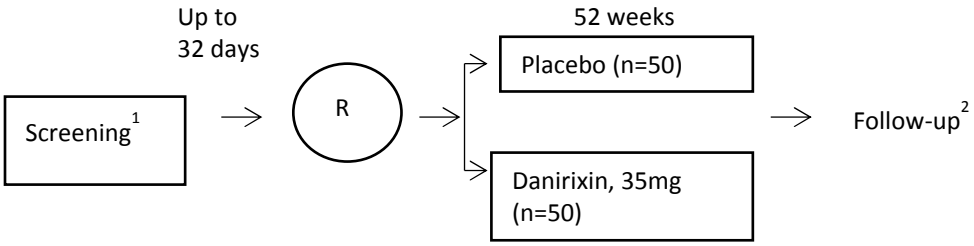
5. STUDY DESIGN

5.1. Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -32 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit

[2] Follow-up visit to occur within 28days of last dose of study medication

5.2. Number of Participants

Approximately 130 participants will be screened to achieve 100 randomized in this study. It is anticipated that approximately 85 participants will complete the 12 months of treatment (assuming a 15% drop out rate).

For the analysis of study assessments, several analysis populations are defined in Section 10.3.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all planned study visits 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. With the use of an enriched population, it is anticipated that one year of treatment will be sufficient to detect a trend in altering disease progression. Danirixin has already been clinically investigated over one year treatment duration (GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163).

The data from this study will provide useful information in determining whether or not to progress to a Phase III study to explore an indication for slowing disease progression.

5.5. Dose Justification

One dose of danirixin is proposed for this study, 35mg tablets BID. This dose was selected based on integrating information on:

- Dose-exposure-biomarker response using inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils over the dose range of 0-400mg (free base tablet) in healthy volunteers (GSK Study No. CX3 112483).
- Evidence of reduced respiratory symptoms and improvement in health status in mild to moderate COPD participants from interim data in the Phase IIa study (GSK Study No. 200163).
- Relative bioavailability study comparing danirixin free base vs HBr (GSK Study No. 201037).

In the previous 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 (GlaxoSmithKline Document Number 2015N248339_00, Study ID 201037). Thus the danirixin (hydrobromide tablet) 35mg BID dose for investigation in this study is expected to provide steady-state systemic exposure approximately equivalent to the 75mg BID (free base tablet) used in Study 200163. 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 (5^{th}, 95^{th} percentile)			Cavg multiple of IC50*	Cmin multiple of IC50*
	AUC(0-24) steady-state (ug.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4

#Model derived based on PK data in healthy elderly participants from GSK Study No. 201037 (GlaxoSmithKline Document Number. 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.

6. STUDY POPULATION

This study will identify specific COPD patients most likely to decline from well established cohorts like COPDGene [NCT00608764]. This study will be an ancillary study within COPDGene and any other relevant cohort investigating the enrichment strategy for assessing disease progression. These potential participants will be identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a demonstrated decline of at least 15mL/yr over the initial 5 year period. Once participants are identified from the COPDGene dataset, the following criteria will be verified at initial study visit following signing of consent. Equivalent cirteria may be identified within other cohorts if necessary to broaden recruitment pool.

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 76 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. At the screening visit, the subject must have an FEV_1 >40% of the predicted normal.
3. Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD

Weight

4. Body Mass Index ≥ 21

5. **Sex**

   Male or female

   Female participants:

   A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Informed Consent

6. Capable of giving signed informed consent as described in Section 12.3 (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 disease (other than COPD), e.g. sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer
2. COPD due to alpha-1-antitrypsin deficiency
3. Pulse oximetry < 88% at rest at screening. Participants should be tested while breathing room air. However, participants living at high altitudes (above 5000 ft or 1500 m above sea level) who are receiving supplemental oxygen can be included provided they are receiving the equivalent of < 4L/min and screening oximetry is measured while on their usual settings.
4. Less than 14 days have elapsed from completion of a course of antibiotics or oral corticosteroids for a recent COPD exacerbation
5. Participants with a peripheral blood neutrophil count < 1 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 with lateral) or CT scan reveals evidence of a clinically significant abnormality not believed to be due to the presence of COPD (historic data up to 1 year may be used).
8. History or current evidence of clinically significant renal disease, diabetes mellitus/metabolic syndrome, hypertension, or any other clinically significant cardiovascular, neurological, immunological, endocrine, or haematological abnormality 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 participants at risk through study participation, or which would affect the safety analysis or other analysis if the disease/condition exacerbated during the study.
9. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator of GSK medical monitor, contraindicates their participation.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude participants who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would

preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- AF with rapid ventricular rate > 120 bpm;
- sustained or non-sustained VT
- second degree heat block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
- QTcF ≥ 500 msec in patients with QRS < 120 msec and QTcF ≥ 530 msec in patients with QRS ≥ 120 msec

12. Previous lung surgery (e.g. lobectomy, pneumonectomy) or lung volume reduction procedure.

Prior/Concomitant Therapy

13. 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.

14. 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.

15. 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

16. 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).
17. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study
18. Exposure to more than four investigational products within 1 year prior to the first dosing day in the current study.

Diagnostic assessments

19. Alanine transferase (ALT) > 2x upper limit of normal (ULN) and bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

20. A positive test for HIV antibody.

21. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening. Note:
22. Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA PCR test is obtained.

Other Exclusions

23. 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.
24. A history of allergy or hypersensitivity to any of the ingredients in the study treatment.
25. A known or suspected history of alcohol or drug abuse within the 2 years prior to screening.
26. 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.
27. 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 not be rescreened unless discussed with the medical monitor.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	**Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)**	**Placebo**
Dosage formulation:	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients
Unit dose strength(s)/Dosage level(s):	35mg tablets (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).

Mobile spirometers (MicroDiary, manufactured by and purchased from CareFusion) are also being provided by GSK for this study. These devices allow participants to conduct spirometry assessments at home. The MicroDiary has US FDA 510(k) clearance to market (Class II medical device) and European Union CE marking (Class I medical device).

Additional descriptive information and instructions for the eMDI monitoring devices and mobile spirometers 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 study. Study participants, all study site staff, and all members of the GSK study team will be blinded to individual participant treatment assignment.

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.

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) bronchodilators, (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.

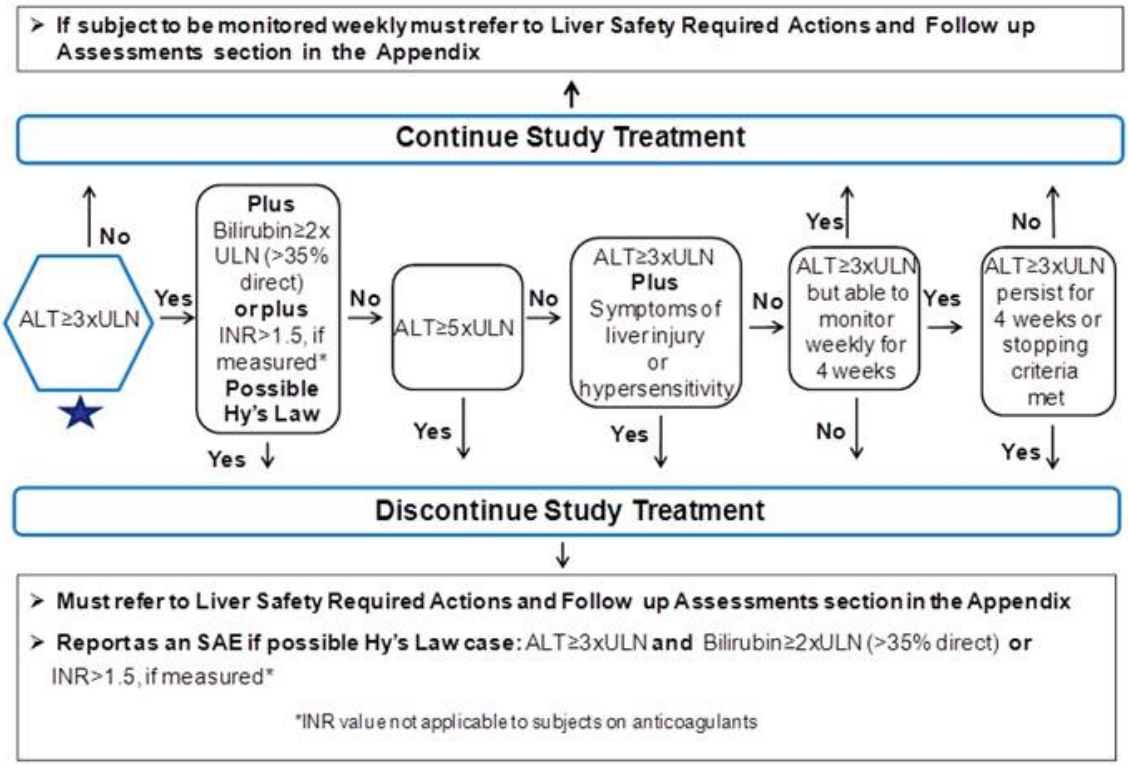
8. DISCONTINUATION CRITERIA

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: Liver Safety: Required Actions and Follow-up Assessments).

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 (Section 12.7) 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. FEV_1

9.1.1.1. Clinic Spirometry

Spirometry using FEV_1 and FVC measurements (FEV%, and FVC% and FEV1/FVC will be calculated) will be performed in triplicate at time points listed in the SoA (Table 1). Spirometry assessments should be performed in accordance with ATS/ERS guidelines as outlined in the SRM.

9.1.1.2. Mobile Spirometry

Spirometry will also be performed weekly by the participants using a mobile spirometer at home. Details will be outlined in the SRM.

9.1.2. 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 SGRQ scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.3. 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.

9.1.4. COPD Exacerbations

An exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment or hospitalization.

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 based on the Investigator's judgement.

9.1.5. 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 final study visit or IP Discontinuation Visit. This single global question will ask participants 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 every visit following randomization (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.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4 (Section 12.4).

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 the time the informed consent is signed by the participant until the follow up visit at the time points specified in the SoA (Table 1).
- All AEs will be collected from the start of study treatment (randomization visit) until the follow-up visit at the time points specified in the SoA (Table 1).
- 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 must be reported immediately and not more than 24 hrs to the sponsor, as indicated in Appendix 4 (Section 12.4). 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 (Section 12.4).

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as

defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information 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 Section 12.4 (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.

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 Section 12.3 (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 Section 12.5 (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 measuring spirometry at home. 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 Section 12.8 (Appendix 8).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Section 12.4 (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 within 24 hours of determining a device-related event.
- The method of documenting Medical Device Incidents is provided in Section 12.8 (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 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.

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, 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 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 measurements 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 10 minutes.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Section 12.2 (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 Section 12.2, 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

Pharmacokinetic parameters are not evaluated in this study.

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 Section 12.6 (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), 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

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

10. STATISTICAL CONSIDERATIONS

The objective of this study is to investigate the effect of danirixin HBr 35mg tablets on COPD disease progression. There are no formal hypothesis tests associated with this objective and no formal significance tests. The information acquired from this study will primarily be used to assess whether or not danirixin impacts disease progression and to quantify the effect that danirixin has on disease progression, specifically change in lung function as measured by FEV_1 decline and change in health-related quality of life as measured by SGRQ total score to further support disease understanding and future studies.

10.1. Sample Size Determination

Sample size is based primarily on feasibility for this study. Since there is much uncertainty around the magnitude of the difference in the decline in FEV_1 and change in SGRQ along with the between-subject variability for the specific patient population, the proposed sample size is unavoidably imprecise. Sample size may be adjusted using the predictions of final study outcome based on simulations and possible interim analyses. It is anticipated that screening 130 participants will allow for approximately 100 participants to enrol.

In order to observe the effect of different sample sizes, various simulations were done to assess the impact of sample sizes of 50, 100, 150 and 200 with a 1:1 allocation to each treatment group [Table 3]. The assumed variability for rate of decline in FEV_1 and change in SGRQ is 25 and 10, respectively. The correlation between rate of decline in FEV1 and change in SGRQ is assumed to be -0.2. [Nagai, 2015]

Table 3 Assumptions used for the Simulations

	Treatment Effect Assumptions (δ_{FEV1}, δ_{SGRQ})	Variability Assumptions (σ_{FEV1}, σ_{SGRQ})	Sample Size
Null	(0,0)	(25,10)	N={50,100,150,200}
Alternate 1	(5,-1)	(25,10)	N={50,100,150,200}
Alternate 2	(5,0)	(25,10)	N={50,100,150,200}
Alternate 3	(0,-1)	(25,10)	N={50,100,150,200}

Data from a bivariate normal distribution were simulated under the four different treatment effect assumptions for samples sizes of 50, 100, 150, and 200. The samples from the posterior probability distribution from the MCMC approximation were divided into four regions based on δ_{FEV1} and δ_{SGRQ} treatment effect cut-off values; $\delta_{FEV1} \geq 0$ and $\delta_{SGRQ} \leq 0$, $\delta_{FEV1} \geq 0$ and $\delta_{SGRQ} > 0$, $\delta_{FEV1} < 0$ and $\delta_{SGRQ} \leq 0$, and $\delta_{FEV1} < 0$ and $\delta_{SGRQ} > 0$. Based on a 70% threshold, the proportion of the 1000 simulations meeting the requirement $P(\delta_{FEV1} \geq 0 \ \& \ \delta_{SGRQ} \leq 0) \geq 70\%$ were considered a success based on the joint definition [Figure 2, Table 4]. If $P(\delta_{FEV1} \geq 0 \ \& \ \delta_{SGRQ} \leq 0) < 70\%$, success could further be defined based on each endpoint independently where $P(\delta_{FEV1} \geq 0) \geq 80\%$ or $P(\delta_{SGRQ} \leq 0) \geq 80\%$.

Figure 2 Total Probability of Success

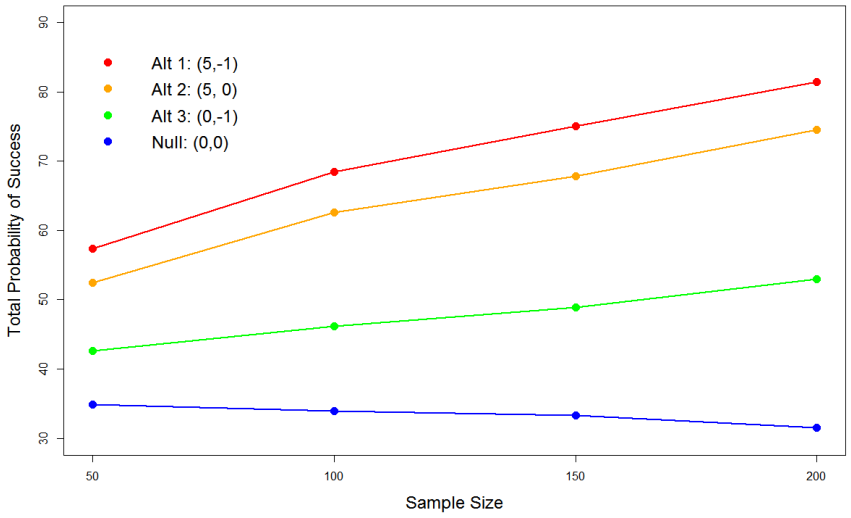


Table 4 Total Probability of Success (Figure 2)

	N=50	N=100	N=150	N=200
(5,-1)	57.4	68.5	75.1	81.4
(5,0)	52.5	62.6	67.8	74.5
(0,-1)	42.6	46.2	48.9	53.0
(0,0)	34.9	33.9	33.3	31.5

Figure 3 Half Width of the 95% Confidence Interval of δFEV$_1$ Point Estimate

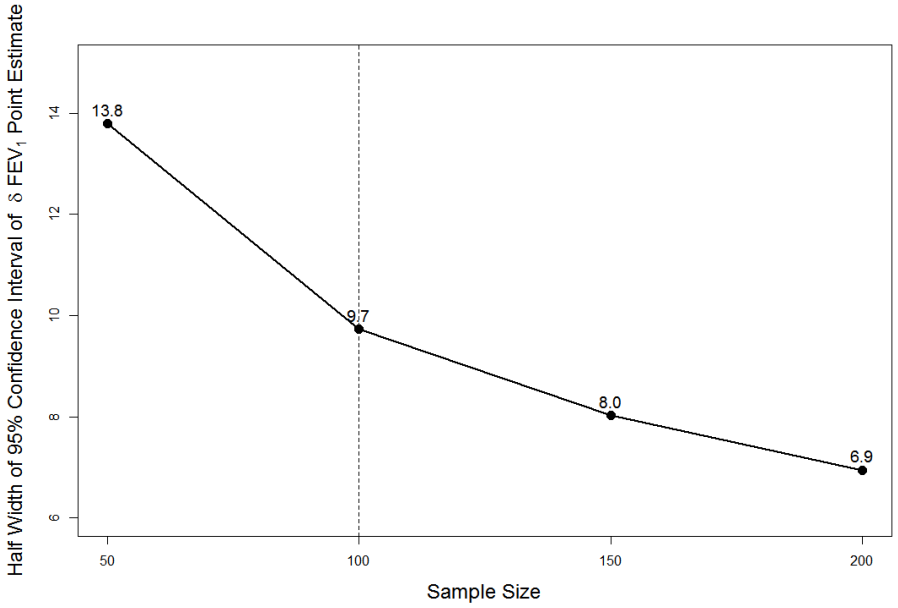
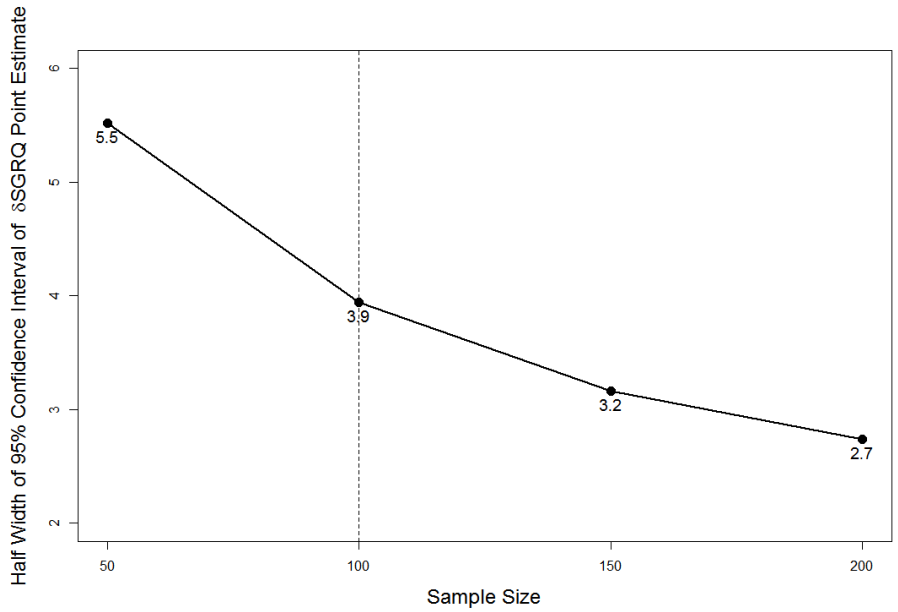


Figure 4 Half Width of the 95% Confidence Interval of δSGRQ Point Estimate



Based on the simulations, under the assumption of an expected treatment difference of (5,-1) which is the most probable scenario, the marginal increase for the total probability of success is greatest when increasing the sample size from 50 to 100 (Figure 2). The half widths of the 95% CI of the point estimate of the marginal treatment differences for FEV$_1$ (Figure 3) and SGRQ (Figure 4) have the greatest reduction from a sample size of 50 to 100. A sample size of 100 will allow for an adequate level of confidence in the study success while also considering the precision of the treatment effect differences.

10.2. Randomization

Participants will be randomized equally (1:1) to the two treatment arms of placebo and 35 mg danirixin HBr. Randomization will be stratified by smoking status (current vs. former).

10.3. 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.
Per-Protocol (PP) Population	This population will comprise of all patients in the ITT population who are not major protocol violators.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.4. Statistical Analyses

Treatment comparisons using all endpoints will be made using appropriate statistical techniques. Analysis methods for key endpoints are described below. Main analysis will use ITT unless noted. Further details on all analyses will be described in the reporting and analysis plan (RAP).

10.4.1. Efficacy Analyses

The total probability of success will be defined as a combination of a joint and conditional statement. The joint probability of success will be defined as the probability of the difference in the rate of decline in FEV_1 between danirixin and placebo is greater than or equal to 0 and the difference in the change in SGRQ total score from baseline between danirixin and placebo is less than or equal to 0 is greater than 70%. If the joint probability of success is less than 70%, success can further be defined based on each endpoint independently, where either the difference in the rate of decline in FEV_1 is

greater than or equal to 0 is greater than 80% or the difference in the change in SGRQ total score is less than or equal to 0 is greater than 80%.

$$Total\ PoS = P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) \geq 70\%$$

$$+\ P\left(\delta_{FEV_1} \geq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

$$+P\left(\delta_{SGRQ} \leq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

Endpoint	Statistical Analysis Methods
Primary	Rate of decline in FEV_1 and change from baseline in SGRQ total score
Exploratory	Will be described in detail in the RAP

Lung Function Decline: Rate of Decline of FEV_1 (mL/yr)

The rate of decline of FEV_1 will be derived from a repeated measures random coefficients model. Post-baseline FEV_1 will be modelled including terms for age, sex, smoking status, FEV_1 at baseline, and BMI along with treatment group, time and treatment by time interaction as fixed effects. Subject will be a random effect. Time will be defined as the number of days since start of treatment. Only FEV_1 values measured after baseline will be used in the model. Based on the results of previous studies, the study team will determine the time point at which post-baseline spirometry assessments will be included in the model to account for the initial treatment response. The estimate of the rate of FEV_1 decline will be the slope of the parameter estimate of the treatment by time interaction term in the model. Contrasts will be calculated for the difference in treatment by time interaction between danirixin and placebo treatment groups to estimate the treatment difference.

FEV_1 = Treatment group + age + sex +smoking status+FEV1_BL+BMI+ time + treatment*time

The rate of decline for each subject, the estimate of the slope parameter of the treatment by time interaction term, will be used as a co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

HRQoL: SGRQ

A co-primary endpoint of interest is change in SGRQ total score (derived from SGRQ-C) from baseline. Change in SGRQ total scores from baseline will be derived using a mixed model with repeated measures (MMRM) including fixed effects of treatment group, age, sex, smoking status, BMI, baseline SGRQ score, time as a categorical variable and a treatment by time interaction term. Subject will be a random effect. Estimated treatment differences at the end of one year will be obtained. The difference of the least square mean change from baseline at 12 months will be derived. The adjusted SGRQ total score

change from baseline will used as the other co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

Joint Analysis
The joint analysis will use the ITT population with all available FEV_1 rate of decline and change in SGRQ data.

The rate of decline (the slope parameter from the random coefficients model) of FEV_1, along with the change in SGRQ from the MMRM model will be extracted for each subject. These values will then be used to obtain MCMC approximations of the joint posterior distribution of the treatment differences between FEV_1 decline and change in SGRQ between the danirixin and placebo groups. Based on the samples from the posterior distribution, the proportion of samples falling within certain treatment difference regions will be calculated and the probability of success will be derived.

10.4.2. 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.

10.4.3. Other Analyses

Exploratory biomarker analyses will be described in the RAP.

10.4.4. Interim Analyses

Conducting an interim analysis or futility assessment may not be practical due to an expected fast recruitment period. By the time enough data will accumulate for any meaningful interim analysis to support changes to the study design, recruitment of all study participants will have concluded. However, if recruitment takes a longer than anticipated, an interim analysis to reassess the variability assumptions, estimate the probability of success at the end of study, and confirm the directionality of the endpoints may be conducted.

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

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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
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
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
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-C 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
CAT

Trademarks not owned by the GlaxoSmithKline group of companies
Combivent
Duoneb

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 • pH, glucose, protein, blood, ketones by dipstick			

Laboratory Assessments	Parameters
	• Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[2] • All study-required laboratory assessments will be performed by a central laboratory

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

Data Protection

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

Committees Structure

- A study charter will be created to describe important governance aspects while the study is being conducted.

- 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 participant's last visit.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: 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. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 sufficient 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 (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- 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.
- 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 and confirmatory testing with additional FSH and estradiol measurements is required.
- 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.

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 will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

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

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek

this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will 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 will 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 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 will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to danirixin 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 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).

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

No country specific requirements

12.11. Appendix 11 Protocol Amendment History

Amendment 1

Table 1 Schedule of activities

Original text:

	Screening/ Visit1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -7 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Urine or serum Pregnancy test[g]	X											X	X	
HIV, Hepatitis B and C screeninge														
AE review		←	←	←	←	←	←	←	←	←	←			
SAE review		←	←	←	←	←	←	←	←	←				

Revised text:

	Screening/ Visit1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
HIV, Hepatitis B and C screeninge	X													
AE review		←	←	←	←	←	←	←	←	←	←		X	X
SAE review		←	←	←	←	←	←	←	←	←			X	X

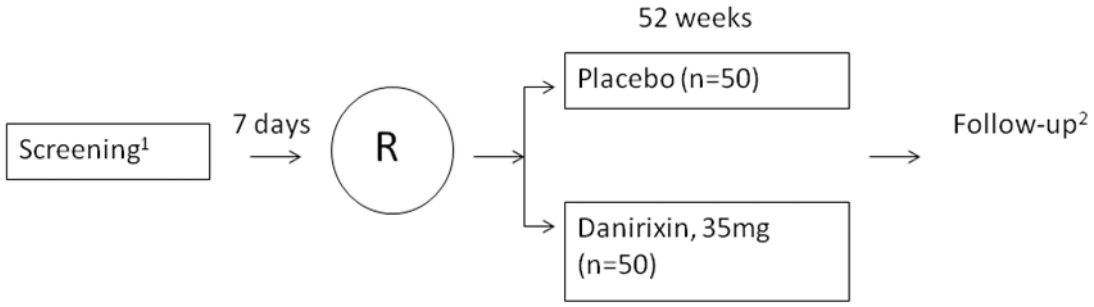
Section 5.1 Overall Design

Original text:

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -7 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



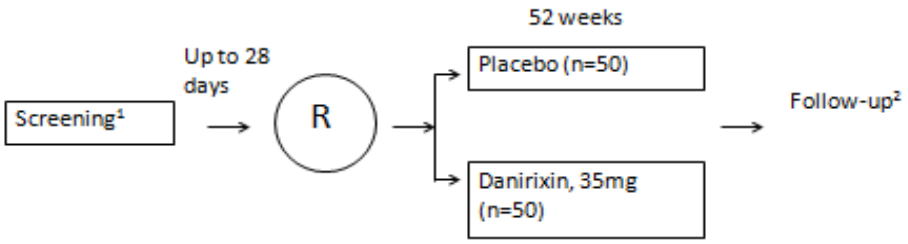
[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

Amended text:

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -28 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

Section 6.1 Inclusion Criteria

Original text:

2 Male or female

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.

Female participants:

A female participant is eligible to participate if she is not pregnant (see Section 12.5; Appendix 5), not breastfeeding, and at least one of the following conditions applies:

i. Not a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Section 12.5 (Appendix 5) during the treatment period and for at least 60 hours after the last dose of study treatment.

Revised text:

3 Male or female

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.

Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Section 12.2 Appendix 2:

Original text:

Table 7 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	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • 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

Amended text:

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC	<u>WBC count with Differential</u>: 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 • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[2] • All study-required laboratory assessments will be performed by a central laboratory			

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. 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

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

Original text:

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 9 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.)*

Amended text:

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 and confirmatory testing with additional FSH and estradiol measurements is required.
    - 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.

Table 10 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.)*

Amendment 2

Original text:

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	Standard safety monitoring will be employed. The potential risk of testicular injury has been conveyed in the informed consent. PK modelling predicts that in a participant receiving 35 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**
	No adverse events related to testicular effects have been observed in clinical studies to date.	
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	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**
	in nonclinical studies with danirixin. In healthy volunteer studies and a phase 2a study in patients with Influenza (GSK Study 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

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

Amended text:

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	Standard safety monitoring will be employed. The potential risk of testicular injury has been conveyed in the informed consent. PK modelling predicts that in a participant receiving 35 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**
	studies to date.	
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	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**
	study in patients with Influenza (GSK Study 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

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

Section 6.1 Inclusion Criteria

Original text:

Sex

6. Male or female

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.

Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Revised text:

7. Male or female

Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

7.1.1 Medical Devices

Original text:

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).

Additional descriptive information and instructions for the eMDI 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).

Revised text:

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).

Mobile spirometers (MicroDiary, manusfactured by and purchased from CareFusion) are also being provided by GSK for this study. These devices allow participants to conduct spirometry assessments at home. The MicroDiary has US FDA 510(k) clearance to market (Class II medical device) and European Union CE marking (Class I medical device).

Additional descriptive information and instructions for the eMDI monitoring devices and mobile spirometers 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).

9.2.8 Medical Device Incidents (Including Malfunctions)

Original text:

Medical devices are being provided for use in this study for the purposes of monitoring inhaled rescue medication use. 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.

Revised text:

Medical devices are being provided for use in this study for the purposes of monitoring inhaled rescue medication use and measuring spirometry at home. 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.

12.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Original text:

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.

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.)*

Revised text:

Text deleted.

12.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Original text:

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.

Revised text:

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will not routinely attempt to collect pregnancy information on any male participant's female partner(s) who becomes pregnant while the male participant is participating in this study; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism. This applies only to male participants who receive double-blind study treatment.

- If pregnancy information for a male participant's female partner(s) is voluntarily reported, after obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.

- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK

- Generally, follow-up will be no longer than 6 to 8 weeks following the estimateddelivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Amendment 03

Original text:

Schedule of Activities (only section relevant for the change):

	Screening/ Visit1[a]	**Visit 2**
	up to -28 days	Week 0 / D1
Assessment window		+3d
Eligibility		
Informed Consent	X	
Genetics Informed Consent[b]	X	
Demography	X	
Inclusion and Exclusion Criteria	X	
Smoking Status[c]	X	
Smoking History[c]	X	X

Amended text:

Schedule of Activities (only section relevant for the change):

	Screening/ Visit1[a]	**Visit 2**
	up to -32 days	Week 0 / D1
Assessment window		+3d
Eligibility		
Informed Consent	X	
Genetics Informed Consent[b]	X	
Demography	X	
Inclusion and Exclusion Criteria	X	
Smoking Status[c]	X	X
Smoking History[c]	X	

Original text:

3.1 Study Rationale

This protocol describes a pilot study to investigate the effect of danirixin HBr 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction identified from the COPDGene cohort. 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.

Specifically, this study aims to assess whether or not danirixin has the potential to impact disease progression in participants with a COPD progression score indicating they are likely to decline based on 5 year data from COPDGene and support the conduct of a larger Phase III study for disease progression. In addition to lung function and HRQoL, this study will assess moderate/severe COPD exacerbations, health status (CAT), and rescue medication use.

Amended text:

3.1 Study Rationale

This protocol describes a pilot study to investigate the effect of danirixin HBr 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction identified from the COPDGene cohort. 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.

Specifically, this study aims to assess whether or not danirixin has the potential to impact disease progression in participants with a demonstrated history of decline in FEV_1 based on 5 year data from COPDGene and support the conduct of a larger Phase III study for disease progression. In addition to lung function and HRQoL, this study will assess moderate/severe COPD exacerbations, health status (CAT), and rescue medication use.

Original text (relevant section only):

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary • To assess whether danirixin HBr 35mg tablets impacts disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers

Amended text (relevant section only)

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary • To assess whether danirixin HBr 35mg tablets impacts disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
Secondary • To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers

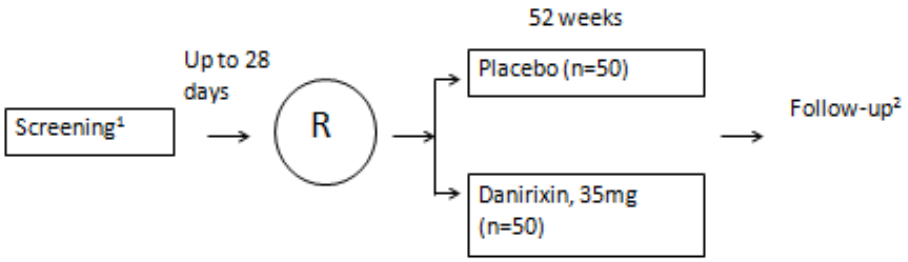
Original text:

5.1 Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -28 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal safety review team will meet approximately every 3 months (or as needed based on emerging data) to review available safety information.

Figure 5 Study Schematic



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

Amended text:

5.1 Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -32 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

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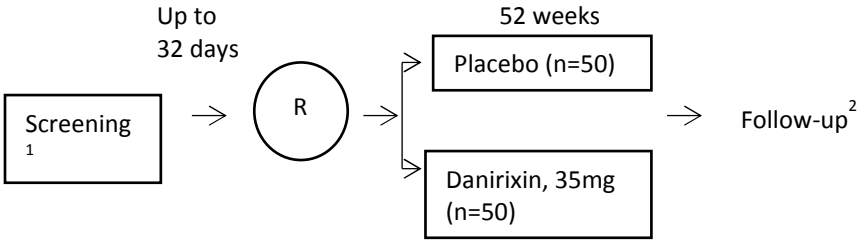
Figure 6 Study Schematic



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit

[2] Follow-up visit to occur within 28days of last dose of study medication

Original text:

6 Study Population

This study will identify specific patients most likely to decline from the well established COPDGene cohort [NCT00608764]. This study will be an ancillary study within COPDGene investigating the enrichment strategy for assessing disease progression. These potential participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period. Once participants are identified from the COPDGene dataset, the following criteria will be verified at initial study visit following signing of consent.

Amended text:

6 Study Population

This study will identify specific COPD patients most likely to decline from well established cohorts like COPDGene [NCT00608764]. This study will be an ancillary study within COPDGene and any other relevant cohort investigating the enrichment strategy for assessing disease progression. These potential participants will be identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a demonstrated decline of at least 15mL/yr over the initial 5 year period. Once participants are identified from the COPDGene dataset, the following criteria will be verified at initial study visit following signing of consent. Equivalent cirteria may be identified within other cohorts if necessary to broaden recruitment pool.

Original text:

Inclusion Criteria

Weight

4. Body weight >45kg

Amended text:

Weight

4, Body Mass Index ≥ 21

Original text:

Exclusion Criteira

Diagnostic assessments

19. 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%).

20. A positive test for HIV antibody.

21. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Amended text:

Exclusion Criteria

19. Alanine transferase (ALT) > 2x upper limit of normal (ULN) and bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

20. A positive test for HIV antibody.

21. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Note:
Participants with positive Hepatitis C antibody due to prior resolved disease can be

Original text:

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 and confirmatory testing with additional FSH and estradiol measurements is required.
- 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.

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 will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Amended text:

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

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

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- 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.

TITLE PAGE

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Protocol Number: 205864 Amendment 2

Short Title: Danirixin Pilot Study for Disease Progression

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

Approval Date: 24-JUL-2017

SPONSOR SIGNATORY:

PPD

24 July 2017

Aili Lazaar, MD PPD
Clinical Development Director
Respiratory Therapy Are Unit

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	24-Jul-2017
Amendment 1	17-May-2017
Original Protocol	21-Mar-2017

Amendment 1: 17-MAY-2017

Overall Rationale for the Amendment: This amendment excludes the enrolment of women of childbearing potential and clarifies the testing required for determination of post menopausal status in specific situations.

Section # and Name	**Description of Change**	**Brief Rationale**
Table 1 – Schedule of Activities	• Remove pregnancy testing • Added missing check marks • Updated screening period	• Not required as no longer enrolling WOCBP • Error in original protocol • Required to allow for screening lab tests
Section 6.1 Inclusion Criteria	Update to only allow females to participate if they are not women of childbearing potential (WOCBP)	To remove additional burden on female subjects of childbearing potential requiring additional visits for pregnancy testing only.
Section 12.2 – Appendix 2 Clinical Laboratory Tests	Update Table 6 – Protocol-Required Safety Laboratory Assessments to remove pregnancy testing	Removed pregnancy testing based on the exclusion of WOCBP
Section 12.5 – Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information	• Adding clarification on determination of post menopausal state in the absence of 12 months of amenorrhea • Updated wording to be in line with exclusion of WOCBP	• Current wording in template is not clear on testing required • Clarification of wording

Amendment 2: 24-JUL-2017

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 3.3.1 Risk Assessment	Removal of the following text from the mitigation strategy of the reproductive toxicology section: "Male participants with female partners of child-bearing potential must comply with the contraception requirements."	Additional data available demonstrating absence of genotoxic effects
Section 7.1.1 and Section 9.2.8 Medical Devices and Medical Device Incidents	Update to add mobile spirometer (MicroDiary) as a medical device	This device is being used in the study and was inadvertently omitted from the previous versions of the protocol
Section 6.1 and Section 12.5 (Appendix 5) Inclusion Criteria and Contraceptive Guidance and Collection of Pregnancy Information	Removal of requirement for male contraception with partners of WOCBP	Additional data available demonstrating absence of genotoxic effects

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Short Title: Danirixin Pilot Study for Disease Progression in COPD

Rationale: This is a pilot study to investigate the effect of danirixin hydrobromide (HBr) 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction and a demonstrated history of decline in FEV_1. This study aims to assess whether danirixin has the potential to impact disease progression in participants with COPD and with a demonstrated history of disease progression measured by lung function.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess whether danirixin HBr 35mg tablets impact disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
Secondary	
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events • Vital Signs • ECG • Clinical Laboratory Assessments (hematology, clinical chemistry, urinalysis)
• To further characterize the clinical activity of danirixin HBr 35mg tablets compared with placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use

Overall Design:

This is a Phase 2 study to investigate the potential impact of danirixin HBr 35mg tablets compared with placebo on disease progression in participants with mild to moderate

airflow obstruction. The study will also assess the enrichment strategy of enrolling participants identified from the COPDGene study. These participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period.

Number of Participants:

Approximately 130 participants will be screened to enrol 100 participants in this study. It is anticipated that approximately 85 participants will complete the 52 weeks of treatment (assuming a 15% drop out rate).

Treatment Groups and Duration:

Participants will receive either placebo or danirixin 35mg tablets (as hydrobromide hemihydrate salt) twice daily for 52 weeks (12months).

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Eligibility														
Informed Consent	X													
Genetics Informed Consent[b]	X													
Demography	X													
Inclusion and Exclusion Criteria	X													
Smoking Status[c]	X													
Smoking History[c]	X	X												
Medical History[d]	X													
Full physical	X													
Chest X-ray (historical within 1 year acceptable)	X													
HIV, Hepatitis B and C screening[e]	X													
Additional Eligibility and In Study Assessments														
Verify Eligibility[f]	X	X												
Brief physical		X				X			X			X	X	
Laboratory assessments (clinical chemistry, including liver chemistries), hematology, urinalysis	X	X		X					X			X	X	
Additional Liver chemistries only			X		X	X	X	X		X	X			
12 lead ECG	X	X		X		X			X			X	X	
Vital Signs	X	X		X		X			X			X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Office spirometry (centralized)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Home spirometry - (weekly)	X	←	—	—	—	—	—	—	—	→		X	X	
Randomization		X												
Dispense study medication		X		X	X	X	X	X	X	X	X			
Dispense log pad and provide training	X													
Dispense MDI sensors and provide training	X													
Study Treatment		←	—	—	—	—	—	—	—	—	→			
Study Treatment Compliance (ediary)		←	—	—	—	—	—	—	—	—	→			
Collect IP				←	—	—	—	—	—	—	→			
Collect MDI sensors												X	X	
Collect log pad												X	X	
AE review		←	—	—	—	—	—	—	—	—	→		X	X
SAE review	←	—	—	—	—	—	—	—	—	—	→		X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Outcomes Assessments														
COPD exacerbation review		X	X	X	X	X	X	X	X	X	X	X	X	
Rescue medication Use	←	—	—	—	—	—	—	—	—	—	—	→		
SGRQ-C		X				X			X	X		X	X	
COPD Assessment Test (CAT)		X				X			X	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	X	X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Genetic, Pharmacokinetic and Biomarker Blood Collections														
Blood sample for Genetics		X												
Blood sample for CRP		X							X			X	X	
Blood sample for exploratory biomarkers		X							X			X	X	

a Informed consent may be signed prior to screening visit in the case that any changes in medications are necessary
b Agreeing to genetic sample consent is not required for study participation
c Smoking status/history assessed at screening; smoking status re-checked at Visit 2
d Includes substance usage, past and present medical conditions and family history of premature CV disease
e 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.
f Participant's clinical status should be reviewed

The timing and number of planned study assessments, including safety and biomarker assessments may be altered during the course of the study based on newly available data to ensure appropriate data collection. Any changes in the timing or addition of time points for any planned study assess 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 Number 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 [GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163]. 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. Analyses 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 pilot study to investigate the effect of danirixin HBr 35mg tablets on lung function and health related quality of life (HRQoL) in participants with

mild to moderate airflow obstruction identified from the COPDGene cohort. 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.

Specifically, this study aims to assess whether or not danirixin has the potential to impact disease progression in participants with a COPD progression score indicating they are likely to decline based on 5 year data from COPDGene and support the conduct of a larger Phase III study for disease progression. In addition to lung function and HRQoL, this study will assess moderate/severe COPD exacerbations, health status (CAT), and rescue medication use.

3.2. Background

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

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

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

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Testicular effects and male fertility	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. PK modelling predicts that in a participant receiving 35 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 participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

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

3.3.2. Benefit Assessment

- 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 or 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 assess whether danirixin HBr 35mg tablets impacts disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers
Secondary • To further characterize the clinical activity of danirixin HBr 35mg tablets compared to placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use
Exploratory	
• To characterize the effect of danirixin on lung matrix destruction/remodelling and inflammation • Further characterize efficacy of danirixin	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes) and inflammation (e.g. CRP) • Global assessment of COPD severity

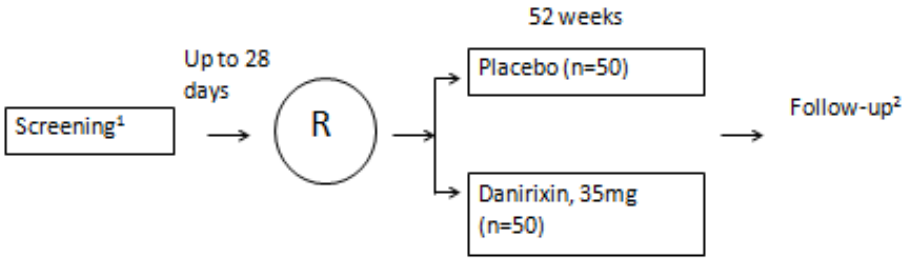
5. STUDY DESIGN

5.1. Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -28 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

5.2. Number of Participants

Approximately 130 participants will be screened to achieve 100 randomized in this study. It is anticipated that approximately 85 participants will complete the 12 months of treatment (assuming a 15% drop out rate).

For the analysis of study assessments, several analysis populations are defined in Section 10.3.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all planned study visits 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. With the use of an enriched population, it is anticipated that one year of treatment will be sufficient to detect a trend in altering disease progression. Danirixin has already been clinically investigated over one year treatment duration (GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163).

The data from this study will provide useful information in determining whether or not to progress to a Phase III study to explore an indication for slowing disease progression.

5.5. Dose Justification

One dose of danirixin is proposed for this study, 35mg tablets BID. This dose was selected based on integrating information on:

- Dose-exposure-biomarker response using inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils over the dose range of 0-400mg (free base tablet) in healthy volunteers (GSK Study No. CX3 112483).

- Evidence of reduced respiratory symptoms and improvement in health status in mild to moderate COPD participants from interim data in the Phase IIa study (GSK Study No. 200163).

- Relative bioavailability study comparing danirixin free base vs HBr (GSK Study No. 201037).

In the previous 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 (GlaxoSmithKline Document Number 2015N248339_00, Study ID 201037). Thus the danirixin (hydrobromide tablet) 35mg BID dose for investigation in this study is expected to provide steady-state systemic exposure approximately equivalent to the 75mg BID (free base tablet) used in Study 200163. 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)			Cavg multiple of IC50*	Cmin multiple of IC50*
	AUC(0-24) steady-state (ug.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4

#Model derived based on PK data in healthy elderly participants from GSK Study No. 201037 (GlaxoSmithKline Document Number. 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.

6. STUDY POPULATION

This study will identify specific patients most likely to decline from the well established COPDGene cohort [NCT00608764]. This study will be an ancillary study within COPDGene investigating the enrichment strategy for assessing disease progression. These potential participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period. Once participants are identified from the COPDGene dataset, the following criteria will be verified at initial study visit following signing of consent.

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 76 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. At the screening visit, the subject must have an FEV1 >40% of the predicted normal.
3. Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD

Weight

4. Body weight ≥ 45 kg

Sex

5. Male or female

   Female participants:

   A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Informed Consent

6. Capable of giving signed informed consent as described in Section 12.3 (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 disease (other than COPD), e.g. sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer
2. COPD due to alpha-1-antitrypsin deficiency
3. Pulse oximetry < 88% at rest at screening. Participants should be tested while breathing room air. However, participants living at high altitudes (above 5000 ft or 1500 m above sea level) who are receiving supplemental oxygen can be included provided they are receiving the equivalent of < 4L/min and screening oximetry is measured while on their usual settings.
4. Less than 14 days have elapsed from completion of a course of antibiotics or oral corticosteroids for a recent COPD exacerbation
5. Participants with a peripheral blood neutrophil count < 1 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 with lateral) or CT scan reveals evidence of a clinically significant abnormality not believed to be due to the presence of COPD (historic data up to 1 year may be used).
8. History or current evidence of clinically significant renal disease, diabetes mellitus/metabolic syndrome, hypertension, or any other clinically significant cardiovascular, neurological, immunological, endocrine, or haematological abnormality 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 participants

at risk through study participation, or which would affect the safety analysis or other analysis if the disease/condition exacerbated during the study.

9. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator of GSK medical monitor, contraindicates their participation.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude participants who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
    - AF with rapid ventricular rate > 120 bpm;
    - sustained or non-sustained VT
    - second degree heat block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
    - QTcF ≥ 500 msec in patients with QRS < 120 msec and QTcF ≥ 530 msec in patients with QRS ≥ 120 msec
12. Previous lung surgery (e.g. lobectomy, pneumonectomy) or lung volume reduction procedure.

Prior/Concomitant Therapy

13. 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.
14. 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.
15. 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

16. 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).

17. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study
18. Exposure to more than four investigational products within 1 year prior to the first dosing day in the current study.

Diagnostic assessments

19. 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%).
20. A positive test for HIV antibody.
21. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Other Exclusions

22. 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.
23. A history of allergy or hypersensitivity to any of the ingredients in the study treatment.
24. A known or suspected history of alcohol or drug abuse within the 2 years prior to screening.
25. 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.
26. 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 not be rescreened unless discussed with the medical monitor.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Placebo
Dosage formulation:	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients
Unit dose strength(s)/Dosage level(s):	35mg tablets (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).

Mobile spirometers (MicroDiary, manufactured by and purchased from CareFusion) are also being provided by GSK for this study. These devices allow participants to conduct spirometry assessments at home. The MicroDiary has US FDA 510(k) clearance to market (Class II medical device) and European Union CE marking (Class I medical device).

Additional descriptive information and instructions for the eMDI monitoring devices and mobile spirometers 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 study. Study participants, all study site staff, and all members of the GSK study team will be blinded to individual participant treatment assignment.

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.

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) bronchodilators, (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.

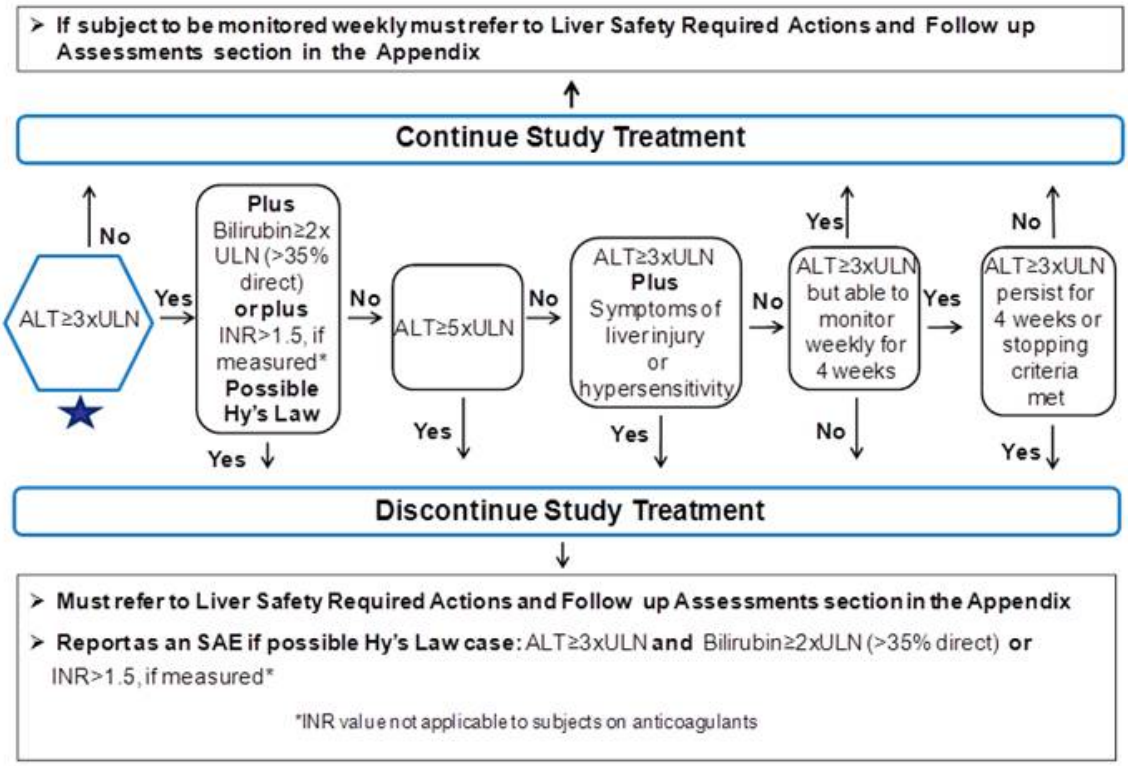
8. DISCONTINUATION CRITERIA

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: Liver Safety: Required Actions and Follow-up Assessments).

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 (Section 12.7) 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. FEV_1

9.1.1.1. Clinic Spirometry

Spirometry using FEV_1 and FVC measurements (FEV%, and FVC% and FEV1/FVC will be calculated) will be performed in triplicate at time points listed in the SoA (Table 1). Spirometry assessments should be performed in accordance with ATS/ERS guidelines as outlined in the SRM.

9.1.1.2. Mobile Spirometry

Spirometry will also be performed weekly by the participants using a mobile spirometer at home. Details will be outlined in the SRM.

9.1.2. 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 SGRQ scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.3. 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.

9.1.4. COPD Exacerbations

An exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment or hospitalization.

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 based on the Investigator's judgement.

9.1.5. 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 final study visit or IP Discontinuation Visit. This single global question will ask participants 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 every visit following randomization (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.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4 (Section 12.4).

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 the time the informed consent is signed by the participant until the follow up visit at the time points specified in the SoA (Table 1).
- All AEs will be collected from the start of study treatment (randomization visit) until the follow-up visit at the time points specified in the SoA (Table 1).
- 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 must be reported immediately and not more than 24 hrs to the sponsor, as indicated in Appendix 4 (Section 12.4). 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 (Section 12.4).

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as

defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information 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 Section 12.4 (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.

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 Section 12.3 (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 Section 12.5 (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 measuring spirometry at home. 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 Section 12.8 (Appendix 8).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Section 12.4 (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 Section 12.8 (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 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.

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, 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 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 measurements 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 10 minutes.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Section 12.2 (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 Section 12.2, 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

Pharmacokinetic parameters are not evaluated in this study.

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 Section 12.6 (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), 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

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

10. STATISTICAL CONSIDERATIONS

The objective of this study is to investigate the effect of danirixin HBr 35mg tablets on COPD disease progression. There are no formal hypothesis tests associated with this objective and no formal significance tests. The information acquired from this study will primarily be used to assess whether or not danirixin impacts disease progression and to quantify the effect that danirixin has on disease progression, specifically change in lung function as measured by FEV_1 decline and change in health-related quality of life as measured by SGRQ total score to further support disease understanding and future studies.

10.1. Sample Size Determination

Sample size is based primarily on feasibility for this study. Since there is much uncertainty around the magnitude of the difference in the decline in FEV_1 and change in SGRQ along with the between-subject variability for the specific patient population, the proposed sample size is unavoidably imprecise. Sample size may be adjusted using the predictions of final study outcome based on simulations and possible interim analyses. It is anticipated that screening 130 participants will allow for approximately 100 participants to enrol.

In order to observe the effect of different sample sizes, various simulations were done to assess the impact of sample sizes of 50, 100, 150 and 200 with a 1:1 allocation to each treatment group [Table 3]. The assumed variability for rate of decline in FEV_1 and change in SGRQ is 25 and 10, respectively. The correlation between rate of decline in FEV1 and change in SGRQ is assumed to be -0.2. [Nagai, 2015]

Table 3 Assumptions used for the Simulations

	Treatment Effect Assumptions (δ_{FEV1}, δ_{SGRQ})	Variability Assumptions (σ_{FEV1}, σ_{SGRQ})	Sample Size
Null	(0,0)	(25,10)	N={50,100,150,200}
Alternate 1	(5,-1)	(25,10)	N={50,100,150,200}
Alternate 2	(5,0)	(25,10)	N={50,100,150,200}
Alternate 3	(0,-1)	(25,10)	N={50,100,150,200}

Data from a bivariate normal distribution were simulated under the four different treatment effect assumptions for samples sizes of 50, 100, 150, and 200. The samples from the posterior probability distribution from the MCMC approximation were divided into four regions based on δ_{FEV1} and δ_{SGRQ} treatment effect cut-off values; $\delta_{FEV1} \geq 0$ and $\delta_{SGRQ} \leq 0$, $\delta_{FEV1} \geq 0$ and $\delta_{SGRQ} > 0$, $\delta_{FEV1} < 0$ and $\delta_{SGRQ} \leq 0$, and $\delta_{FEV1} < 0$ and $\delta_{SGRQ} > 0$. Based on a 70% threshold, the proportion of the 1000 simulations meeting the requirement $P(\delta_{FEV1} \geq 0 \ \& \ \delta_{SGRQ} \leq 0) \geq 70\%$ were considered a success based on the joint definition

[Figure 2, Table 4]. If $P(\delta_{FEV1} \geq 0 \ \& \ \delta_{SGRQ} \leq 0) < 70\%$, success could further be defined based on each endpoint independently where $P(\delta_{FEV1} \geq 0) \geq 80\%$ or $P(\delta_{SGRQ} \leq 0) \geq 80\%$.

Figure 2 Total Probability of Success

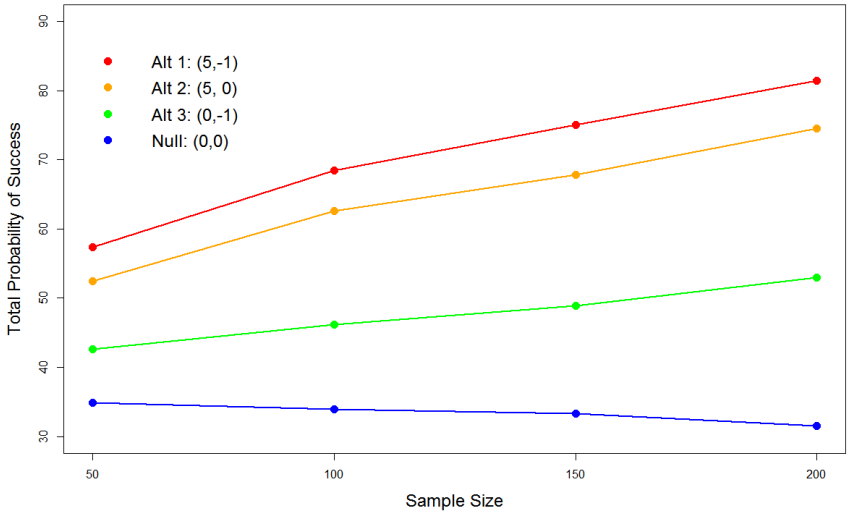


Table 4 Total Probability of Success (Figure 2)

	N=50	N=100	N=150	N=200
(5,-1)	57.4	68.5	75.1	81.4
(5,0)	52.5	62.6	67.8	74.5
(0,-1)	42.6	46.2	48.9	53.0
(0,0)	34.9	33.9	33.3	31.5

Figure 3 Half Width of the 95% Confidence Interval of δFEV$_1$ Point Estimate

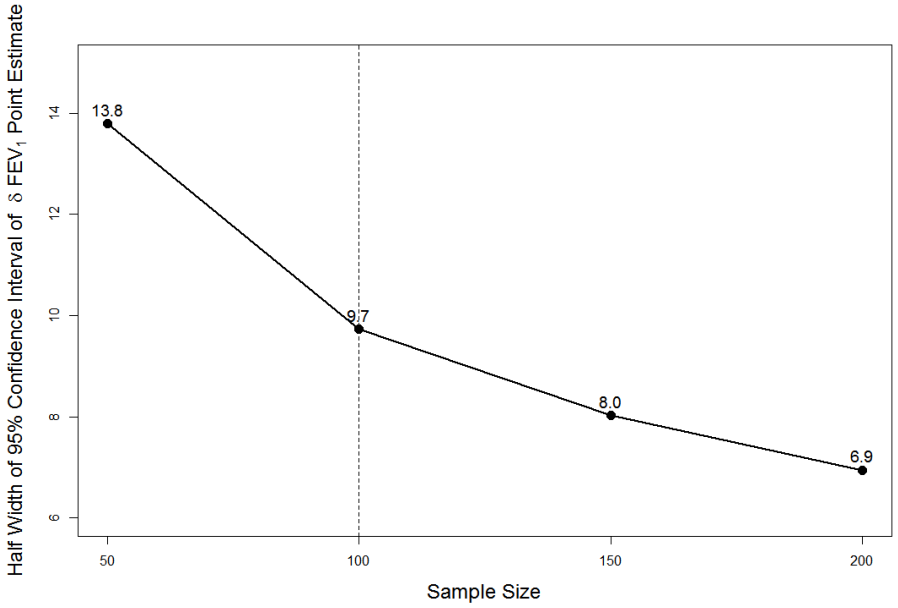
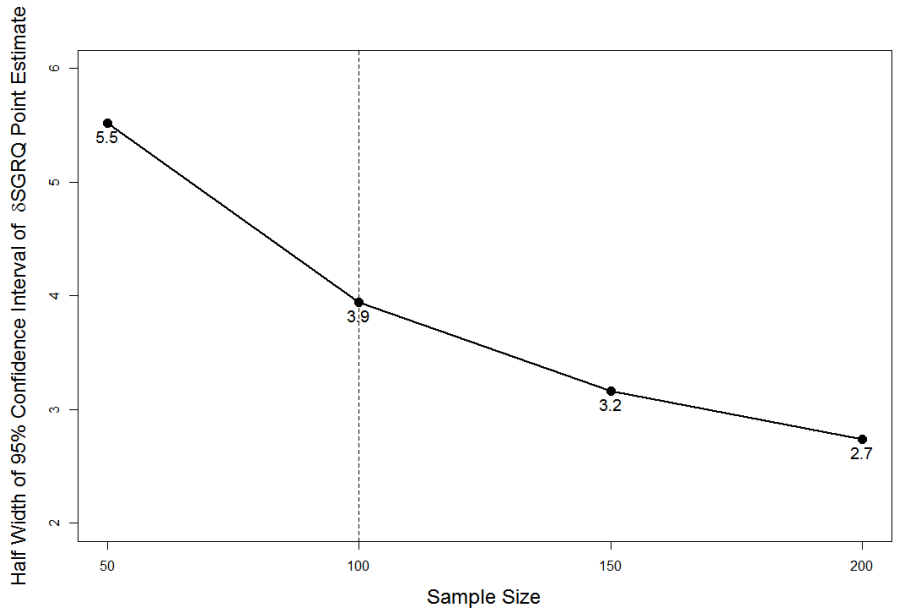


Figure 4 Half Width of the 95% Confidence Interval of δSGRQ Point Estimate



Based on the simulations, under the assumption of an expected treatment difference of (5,-1) which is the most probable scenario, the marginal increase for the total probability of success is greatest when increasing the sample size from 50 to 100 (Figure 2). The half widths of the 95% CI of the point estimate of the marginal treatment differences for FEV$_1$ (Figure 3) and SGRQ (Figure 4) have the greatest reduction from a sample size of 50 to 100. A sample size of 100 will allow for an adequate level of confidence in the study success while also considering the precision of the treatment effect differences.

10.2. Randomization

Participants will be randomized equally (1:1) to the two treatment arms of placebo and 35 mg danirixin HBr. Randomization will be stratified by smoking status (current vs. former).

10.3. 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.
Per-Protocol (PP) Population	This population will comprise of all patients in the ITT population who are not major protocol violators.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.4. Statistical Analyses

Treatment comparisons using all endpoints will be made using appropriate statistical techniques. Analysis methods for key endpoints are described below. Main analysis will use ITT unless noted. Further details on all analyses will be described in the reporting and analysis plan (RAP).

10.4.1. Efficacy Analyses

The total probability of success will be defined as a combination of a joint and conditional statement. The joint probability of success will be defined as the probability of the difference in the rate of decline in FEV_1 between danirixin and placebo is greater than or equal to 0 and the difference in the change in SGRQ total score from baseline between danirixin and placebo is less than or equal to 0 is greater than 70%. If the joint probability of success is less than 70%, success can further be defined based on each endpoint independently, where either the difference in the rate of decline in FEV_1 is

greater than or equal to 0 is greater than 80% or the difference in the change in SGRQ total score is less than or equal to 0 is greater than 80%.

$$Total\ PoS = P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) \geq 70\%$$

$$+\ P\left(\delta_{FEV_1} \geq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

$$+P\left(\delta_{SGRQ} \leq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

Endpoint	Statistical Analysis Methods
Primary	Rate of decline in FEV_1 and change from baseline in SGRQ total score
Exploratory	Will be described in detail in the RAP

Lung Function Decline: Rate of Decline of FEV_1 (mL/yr)

The rate of decline of FEV_1 will be derived from a repeated measures random coefficients model. Post-baseline FEV_1 will be modelled including terms for age, sex, smoking status, FEV_1 at baseline, and BMI along with treatment group, time and treatment by time interaction as fixed effects. Subject will be a random effect. Time will be defined as the number of days since start of treatment. Only FEV_1 values measured after baseline will be used in the model. Based on the results of previous studies, the study team will determine the time point at which post-baseline spirometry assessments will be included in the model to account for the initial treatment response. The estimate of the rate of FEV_1 decline will be the slope of the parameter estimate of the treatment by time interaction term in the model. Contrasts will be calculated for the difference in treatment by time interaction between danirixin and placebo treatment groups to estimate the treatment difference.

FEV_1 = Treatment group + age + sex +smoking status+FEV1_BL+BMI+ time + treatment*time

The rate of decline for each subject, the estimate of the slope parameter of the treatment by time interaction term, will be used as a co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

HRQoL: SGRQ

A co-primary endpoint of interest is change in SGRQ total score (derived from SGRQ-C) from baseline. Change in SGRQ total scores from baseline will be derived using a mixed model with repeated measures (MMRM) including fixed effects of treatment group, age, sex, smoking status, BMI, baseline SGRQ score, time as a categorical variable and a treatment by time interaction term. Subject will be a random effect. Estimated treatment differences at the end of one year will be obtained. The difference of the least square mean change from baseline at 12 months will be derived. The adjusted SGRQ total score

change from baseline will used as the other co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

Joint Analysis
The joint analysis will use the ITT population with all available FEV_1 rate of decline and change in SGRQ data.

The rate of decline (the slope parameter from the random coefficients model) of FEV_1, along with the change in SGRQ from the MMRM model will be extracted for each subject. These values will then be used to obtain MCMC approximations of the joint posterior distribution of the treatment differences between FEV_1 decline and change in SGRQ between the danirixin and placebo groups. Based on the samples from the posterior distribution, the proportion of samples falling within certain treatment difference regions will be calculated and the probability of success will be derived.

10.4.2. 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.

10.4.3. Other Analyses

Exploratory biomarker analyses will be described in the RAP.

10.4.4. Interim Analyses

Conducting an interim analysis or futility assessment may not be practical due to an expected fast recruitment period. By the time enough data will accumulate for any meaningful interim analysis to support changes to the study design, recruitment of all study participants will have concluded. However, if recruitment takes a longer than anticipated, an interim analysis to reassess the variability assumptions, estimate the probability of success at the end of study, and confirm the directionality of the endpoints may be conducted.

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

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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
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
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
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-C 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
CAT

Trademarks not owned by the GlaxoSmithKline group of companies
Combivent
Duoneb

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 • pH, glucose, protein, blood, ketones by dipstick			

Laboratory Assessments	Parameters
	• Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[2] • All study-required laboratory assessments will be performed by a central laboratory

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

Data Protection

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

Committees Structure

- A study charter will be created to describe important governance aspects while the study is being conducted.

- 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 participant's last visit.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

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

Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions.

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

Is a congenital anomaly/birth defect

Other situations:

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

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

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 sufficient 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 (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- 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.
- 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 and confirmatory testing with additional FSH and estradiol measurements is required.
- 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.

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 will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

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

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek

this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will 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 will 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 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 will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to danirixin 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 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).

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

No country specific requirements

12.11. Appendix 11 Protocol Amendment History

Amendment 1

Table 1 Schedule of activities

Original text:

	Screening/ Visit1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -7 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Urine or serum Pregnancy test[g]	X											X	X	
HIV, Hepatitis B and C screeninge														
AE review		←										→		
SAE review		←										→		

Revised text:

	Screening/ Visit1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
HIV, Hepatitis B and C screeninge	X													
AE review		←										→	X	X

SAE review	◄——————►	X	X

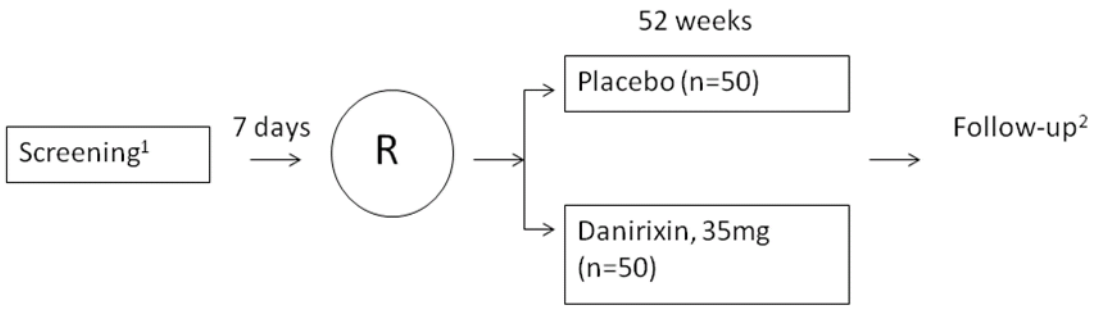
Section 5.1 Overall Design

Original text:

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -7 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

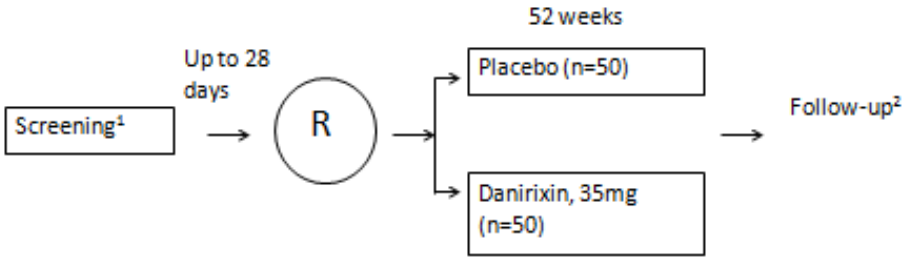
Amended text:

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -28 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

Section 6.1 Inclusion Criteria

Original text:

2 Male or female

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.

Female participants:

A female participant is eligible to participate if she is not pregnant (see Section 12.5; Appendix 5), not breastfeeding, and at least one of the following conditions applies:

i. Not a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Section 12.5 (Appendix 5) during the treatment period and for at least 60 hours after the last dose of study treatment.

Revised text:

3 Male or female

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.

Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Section 12.2 Appendix 2:

Original text:

Table 7 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	Calcium	Alkaline	

Laboratory Assessments	**Parameters**			
	required for screening)		phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • 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

Amended text:

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC	<u>WBC count with Differential</u>: 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 • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[2] • All study-required laboratory assessments will be performed by a central laboratory			

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. 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

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

Original text:

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 9 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.)*

Amended text:

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 and confirmatory testing with additional FSH and estradiol measurements is required.
    - 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.

Table 10 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.)*

Amendment 2

Original text:

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	Standard safety monitoring will be employed. The potential risk of testicular injury has been conveyed in the informed consent. PK modelling predicts that in a participant receiving 35 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**
	No adverse events related to testicular effects have been observed in clinical studies to date.	
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	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**
	in nonclinical studies with danirixin. In healthy volunteer studies and a phase 2a study in patients with Influenza (GSK Study 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

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

Amended text:

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	Standard safety monitoring will be employed. The potential risk of testicular injury has been conveyed in the informed consent. PK modelling predicts that in a participant receiving 35 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**
	studies to date.	
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	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**
	study in patients with Influenza (GSK Study 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

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

Section 6.1 Inclusion Criteria

Original text:

Sex

4. Male or female

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.

Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Revised text:

5. Male or female

Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

7.1.1 Medical Devices

Original text:

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).

Additional descriptive information and instructions for the eMDI 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).

Revised text:

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).

Mobile spirometers (MicroDiary, manusfactured by and purchased from CareFusion) are also being provided by GSK for this study. These devices allow participants to conduct spirometry assessments at home. The MicroDiary has US FDA 510(k) clearance to market (Class II medical device) and European Union CE marking (Class I medical device).

Additional descriptive information and instructions for the eMDI monitoring devices and mobile spirometers 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).

9.2.8 Medical Device Incidents (Including Malfunctions)

Original text:

Medical devices are being provided for use in this study for the purposes of monitoring inhaled rescue medication use. 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.

Revised text:

Medical devices are being provided for use in this study for the purposes of monitoring inhaled rescue medication use and measuring spirometry at home. 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.

12.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Original text:

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.

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.)*

Revised text:

Text deleted.

12.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Original text:

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.

Revised text:

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will not routinely attempt to collect pregnancy information on any male participant's female partner(s) who becomes pregnant while the male participant is participating in this study; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism. This applies only to male participants who receive double-blind study treatment.

- If pregnancy information for a male participant's female partner(s) is voluntarily reported, after obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.

- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK

- Generally, follow-up will be no longer than 6 to 8 weeks following the estimateddelivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

TITLE PAGE

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluation the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Protocol Number: 205864 Amendment 1

Short Title: Danirixin Pilot Study for Disease Progression

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

Approval Date: 17-MAY-2017

SPONSOR SIGNATORY:

PPD

17-May-2017

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

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	17-May-2017
Original Protocol	21-Mar-2017

Amendment 1 17-May-2017

Overall Rationale for the Amendment: This amendment excludes the enrolment of women of childbearing potential and clarifies the testing required for determination of post menopausal status in specific situations.

Section # and Name	Description of Change	Brief Rationale
Table 1 – Schedule of Activities	• Remove pregnancy testing • Added missing check marks • Updated screening period	• Not required as no longer enrolling WOCBP • Error in original protocol • Required to allow for screening lab tests
Section 6.1 Inclusion Criteria	Update to only allow females to participate if they are not women of childbearing potential (WOCBP)	To remove additional burden on female subjects of childbearing potential requiring additional visits for pregnancy testing only.
Section 12.2 – Appendix 2 Clinical Laboratory Tests	Update Table 6 – Protocol-Required Safety Laboratory Assessments to remove pregnancy testing	Removed pregnancy testing based on the exclusion of WOCBP
Section 12.5 – Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information	• Adding clarification on determination of post menopausal state in the absence of 12 months of amenorrhea • Updated wording to be in line with exclusion of WOCBP	• Current wording in template is not clear on testing required • Clarification of wording

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Short Title: Danirixin Pilot Study for Disease Progression in COPD

Rationale: This is a pilot study to investigate the effect of danirixin hydrobromide (HBr) 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction and a demonstrated history of decline in FEV_1. This study aims to assess whether danirixin has the potential to impact disease progression in participants with COPD and with a demonstrated history of disease progression measured by lung function.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess whether danirixin HBr 35mg tablets impact disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
Secondary	
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events • Vital Signs • ECG • Clinical Laboratory Assessments (hematology, clinical chemistry, urinalysis)
• To further characterize the clinical activity of danirixin HBr 35mg tablets compared with placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use

Overall Design:

This is a Phase 2 study to investigate the potential impact of danirixin HBr 35mg tablets compared with placebo on disease progression in participants with mild to moderate

airflow obstruction. The study will also assess the enrichment strategy of enrolling participants identified from the COPDGene study. These participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period.

Number of Participants:

Approximately 130 participants will be screened to enrol 100 participants in this study. It is anticipated that approximately 85 participants will complete the 52 weeks of treatment (assuming a 15% drop out rate).

Treatment Groups and Duration:

Participants will receive either placebo or danirixin 35mg tablets (as hydrobromide hemihydrate salt) twice daily for 52 weeks (12months).

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Eligibility														
Informed Consent	X													
Genetics Informed Consent[b]	X													
Demography	X													
Inclusion and Exclusion Criteria	X													
Smoking Status[c]	X													
Smoking History[c]	X	X												
Medical History[d]	X													
Full physical	X													
Chest X-ray (historical within 1 year acceptable)	X													
HIV, Hepatitis B and C screening[e]	X													
Additional Eligibility and In Study Assessments														
Verify Eligibility[f]	X	X												
Brief physical		X				X			X			X	X	
Laboratory assessments (clinical chemistry, including liver chemistries), hematology, urinalysis	X	X		X					X			X	X	
Additional Liver chemistries only			X		X	X	X	X		X	X			
12 lead ECG	X	X		X		X			X			X	X	
Vital Signs	X	X		X		X			X			X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Office spirometry (centralized)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Home spirometry - (weekly)	X	←	—	—	—	—	—	—	—	→		X	X	
Randomization		X												
Dispense study medication		X		X	X	X	X	X	X	X	X			
Dispense log pad and provide training	X													
Dispense MDI sensors and provide training	X													
Study Treatment		←	—	—	—	—	—	—	—	—	→			
Study Treatment Compliance (ediary)		←	—	—	—	—	—	—	—	—	→			
Collect IP				←	—	—	—	—	—	—	→			
Collect MDI sensors												X	X	
Collect log pad												X	X	
AE review		←	—	—	—	—	—	—	—	—	→		X	X
SAE review	←	—	—	—	—	—	—	—	—	—	→		X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Outcomes Assessments														
COPD exacerbation review		X	X	X	X	X	X	X	X	X	X	X	X	
Rescue medication Use	←	—	—	—	—	—	—	—	—	—	—	→		
SGRQ-C		X				X			X	X		X	X	
COPD Assessment Test (CAT)		X				X			X	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	X	X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Genetic, Pharmacokinetic and Biomarker Blood Collections														
Blood sample for Genetics		X												
Blood sample for CRP		X							X			X	X	
Blood sample for exploratory biomarkers		X							X			X	X	

a Informed consent may be signed prior to screening visit in the case that any changes in medications are necessary
b Agreeing to genetic sample consent is not required for study participation
c Smoking status/history assessed at screening; smoking status re-checked at Visit 2
d Includes substance usage, past and present medical conditions and family history of premature CV disease
e 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.
f Participant's clinical status should be reviewed

The timing and number of planned study assessments, including safety and biomarker assessments may be altered during the course of the study based on newly available data to ensure appropriate data collection. Any changes in the timing or addition of time points for any planned study assess 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 Number 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 [GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163]. 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. Analyses 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 pilot study to investigate the effect of danirixin HBr 35mg tablets on lung function and health related quality of life (HRQoL) in participants with

mild to moderate airflow obstruction identified from the COPDGene cohort. 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.

Specifically, this study aims to assess whether or not danirixin has the potential to impact disease progression in participants with a COPD progression score indicating they are likely to decline based on 5 year data from COPDGene and support the conduct of a larger Phase III study for disease progression. In addition to lung function and HRQoL, this study will assess moderate/severe COPD exacerbations, health status (CAT), and rescue medication use.

3.2. Background

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

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

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

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Testicular effects and male fertility	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. PK modelling predicts that in a participant receiving 35 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 participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Reproductive toxicology (Embryofetal development)	In a rat embryofetal development study, an oral dose of 300 mg/kg/day resulted in fetal skeletal variations in the skull (reductions in ossification). There were no test article-related effects on numbers of corpora lutea, implantations, embryofetal survival, placental morphology, gravid uterine weight, sex ratio, fetal body weight, or fetal morphology (external and visceral).	As danirixin HBr has shown the potential to cause fetal malformations, danirixin or danirixin HBr must not be administered to pregnant women or nursing mothers. Women of childbearing potential should only be included in clinical trials with the use of appropriate precautions against pregnancy. 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 or 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 assess whether danirixin HBr 35mg tablets impacts disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers
Secondary • To further characterize the clinical activity of danirixin HBr 35mg tablets compared to placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use
Exploratory	
• To characterize the effect of danirixin on lung matrix destruction/remodelling and inflammation • Further characterize efficacy of danirixin	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes) and inflammation (e.g. CRP) • Global assessment of COPD severity

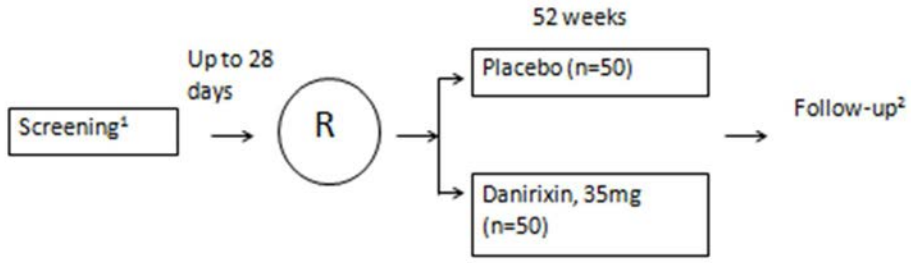
5. STUDY DESIGN

5.1. Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -28 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

5.2. Number of Participants

Approximately 130 participants will be screened to achieve 100 randomized in this study. It is anticipated that approximately 85 participants will complete the 12 months of treatment (assuming a 15% drop out rate).

For the analysis of study assessments, several analysis populations are defined in Section 10.3.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all planned study visits 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. With the use of an enriched population, it is anticipated that one year of treatment will be sufficient to detect a trend in altering disease progression. Danirixin has already been clinically investigated over one year treatment duration (GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163).

The data from this study will provide useful information in determining whether or not to progress to a Phase III study to explore an indication for slowing disease progression.

5.5. Dose Justification

One dose of danirixin is proposed for this study, 35mg tablets BID. This dose was selected based on integrating information on:

- Dose-exposure-biomarker response using inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils over the dose range of 0-400mg (free base tablet) in healthy volunteers (GSK Study No. CX3 112483).

- Evidence of reduced respiratory symptoms and improvement in health status in mild to moderate COPD participants from interim data in the Phase IIa study (GSK Study No. 200163).

- Relative bioavailability study comparing danirixin free base vs HBr (GSK Study No. 201037).

In the previous 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 (GlaxoSmithKline Document Number 2015N248339_00, Study ID 201037). Thus the danirixin (hydrobromide tablet) 35mg BID dose for investigation in this study is expected to provide steady-state systemic exposure approximately equivalent to the 75mg BID (free base tablet) used in Study 200163. 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)			Cavg multiple of IC50*	Cmin multiple of IC50*
	AUC(0-24) steady-state (ug.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4

#Model derived based on PK data in healthy elderly participants from GSK Study No. 201037 (GlaxoSmithKline Document Number. 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.

6. STUDY POPULATION

This study will identify specific patients most likely to decline from the well established COPDGene cohort [NCT00608764]. This study will be an ancillary study within COPDGene investigating the enrichment strategy for assessing disease progression. These potential participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period. Once participants are identified from the COPDGene dataset, the following criteria will be verified at initial study visit following signing of consent.

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 76 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. At the screening visit, the subject must have an FEV1 >40% of the predicted normal.
3. Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD

Weight

4. Body weight ≥ 45 kg

Sex

5. 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** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Informed Consent

6. Capable of giving signed informed consent as described in Section 12.3 (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 disease (other than COPD), e.g. sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer
2. COPD due to alpha-1-antitrypsin deficiency
3. Pulse oximetry < 88% at rest at screening. Participants should be tested while breathing room air. However, participants living at high altitudes (above 5000 ft or 1500 m above sea level) who are receiving supplemental oxygen can be included provided they are receiving the equivalent of < 4L/min and screening oximetry is measured while on their usual settings.
4. Less than 14 days have elapsed from completion of a course of antibiotics or oral corticosteroids for a recent COPD exacerbation
5. Participants with a peripheral blood neutrophil count < 1 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 with lateral) or CT scan reveals evidence of a clinically significant abnormality not believed to be due to the presence of COPD (historic data up to 1 year may be used).

8. History or current evidence of clinically significant renal disease, diabetes mellitus/metabolic syndrome, hypertension, or any other clinically significant cardiovascular, neurological, immunological, endocrine, or haematological abnormality 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 participants at risk through study participation, or which would affect the safety analysis or other analysis if the disease/condition exacerbated during the study.
9. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator of GSK medical monitor, contraindicates their participation.
10. Current of chronic history of liver disease, or know hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude participants who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
    - AF with rapid ventricular rate > 120 bpm;
    - sustained or non-sustained VT
    - second degree heat block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
    - QTcF ≥ 500 msec in patients with QRS < 120 msec and QTcF ≥ 530 msec in patients with QRS ≥ 120 msec
12. Previous lung surgery (e.g. lobectomy, pneumonectomy) or lung volume reduction procedure.

Prior/Concomitant Therapy

13. 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.

14. 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.

15. 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

16. 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).
17. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study
18. Exposure to more than four investigational products within 1 year prior to the first dosing day in the current study.

Diagnostic assessments

19. 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%).
20. A positive test for HIV antibody.
21. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Other Exclusions

22. 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.
23. A history of allergy or hypersensitivity to any of the ingredients in the study treatment.
24. A known or suspected history of alcohol or drug abuse within the 2 years prior to screening.
25. 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.
26. 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 not be rescreened unless discussed with the medical monitor.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Placebo
Dosage formulation:	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients
Unit dose strength(s)/Dosage level(s):	35mg tablets (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).

Additional descriptive information and instructions for the eMDI 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 study. Study participants, all study site staff, and all members of the GSK study team will be blinded to individual participant treatment assignment.

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.

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) bronchodilators, (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.

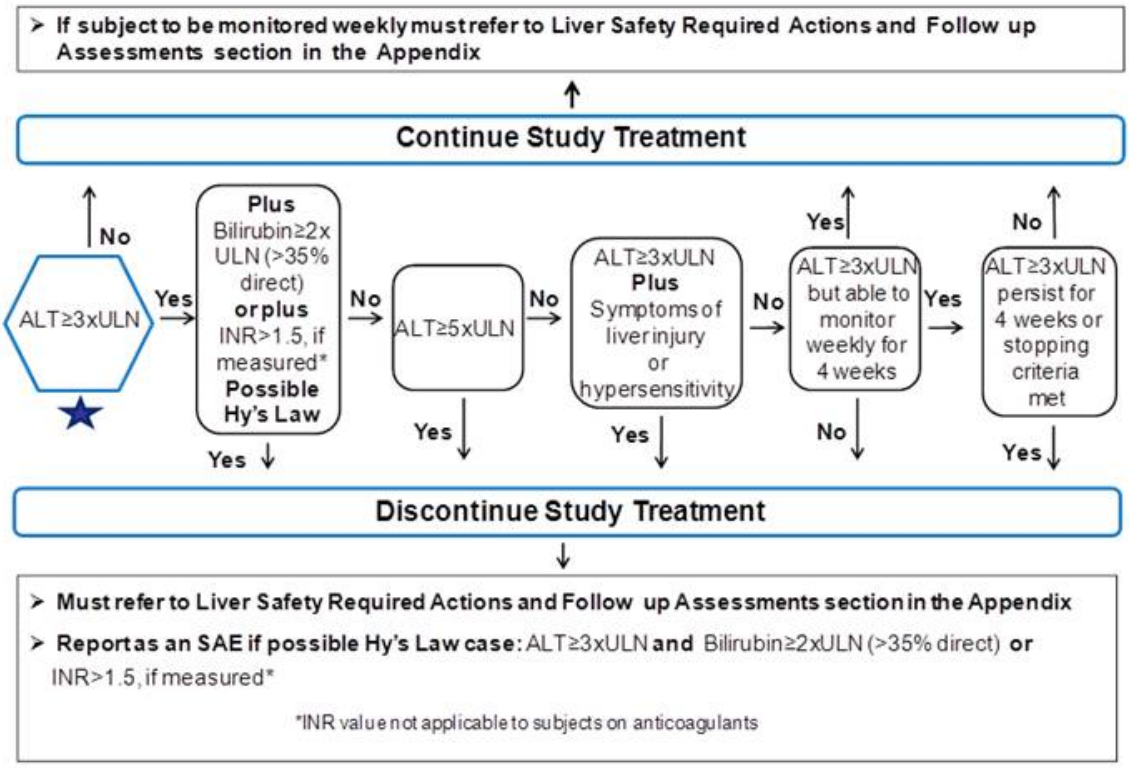
8. DISCONTINUATION CRITERIA

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: Liver Safety: Required Actions and Follow-up Assessments).

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 (Section 12.7) 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. FEV_1

9.1.1.1. Clinic Spirometry

Spirometry using FEV_1 and FVC measurements (FEV%, and FVC% and FEV1/FVC will be calculated) will be performed in triplicate at time points listed in the SoA (Table 1). Spirometry assessments should be performed in accordance with ATS/ERS guidelines as outlined in the SRM.

9.1.1.2. Mobile Spirometry

Spirometry will also be performed weekly by the participants using a mobile spirometer at home. Details will be outlined in the SRM.

9.1.2. 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 SGRQ scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.3. 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.

9.1.4. COPD Exacerbations

An exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment or hospitalization.

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 based on the Investigator's judgement.

9.1.5. 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 final study visit or IP Discontinuation Visit. This single global question will ask participants 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 every visit following randomization (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.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4 (Section 12.4).

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 the time the informed consent is signed by the participant until the follow up visit at the time points specified in the SoA (Table 1).
- All AEs will be collected from the start of study treatment (randomization visit) until the follow-up visit at the time points specified in the SoA (Table 1).
- 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 must be reported immediately and not more than 24 hrs to the sponsor, as indicated in Appendix 4 (Section 12.4). 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 (Section 12.4).

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is

resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information 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 Section 12.4 (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.

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 Section 12.3 (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 Section 12.5 (Appendix 5).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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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. 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 Section 12.8 (Appendix 8).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Section 12.4 (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 Section 12.8 (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 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.

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, 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 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 measurements 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 10 minutes.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Section 12.2 (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 Section 12.2, 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

Pharmacokinetic parameters are not evaluated in this study.

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 Section 12.6 (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), 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

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

10. STATISTICAL CONSIDERATIONS

The objective of this study is to investigate the effect of danirixin HBr 35mg tablets on COPD disease progression. There are no formal hypothesis tests associated with this objective and no formal significance tests. The information acquired from this study will primarily be used to assess whether or not danirixin impacts disease progression and to quantify the effect that danirixin has on disease progression, specifically change in lung function as measured by FEV_1 decline and change in health-related quality of life as measured by SGRQ total score to further support disease understanding and future studies.

10.1. Sample Size Determination

Sample size is based primarily on feasibility for this study. Since there is much uncertainty around the magnitude of the difference in the decline in FEV_1 and change in SGRQ along with the between-subject variability for the specific patient population, the proposed sample size is unavoidably imprecise. Sample size may be adjusted using the predictions of final study outcome based on simulations and possible interim analyses. It is anticipated that screening 130 participants will allow for approximately 100 participants to enrol.

In order to observe the effect of different sample sizes, various simulations were done to assess the impact of sample sizes of 50, 100, 150 and 200 with a 1:1 allocation to each treatment group [Table 3]. The assumed variability for rate of decline in FEV_1 and change in SGRQ is 25 and 10, respectively. The correlation between rate of decline in FEV1 and change in SGRQ is assumed to be -0.2. [Nagai, 2015]

Table 3 Assumptions used for the Simulations

	Treatment Effect Assumptions (δ_{FEV1}, δ_{SGRQ})	Variability Assumptions (σ_{FEV1}, σ_{SGRQ})	Sample Size
Null	(0,0)	(25,10)	N={50,100,150,200}
Alternate 1	(5,-1)	(25,10)	N={50,100,150,200}
Alternate 2	(5,0)	(25,10)	N={50,100,150,200}
Alternate 3	(0,-1)	(25,10)	N={50,100,150,200}

Data from a bivariate normal distribution were simulated under the four different treatment effect assumptions for samples sizes of 50, 100, 150, and 200. The samples from the posterior probability distribution from the MCMC approximation were divided into four regions based on δ_{FEV1} and δ_{SGRQ} treatment effect cut-off values; $\delta_{FEV1} \geq 0$ and $\delta_{SGRQ} \leq 0$, $\delta_{FEV1} \geq 0$ and $\delta_{SGRQ} > 0$, $\delta_{FEV1} < 0$ and $\delta_{SGRQ} \leq 0$, and $\delta_{FEV1} < 0$ and $\delta_{SGRQ} > 0$. Based on a 70% threshold, the proportion of the 1000 simulations meeting the requirement $P(\delta_{FEV1} \geq 0 \ \& \ \delta_{SGRQ} \leq 0) \geq 70\%$ were considered a success based on the joint definition [Figure 2, Table 4]. If $P(\delta_{FEV1} \geq 0 \ \& \ \delta_{SGRQ} \leq 0) < 70\%$, success could further be defined based on each endpoint independently where $P(\delta_{FEV1} \geq 0) \geq 80\%$ or $P(\delta_{SGRQ} \leq 0) \geq 80\%$.

Figure 2 Total Probability of Success

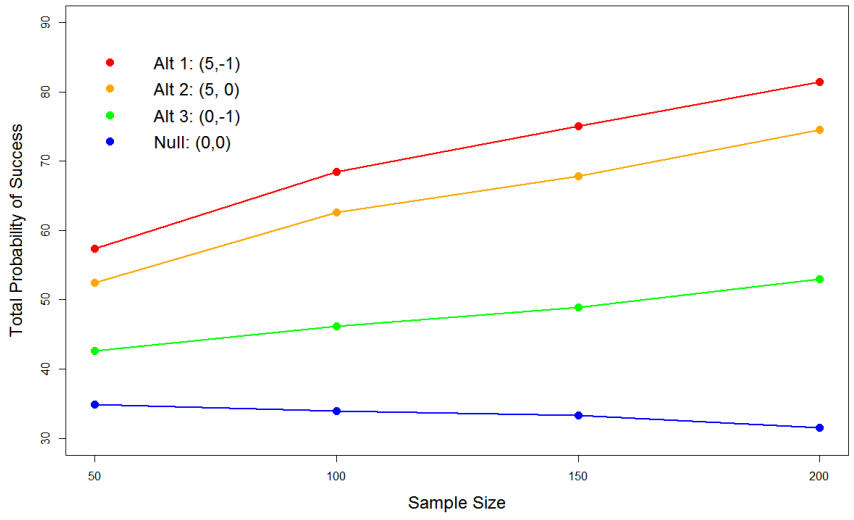


Table 4 Total Probability of Success (Figure 2)

	N=50	N=100	N=150	N=200
(5,-1)	57.4	68.5	75.1	81.4
(5,0)	52.5	62.6	67.8	74.5
(0,-1)	42.6	46.2	48.9	53.0
(0,0)	34.9	33.9	33.3	31.5

Figure 3 Half Width of the 95% Confidence Interval of δFEV$_1$ Point Estimate

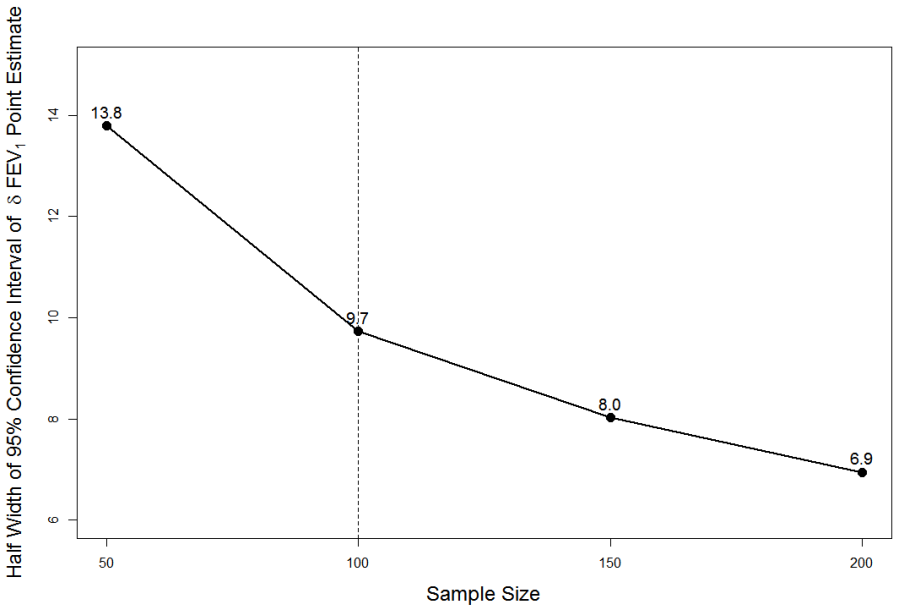
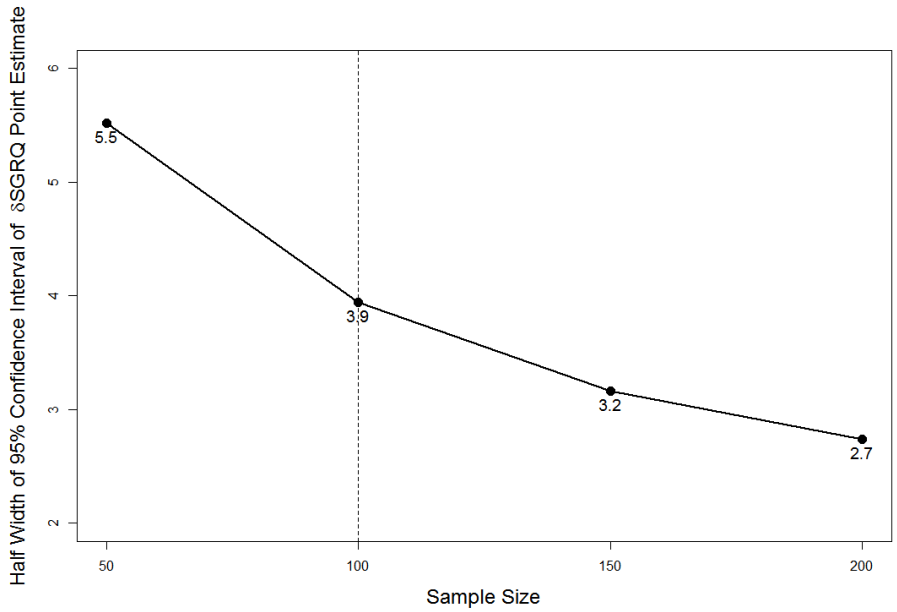


Figure 4 Half Width of the 95% Confidence Interval of δSGRQ Point Estimate



Based on the simulations, under the assumption of an expected treatment difference of (5,-1) which is the most probable scenario, the marginal increase for the total probability of success is greatest when increasing the sample size from 50 to 100 (Figure 2). The half widths of the 95% CI of the point estimate of the marginal treatment differences for FEV$_1$ (Figure 3) and SGRQ (Figure 4) have the greatest reduction from a sample size of 50 to 100. A sample size of 100 will allow for an adequate level of confidence in the study success while also considering the precision of the treatment effect differences.

10.2. Randomization

Participants will be randomized equally (1:1) to the two treatment arms of placebo and 35 mg danirixin HBr. Randomization will be stratified by smoking status (current vs. former).

10.3. 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.
Per-Protocol (PP) Population	This population will comprise of all patients in the ITT population who are not major protocol violators.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.4. Statistical Analyses

Treatment comparisons using all endpoints will be made using appropriate statistical techniques. Analysis methods for key endpoints are described below. Main analysis will use ITT unless noted. Further details on all analyses will be described in the reporting and analysis plan (RAP).

10.4.1. Efficacy Analyses

The total probability of success will be defined as a combination of a joint and conditional statement. The joint probability of success will be defined as the probability of the difference in the rate of decline in FEV_1 between danirixin and placebo is greater than or equal to 0 and the difference in the change in SGRQ total score from baseline between danirixin and placebo is less than or equal to 0 is greater than 70%. If the joint probability of success is less than 70%, success can further be defined based on each endpoint independently, where either the difference in the rate of decline in FEV_1 is

greater than or equal to 0 is greater than 80% or the difference in the change in SGRQ total score is less than or equal to 0 is greater than 80%.

$$Total\ PoS = P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) \geq 70\%$$

$$+\ P\left(\delta_{FEV_1} \geq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

$$+P\left(\delta_{SGRQ} \leq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

Endpoint	**Statistical Analysis Methods**
Primary	Rate of decline in FEV_1 and change from baseline in SGRQ total score
Exploratory	Will be described in detail in the RAP

Lung Function Decline: Rate of Decline of FEV_1 (mL/yr)

The rate of decline of FEV_1 will be derived from a repeated measures random coefficients model. Post-baseline FEV_1 will be modelled including terms for age, sex, smoking status, FEV_1 at baseline, and BMI along with treatment group, time and treatment by time interaction as fixed effects. Subject will be a random effect. Time will be defined as the number of days since start of treatment. Only FEV_1 values measured after baseline will be used in the model. Based on the results of previous studies, the study team will determine the time point at which post-baseline spirometry assessments will be included in the model to account for the initial treatment response. The estimate of the rate of FEV_1 decline will be the slope of the parameter estimate of the treatment by time interaction term in the model. Contrasts will be calculated for the difference in treatment by time interaction between danirixin and placebo treatment groups to estimate the treatment difference.

FEV_1 = Treatment group + age + sex +smoking status+FEV1_BL+BMI+ time + treatment*time

The rate of decline for each subject, the estimate of the slope parameter of the treatment by time interaction term, will be used as a co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

HRQoL: SGRQ

A co-primary endpoint of interest is change in SGRQ total score (derived from SGRQ-C) from baseline. Change in SGRQ total scores from baseline will be derived using a mixed model with repeated measures (MMRM) including fixed effects of treatment group, age, sex, smoking status, BMI, baseline SGRQ score, time as a categorical variable and a treatment by time interaction term. Subject will be a random effect. Estimated treatment differences at the end of one year will be obtained. The difference of the least square mean change from baseline at 12 months will be derived. The adjusted SGRQ total score change from baseline will used as the other co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

Joint Analysis

The joint analysis will use the ITT population with all available FEV_1 rate of decline and change in SGRQ data.

The rate of decline (the slope parameter from the random coefficients model) of FEV_1, along with the change in SGRQ from the MMRM model will be extracted for each subject. These values will then be used to obtain MCMC approximations of the joint posterior distribution of the treatment differences between FEV_1 decline and change in SGRQ between the danirixin and placebo groups. Based on the samples from the posterior distribution, the proportion of samples falling within certain treatment difference regions will be calculated and the probability of success will be derived.

10.4.2. 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.

10.4.3. Other Analyses

Exploratory biomarker analyses will be described in the RAP.

10.4.4. Interim Analyses

Conducting an interim analysis or futility assessment may not be practical due to an expected fast recruitment period. By the time enough data will accumulate for any meaningful interim analysis to support changes to the study design, recruitment of all study participants will have concluded. However, if recruitment takes a longer than anticipated, an interim analysis to reassess the variability assumptions, estimate the probability of success at the end of study, and confirm the directionality of the endpoints may be conducted.

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

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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
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
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
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-C 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
CAT

Trademarks not owned by the GlaxoSmithKline group of companies
Combivent
Duoneb

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	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[2] • All study-required laboratory assessments will be performed by a central laboratory

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

Data Protection

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

Committees Structure

- A study charter will be created to describe important governance aspects while the study is being conducted.

- 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 participant's last visit.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: 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. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions.

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

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 sufficient 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 (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- 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.
- 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 and confirmatory testing with additional FSH and estradiol measurements is required.
- 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.

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 will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- 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 will 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 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 will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to danirixin 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 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).

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

No country specific requirements

12.11. Appendix 11 Protocol Amendment History

Table 1 Schedule of activities

Original text:

	Screening/ Visit1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -7 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Urine or serum Pregnancy test[g]	X											X	X	
HIV, Hepatitis B and C screeninge														
AE review		←										→		
SAE review		←										→		

Revised text:

	Screening/ Visit1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -28 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
HIV, Hepatitis B and C screeninge	X													
AE review		←										→	X	X
SAE review		←										→	X	X

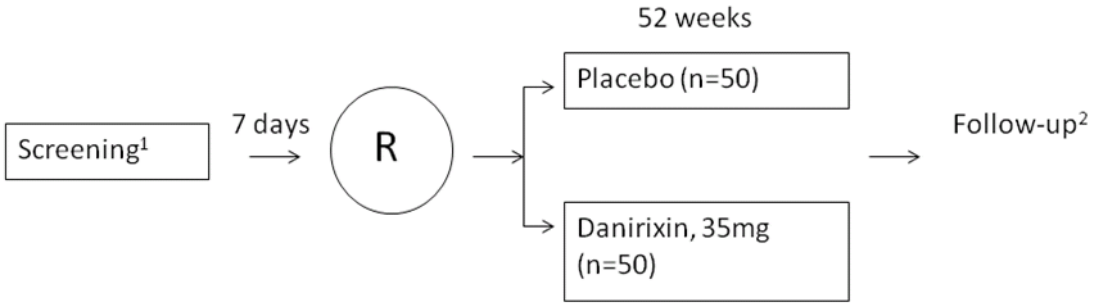
Section 5.1 Overall Design

Original text:

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -7 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



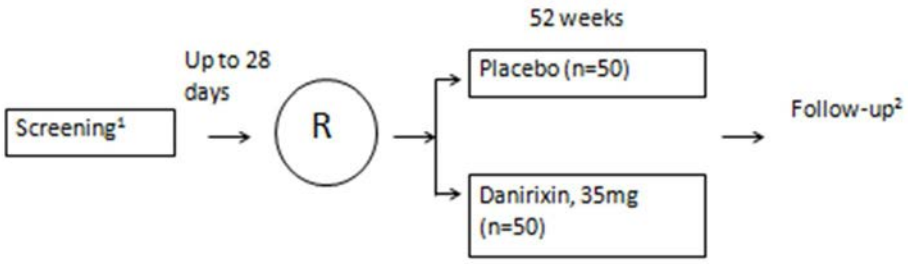
[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

Amended text:

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -28 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

Section 6.1 Inclusion Criteria

Original text:

2. Male or female

g. 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.

h. Female participants:

A female participant is eligible to participate if she is not pregnant (see Section 12.5; Appendix 5), not breastfeeding, and at least one of the following conditions applies:

i. Not a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Section 12.5 (Appendix 5) during the treatment period and for at least 60 hours after the last dose of study treatment.

Revised text:

3. Male or female

i. 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.

j. Female participants:

A female participant is eligible to participate if she is **not** a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

Section 12.2 Appendix 2:

Original text:

Table 7 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 • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • 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

Amended text:

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC	<u>WBC count with Differential</u>: 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 • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other	• Follicle-stimulating hormone and estradiol (as needed in women of non-			

Laboratory Assessments	Parameters
Screening Tests	childbearing potential only) • HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody[2] • All study-required laboratory assessments will be performed by a central laboratory

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. 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

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

Original text:

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 9 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.)*

Amended text:

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 and confirmatory testing with additional FSH and estradiol measurements is required.
    - 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.

Table 10 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.)*

TITLE PAGE

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Protocol Number: 205864

Short Title: Danirixin Pilot Study for Disease Progression in 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

Approval Date: 21-MAR-2017

SPONSOR SIGNATORY:

PPD

21-Mar-2017

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

Date

PPD

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, Sponsor open, placebo-controlled, 52 week study evaluating the effect of danirixin (GSK1325756) on lung function and health related quality of life in participants with mild to moderate Chronic Obstructive Pulmonary Disease (COPD).

Short Title: Danirixin Pilot Study for Disease Progression in COPD

Rationale: This is a pilot study to investigate the effect of danirixin hydrobromide (HBr) 35mg tablets on lung function and health related quality of life (HRQoL) in participants with mild to moderate airflow obstruction and a demonstrated history of decline in FEV_1. This study aims to assess whether danirixin has the potential to impact disease progression in participants with COPD and with a demonstrated history of disease progression measured by lung function.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess whether danirixin HBr 35mg tablets impact disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
Secondary	
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events • Vital Signs • ECG • Clinical Laboratory Assessments (hematology, clinical chemistry, urinalysis)
• To further characterize the clinical activity of danirixin HBr 35mg tablets compared with placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use

Overall Design:

This is a Phase 2 study to investigate the potential impact of danirixin HBr 35mg tablets compared with placebo on disease progression in participants with mild to moderate

airflow obstruction. The study will also assess the enrichment strategy of enrolling participants identified from the COPDGene study. These participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period.

Number of Participants:

Approximately 130 participants will be screened to enrol 100 participants in this study. It is anticipated that approximately 85 participants will complete the 52 weeks of treatment (assuming a 15% drop out rate).

Treatment Groups and Duration:

Participants will receive either placebo or danirixin 35mg tablets (as hydrobromide hemihydrate salt) twice daily for 52 weeks (12months).

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

	Screening/ Visit1[a]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	EW	FU Up to 28 days post last dose
	up to -7 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Eligibility														
Informed Consent	X													
Genetics Informed Consent[b]	X													
Demography	X													
Inclusion and Exclusion Criteria	X													
Smoking Status[c]	X													
Smoking History[c]	X	X												
Medical History[d]	X													
Full physical	X													
Chest X-ray (historical within 1 year acceptable)	X													
HIV, Hepatitis B and C screening[e]														
Additional Eligibility and In Study Assessments														
Verify Eligibility[f]	X	X												
Brief physical		X				X			X			X	X	
Urine or serum Pregnancy test[g]	X											X	X	
Laboratory assessments (clinical chemistry, including liver chemistries), hematology, urinalysis	X	X		X					X			X	X	
Additional Liver chemistries only			X		X	X	X	X		X	X			
12 lead ECG	X	X		X		X			X			X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -7 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Vital Signs	X	X		X		X			X			X	X	
Office spirometry (centralized)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Home spirometry - (weekly)	X	←	—	—	—	—	—	—	—	→		X	X	
Randomization		X												
Dispense study medication		X		X	X	X	X	X	X	X	X			
Dispense log pad and provide training	X													
Dispense MDI sensors and provide training	X													
Study Treatment		←	—	—	—	—	—	—	—	—	→			
Study Treatment Compliance (ediary)		←	—	—	—	—	—	—	—	—	→			
Collect IP				←	—	—	—	—	—	—	→			
Collect MDI sensors												X	X	
Collect log pad												X	X	
AE review		←	—	—	—	—	—	—	—	—	→			
SAE review	←	—	—	—	—	—	—	—	—	—	→			
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Outcomes Assessments														
COPD exacerbation review		X	X	X	X	X	X	X	X	X	X	X	X	
Rescue medication Use	←	—	—	—	—	—	—	—	—	—	—	→		
SGRQ-C		X				X			X	X		X	X	
COPD Assessment Test (CAT)		X				X			X	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	X	X	X	

	Screening/ Visit1[a]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**EW**	**FU** Up to 28 days post last dose
	up to -7 days	Week 0 / D1	Week 2/ D14	Week 4/ D28	Week 8/ D56	Week 12/ D84	Week 16 / D112	Week 20 / D140	Week 24 /D168	Week 32 /D224	Week 40 / D280	Week 52 / D364		
Assessment window		+3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±6d	±6d	±6d	±6d	
Genetic, Pharmacokinetic and Biomarker Blood Collections														
Blood sample for Genetics		X												
Blood sample for CRP		X							X			X	X	
Blood sample for exploratory biomarkers		X							X			X	X	

a Informed consent may be signed prior to screening visit in the case that any changes in medications are necessary
b Agreeing to genetic sample consent is not required for study participation
c Smoking status/history assessed at screening; smoking status re-checked at Visit 2
d Includes substance usage, past and present medical conditions and family history of premature CV disease
e 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.
f Participant's clinical status should be reviewed
g Pregnancy testing is only required for women of child bearing potential (WOCBP). A positive urine pregnancy test requires confirmation with a serum pregnancy test.

The timing and number of planned study assessments, including safety and biomarker assessments may be altered during the course of the study based on newly available data to ensure appropriate data collection. Any changes in the timing or addition of time points for any planned study assess 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 Number 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 [GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163]. 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. Analyses 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 pilot study to investigate the effect of danirixin HBr 35mg tablets on lung function and health related quality of life (HRQoL) in participants with

mild to moderate airflow obstruction identified from the COPDGene cohort. 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.

Specifically, this study aims to assess whether or not danirixin has the potential to impact disease progression in participants with a COPD progression score indicating they are likely to decline based on 5 year data from COPDGene and support the conduct of a larger Phase III study for disease progression. In addition to lung function and HRQoL, this study will assess moderate/severe COPD exacerbations, health status (CAT), and rescue medication use.

3.2. Background

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

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

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

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Testicular effects and male fertility	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. PK modelling predicts that in a participant receiving 35 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 participants receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy participants, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD who were treated with danirixin for one year. These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established.	

Investigational Product (IP) [Danirixin, GSK1325756]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Reproductive toxicology (Embryofetal development)	In a rat embryofetal development study, an oral dose of 300 mg/kg/day resulted in fetal skeletal variations in the skull (reductions in ossification). There were no test article-related effects on numbers of corpora lutea, implantations, embryofetal survival, placental morphology, gravid uterine weight, sex ratio, fetal body weight, or fetal morphology (external and visceral).	As danirixin HBr has shown the potential to cause fetal malformations, danirixin or danirixin HBr must not be administered to pregnant women or nursing mothers. Women of childbearing potential should only be included in clinical trials with the use of appropriate precautions against pregnancy. 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 or 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 assess whether danirixin HBr 35mg tablets impacts disease progression compared with placebo	• Rate of decline in FEV_1 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (derived from SGRQ-C)
• To further characterize the safety of danirixin HBr 35mg tablets compared with placebo in participants with mild to moderate airflow limitation	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers
Secondary • To further characterize the clinical activity of danirixin HBr 35mg tablets compared to placebo	• Time to first HCRU COPD exacerbation • Change from baseline in FEV_1 • SGRQ responder analysis • SGRQ domains • COPD Assessment Test (CAT) • Rescue medication use
Exploratory	
• To characterize the effect of danirixin on lung matrix destruction/remodelling and inflammation • Further characterize efficacy of danirixin	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes) and inflammation (e.g. CRP) • Global assessment of COPD severity

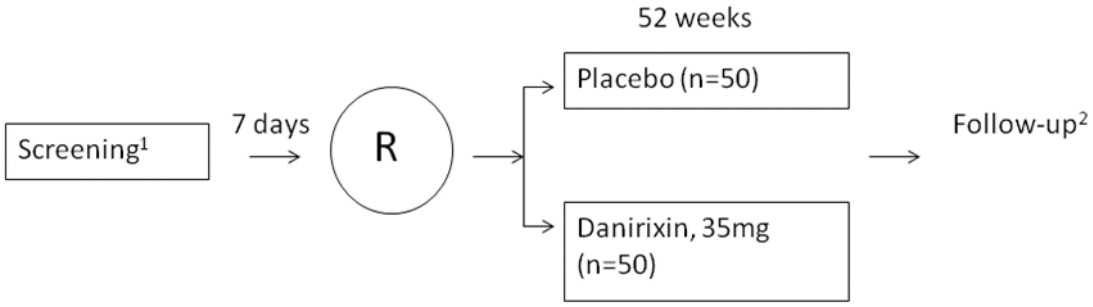
5. STUDY DESIGN

5.1. Overall Design

A study schematic is shown in Figure 1. This is a parallel group study. Following screening and assessment of rescue medication use via a daily diary over study days -7 to 1, participants will be randomized (1:1) to receive either danirixin 35mg tablets or placebo. Study treatment will be administered twice daily for 52 weeks [Figure 1].

There will be no pre-specified interim analysis for this study. An interim analysis may be performed if it is determined that the enrolment is slow enough to allow it to be informative. There will be no IDMC for this study. An internal 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



[1] If changes to medication are required, consent must be signed prior to any changes being made and may occur prior to the Screening Visit
[2] Follow-up visit to occur within 28days of last dose of study medication

5.2. Number of Participants

Approximately 130 participants will be screened to achieve 100 randomized in this study. It is anticipated that approximately 85 participants will complete the 12 months of treatment (assuming a 15% drop out rate).

For the analysis of study assessments, several analysis populations are defined in Section 10.3.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all planned study visits 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. With the use of an enriched population, it is anticipated that one year of treatment will be sufficient to detect a trend in altering disease progression. Danirixin has already been clinically investigated over one year treatment duration (GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163).

The data from this study will provide useful information in determining whether or not to progress to a Phase III study to explore an indication for slowing disease progression.

5.5. Dose Justification

One dose of danirixin is proposed for this study, 35mg tablets BID. This dose was selected based on integrating information on:

- Dose-exposure-biomarker response using inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils over the dose range of 0-400mg (free base tablet) in healthy volunteers (GSK Study No. CX3 112483).

- Evidence of reduced respiratory symptoms and improvement in health status in mild to moderate COPD participants from interim data in the Phase IIa study (GSK Study No. 200163).

- Relative bioavailability study comparing danirixin free base vs HBr (GSK Study No. 201037).

In the previous 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 (GlaxoSmithKline Document Number 2015N248339_00, Study ID 201037). Thus the danirixin (hydrobromide tablet) 35mg BID dose for investigation in this study is expected to provide steady-state systemic exposure approximately equivalent to the 75mg BID (free base tablet) used in Study 200163. 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)			Cavg multiple of IC50*	Cmin multiple of IC50*
	AUC(0-24) steady-state (ug.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4

#Model derived based on PK data in healthy elderly participants from GSK Study No. 201037 (GlaxoSmithKline Document Number. 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.

6. STUDY POPULATION

This study will identify specific patients most likely to decline from the well established COPDGene cohort [NCT00608764]. This study will be an ancillary study within COPDGene investigating the enrichment strategy for assessing disease progression. These potential participants have been identified by COPDGene investigators based on data collected over the initial 5 year period. The participants were identified based on a Random Forest analysis and a demonstrated decline of at least 20mL/yr over the initial 5 year period. Once participants are identified from the COPDGene dataset, the following criteria will be verified at initial study visit following signing of consent.

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 76 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. At the screening visit, the subject must have an FEV_1 >40% of the predicted normal.
3. Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD

Weight

4. Body weight ≥ 45 kg

Sex

5. 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 Section 12.5; Appendix 5), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Section 12.5 (Appendix 5)

   OR

   (ii) A WOCBP who agrees to follow the contraceptive guidance in Section 12.5 (Appendix 5) during the treatment period and for at least 60 hours after the last dose of study treatment.

Informed Consent

6. Capable of giving signed informed consent as described in Section 12.3 (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 disease (other than COPD), e.g. sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer
2. COPD due to alpha-1-antitrypsin deficiency
3. Pulse oximetry < 88% at rest at screening. Participants should be tested while breathing room air. However, participants living at high altitudes (above 5000 ft or 1500 m above sea level) who are receiving supplemental oxygen can be included provided they are receiving the equivalent of < 4L/min and screening oximetry is measured while on their usual settings.
4. Less than 14 days have elapsed from completion of a course of antibiotics or oral corticosteroids for a recent COPD exacerbation

5. Participants with a peripheral blood neutrophil count < 1 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 with lateral) or CT scan reveals evidence of a clinically significant abnormality not believed to be due to the presence of COPD (historic data up to 1 year may be used).
8. History or current evidence of clinically significant renal disease, diabetes mellitus/metabolic syndrome, hypertension, or any other clinically significant cardiovascular, neurological, immunological, endocrine, or haematological abnormality 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 participants at risk through study participation, or which would affect the safety analysis or other analysis if the disease/condition exacerbated during the study.
9. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator of GSK medical monitor, contraindicates their participation.
10. Current of chronic history of liver disease, or know hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude participants who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
    - AF with rapid ventricular rate > 120 bpm;
    - sustained or non-sustained VT
    - second degree heat block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
    - QTcF ≥ 500 msec in patients with QRS < 120 msec and QTcF ≥ 530 msec in patients with QRS ≥ 120 msec
12. Previous lung surgery (e.g. lobectomy, pneumonectomy) or lung volume reduction procedure.

Prior/Concomitant Therapy

13. 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.

14. 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.

15. 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

16. 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).
17. Participation in a previous clinical trial with danirixin within 1 year prior to the first dosing day in the current study
18. Exposure to more than four investigational products within 1 year prior to the first dosing day in the current study.

Diagnostic assessments

19. 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%).
20. A positive test for HIV antibody.
21. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months prior to screening.

Other Exclusions

22. 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.
23. A history of allergy or hypersensitivity to any of the ingredients in the study treatment.
24. A known or suspected history of alcohol or drug abuse within the 2 years prior to screening.
25. 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.
26. 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 not be rescreened unless discussed with the medical monitor.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	Danirixin (GSK1325756H, the hydrobromide hemihydrate salt)	Placebo
Dosage formulation:	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients	White Film coated tablets (oval shaped). Refer to Investigator's Brochure for presentation and excipients
Unit dose strength(s)/Dosage level(s):	35mg tablets (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).

Additional descriptive information and instructions for the eMDI 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 study. Study participants, all study site staff, and all members of the GSK study team will be blinded to individual participant treatment assignment.

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.

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) bronchodilators, (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.

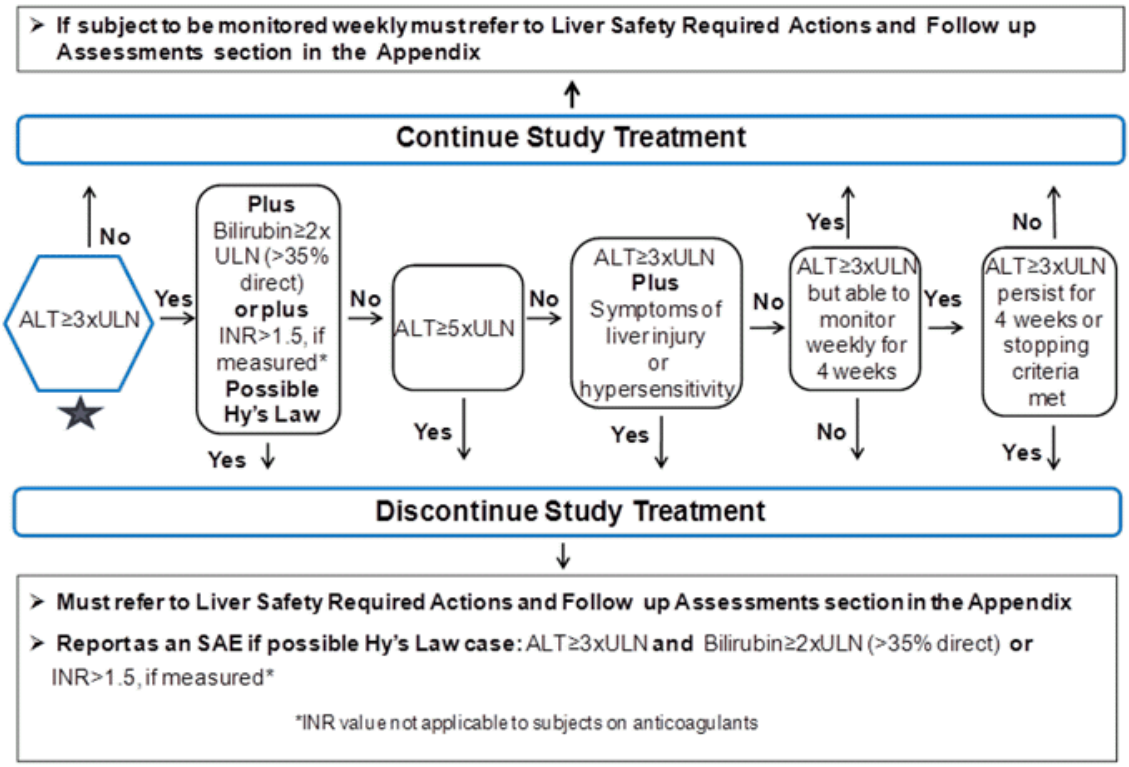
8. DISCONTINUATION CRITERIA

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: Liver Safety: Required Actions and Follow-up Assessments).

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 (Section 12.7) 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. FEV_1

9.1.1.1. Clinic Spirometry

Spirometry using FEV_1 and FVC measurements (FEV%, and FVC% and FEV1/FVC will be calculated) will be performed in triplicate at time points listed in the SoA (Table 1). Spirometry assessments should be performed in accordance with ATS/ERS guidelines as outlined in the SRM.

9.1.1.2. Mobile Spirometry

Spirometry will also be performed weekly by the participants using a mobile spirometer at home. Details will be outlined in the SRM.

9.1.2. 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 SGRQ scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.3. 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.

9.1.4. COPD Exacerbations

An exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment or hospitalization.

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 based on the Investigator's judgement.

9.1.5. 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 final study visit or IP Discontinuation Visit. This single global question will ask participants 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 every visit following randomization (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.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4 (Section 12.4).

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 the time the informed consent is signed by the participant until the follow up visit at the time points specified in the SoA (Table 1).
- All AEs will be collected from the start of study treatment (randomization visit) until the follow-up visit at the time points specified in the SoA (Table 1).
- 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 must be reported immediately and not more than 24 hrs to the sponsor, as indicated in Appendix 4 (Section 12.4). 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 (Section 12.4).

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is

resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information 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 Section 12.4 (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.

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 Section 12.3 (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 Section 12.5 (Appendix 5).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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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. 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 Section 12.8 (Appendix 8).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Section 12.4 (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 Section 12.8 (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 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.

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, 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 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 measurements 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 10 minutes.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Section 12.2 (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 Section 12.2, 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

Pharmacokinetic parameters are not evaluated in this study.

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 Section 12.6 (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), 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

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

10. STATISTICAL CONSIDERATIONS

The objective of this study is to investigate the effect of danirixin HBr 35mg tablets on COPD disease progression. There are no formal hypothesis tests associated with this objective and no formal significance tests. The information acquired from this study will primarily be used to assess whether or not danirixin impacts disease progression and to quantify the effect that danirixin has on disease progression, specifically change in lung function as measured by FEV_1 decline and change in health-related quality of life as measured by SGRQ total score to further support disease understanding and future studies.

10.1. Sample Size Determination

Sample size is based primarily on feasibility for this study. Since there is much uncertainty around the magnitude of the difference in the decline in FEV_1 and change in SGRQ along with the between-subject variability for the specific patient population, the proposed sample size is unavoidably imprecise. Sample size may be adjusted using the predictions of final study outcome based on simulations and possible interim analyses. It is anticipated that screening 130 participants will allow for approximately 100 participants to enrol.

In order to observe the effect of different sample sizes, various simulations were done to assess the impact of sample sizes of 50, 100, 150 and 200 with a 1:1 allocation to each treatment group [Table 3]. The assumed variability for rate of decline in FEV_1 and change in SGRQ is 25 and 10, respectively. The correlation between rate of decline in FEV1 and change in SGRQ is assumed to be -0.2. [Nagai, 2015]

Table 3 Assumptions used for the Simulations

	Treatment Effect Assumptions (δ_{FEV1}, δ_{SGRQ})	Variability Assumptions (σ_{FEV1}, σ_{SGRQ})	Sample Size
Null	(0,0)	(25,10)	N={50,100,150,200}
Alternate 1	(5,-1)	(25,10)	N={50,100,150,200}
Alternate 2	(5,0)	(25,10)	N={50,100,150,200}
Alternate 3	(0,-1)	(25,10)	N={50,100,150,200}

Data from a bivariate normal distribution were simulated under the four different treatment effect assumptions for samples sizes of 50, 100, 150, and 200. The samples from the posterior probability distribution from the MCMC approximation were divided into four regions based on δ_{FEV1} and δ_{SGRQ} treatment effect cut-off values; $\delta_{FEV1}\geq 0$ and $\delta_{SGRQ} \leq 0$, $\delta_{FEV1}\geq 0$ and $\delta_{SGRQ}>0$, $\delta_{FEV1}<0$ and $\delta_{SGRQ}\leq 0$, and $\delta_{FEV1}<0$ and $\delta_{SGRQ}>0$. Based on a 70% threshold, the proportion of the 1000 simulations meeting the requirement $P(\delta_{FEV1}\geq 0 \ \& \ \delta_{SGRQ}\leq 0) \geq 70\%$ were considered a success based on the joint definition [Figure 2, Table 4]. If $P(\delta_{FEV1}\geq 0 \ \& \ \delta_{SGRQ}\leq 0) < 70\%$, success could further be defined based on each endpoint independently where $P(\delta_{FEV1} \geq 0) \geq 80\%$ or $P(\delta_{SGRQ} \leq 0) \geq 80\%$.

Figure 2 Total Probability of Success

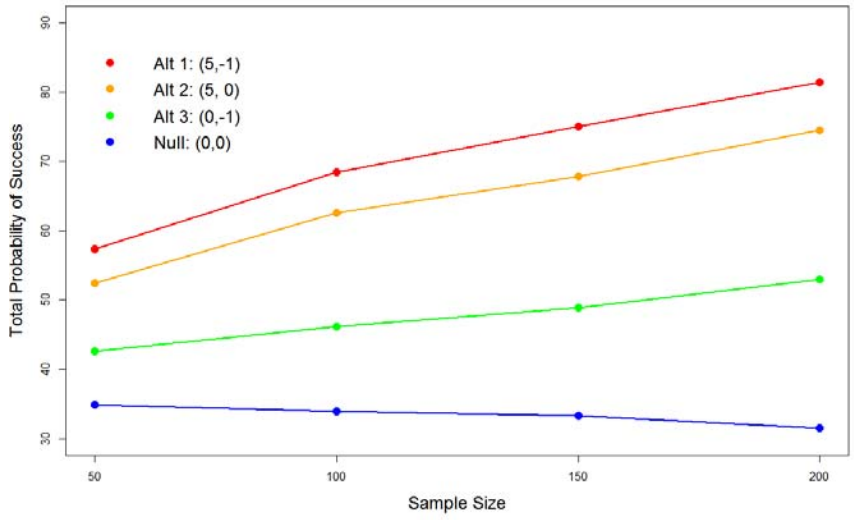


Table 4 Total Probability of Success (Figure 2)

	N=50	**N=100**	**N=150**	**N=200**
(5,-1)	57.4	68.5	75.1	81.4
(5,0)	52.5	62.6	67.8	74.5
(0,-1)	42.6	46.2	48.9	53.0
(0,0)	34.9	33.9	33.3	31.5

Figure 3 Half Width of the 95% Confidence Interval of δFEV$_1$ Point Estimate

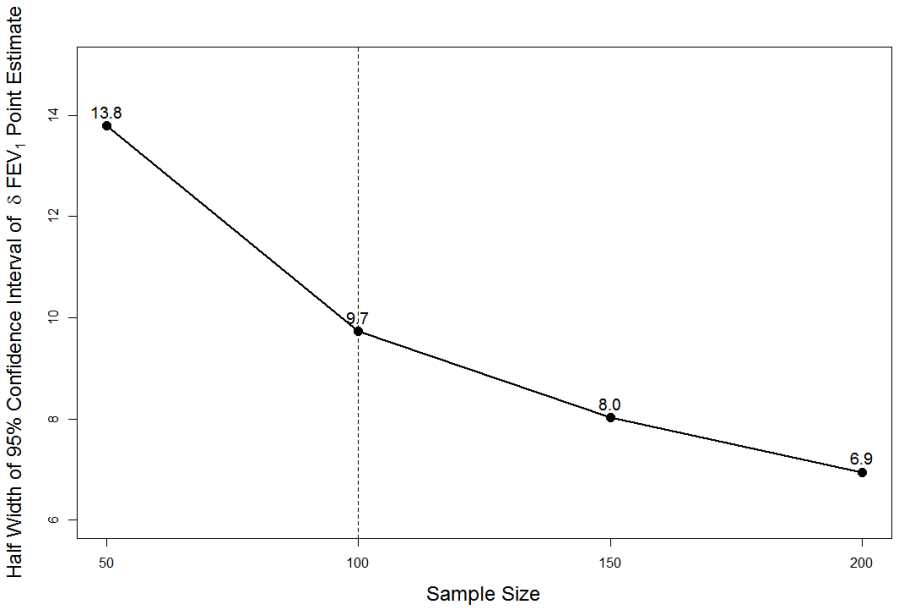
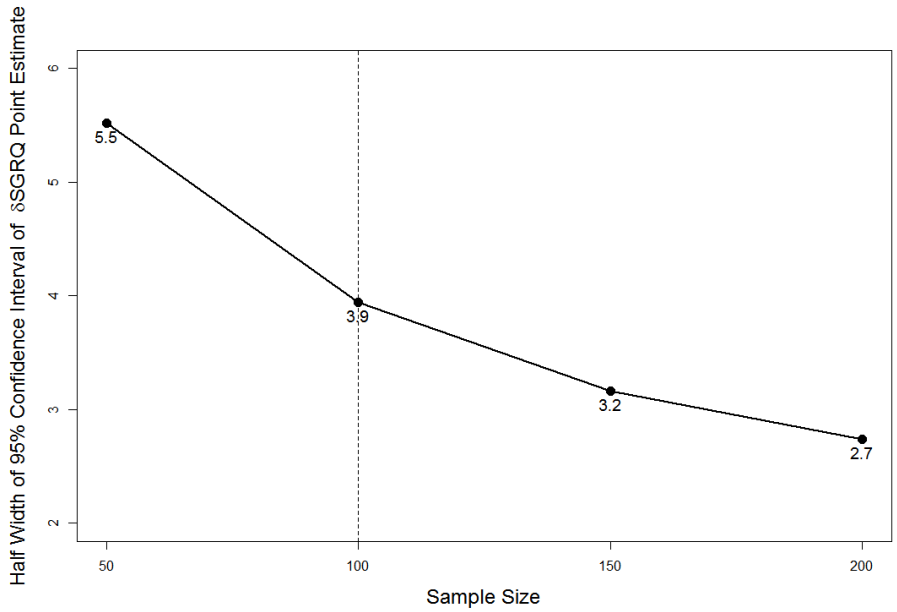


Figure 4 Half Width of the 95% Confidence Interval of δSGRQ Point Estimate



Based on the simulations, under the assumption of an expected treatment difference of (5,-1) which is the most probable scenario, the marginal increase for the total probability of success is greatest when increasing the sample size from 50 to 100 (Figure 2). The half widths of the 95% CI of the point estimate of the marginal treatment differences for FEV$_1$ (Figure 3) and SGRQ (Figure 4) have the greatest reduction from a sample size of 50 to 100. A sample size of 100 will allow for an adequate level of confidence in the study success while also considering the precision of the treatment effect differences.

10.2. Randomization

Participants will be randomized equally (1:1) to the two treatment arms of placebo and 35 mg danirixin HBr. Randomization will be stratified by smoking status (current vs. former).

10.3. 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.
Per-Protocol (PP) Population	This population will comprise of all patients in the ITT population who are not major protocol violators.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.4. Statistical Analyses

Treatment comparisons using all endpoints will be made using appropriate statistical techniques. Analysis methods for key endpoints are described below. Main analysis will use ITT unless noted. Further details on all analyses will be described in the reporting and analysis plan (RAP).

10.4.1. Efficacy Analyses

The total probability of success will be defined as a combination of a joint and conditional statement. The joint probability of success will be defined as the probability of the difference in the rate of decline in FEV_1 between danirixin and placebo is greater than or equal to 0 and the difference in the change in SGRQ total score from baseline between danirixin and placebo is less than or equal to 0 is greater than 70%. If the joint probability of success is less than 70%, success can further be defined based on each endpoint independently, where either the difference in the rate of decline in FEV_1 is

greater than or equal to 0 is greater than 80% or the difference in the change in SGRQ total score is less than or equal to 0 is greater than 80%.

$$Total\ PoS = P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) \geq 70\%$$

$$+ P\left(\delta_{FEV_1} \geq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

$$+ P\left(\delta_{SGRQ} \leq 0\ \right) \geq 80\% | P\left(\delta_{FEV_1} \geq 0\ \&\ \delta_{SGRQ} \leq 0\right) < 70\%$$

Endpoint	**Statistical Analysis Methods**
Primary	Rate of decline in FEV_1 and change from baseline in SGRQ total score
Exploratory	Will be described in detail in the RAP

Lung Function Decline: Rate of Decline of FEV_1 (mL/yr)

The rate of decline of FEV_1 will be derived from a repeated measures random coefficients model. Post-baseline FEV_1 will be modelled including terms for age, sex, smoking status, FEV_1 at baseline, and BMI along with treatment group, time and treatment by time interaction as fixed effects. Subject will be a random effect. Time will be defined as the number of days since start of treatment. Only FEV_1 values measured after baseline will be used in the model. Based on the results of previous studies, the study team will determine the time point at which post-baseline spirometry assessments will be included in the model to account for the initial treatment response. The estimate of the rate of FEV_1 decline will be the slope of the parameter estimate of the treatment by time interaction term in the model. Contrasts will be calculated for the difference in treatment by time interaction between danirixin and placebo treatment groups to estimate the treatment difference.

FEV_1 = Treatment group + age + sex +smoking status+FEV1_BL+BMI+ time + treatment*time

The rate of decline for each subject, the estimate of the slope parameter of the treatment by time interaction term, will be used as a co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

HRQoL: SGRQ

A co-primary endpoint of interest is change in SGRQ total score (derived from SGRQ-C) from baseline. Change in SGRQ total scores from baseline will be derived using a mixed model with repeated measures (MMRM) including fixed effects of treatment group, age, sex, smoking status, BMI, baseline SGRQ score, time as a categorical variable and a treatment by time interaction term. Subject will be a random effect. Estimated treatment differences at the end of one year will be obtained. The difference of the least square mean change from baseline at 12 months will be derived. The adjusted SGRQ total score change from baseline will used as the other co-primary endpoint for the joint analysis using both FEV_1 and SGRQ.

Joint Analysis

The joint analysis will use the ITT population with all available FEV_1 rate of decline and change in SGRQ data.

The rate of decline (the slope parameter from the random coefficients model) of FEV_1, along with the change in SGRQ from the MMRM model will be extracted for each subject. These values will then be used to obtain MCMC approximations of the joint posterior distribution of the treatment differences between FEV_1 decline and change in SGRQ between the danirixin and placebo groups. Based on the samples from the posterior distribution, the proportion of samples falling within certain treatment difference regions will be calculated and the probability of success will be derived.

10.4.2. 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.

10.4.3. Other Analyses

Exploratory biomarker analyses will be described in the RAP.

10.4.4. Interim Analyses

Conducting an interim analysis or futility assessment may not be practical due to an expected fast recruitment period. By the time enough data will accumulate for any meaningful interim analysis to support changes to the study design, recruitment of all study participants will have concluded. However, if recruitment takes a longer than anticipated, an interim analysis to reassess the variability assumptions, estimate the probability of success at the end of study, and confirm the directionality of the endpoints may be conducted.

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

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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
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
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
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-C 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
CAT

Trademarks not owned by the GlaxoSmithKline group of companies
Combivent
Duoneb

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

Data Protection

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

Committees Structure

- A study charter will be created to describe important governance aspects while the study is being conducted.

- 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 participant's last visit.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: 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. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 sufficient 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 (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- 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.
- 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 will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- 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 will 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 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 will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to danirixin 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 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).

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

No country specific requirements