# TITLE PAGE

**Protocol Title:** Randomized double blind (sponsor unblind) study evaluating the effect of 14 days of treatment with danirixin (GSK1325756) on neutrophil extracellular traps (NETs) formation in participants with stable chronic obstructive pulmonary disease (COPD)

**Protocol Number**: 207551

**Short Title**: Randomized study evaluating the effect of danirixin on neutrophil extracellular traps (NETs) in COPD

**Compound Number:** GSK1325756

**Sponsor Name and Legal Registered Address:**

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## SPONSOR SIGNATORY:

PPD

16-May-2017

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# 1. SYNOPSIS

**Protocol Title:** Randomized double blind (sponsor unblind) study evaluating the effect of 14 days of treatment with danirixin (GSK1325756) on neutrophil extracellular traps (NETs) formation in participants with stable chronic obstructive pulmonary disease (COPD)

**Short Title:** Randomized study evaluating the effect of danirixin on neutrophil extracellular traps (NETs) in COPD

**Rationale:**

Danirixin (DNX) is a potent selective CXC chemokine receptor type 2 (CXCR2) antagonist being developed as a potential anti-inflammatory agent for the treatment of chronic obstructive pulmonary disease (COPD) and influenza. Clinical pharmacology studies in healthy volunteers demonstrated the pharmacodynamic activity of danirixin (inhibition of *ex vivo* chemokine (C-X-C motif) ligand 1 [CXCL1]-induced CD11b expression on peripheral blood neutrophils and inhibition of neutrophil trafficking after ozone challenge). The current study is a mechanistic study to evaluate the effect of danirixin on neutrophil extracellular traps (NETs) formation. NETs consist of decondensed chromatin coated in antimicrobial and granular proteins. Whilst NETs can have a protective role against bacterial dissemination, excessive NET formation can cause host tissue damage, and could form one mechanism for disease progression in COPD. This study specifically aims to test the hypothesis that danirixin may reduce NET formation (NETosis) in participants with COPD; this study will help to better understand the pharmacology of danirixin and is the first study of its kind in COPD.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the change from baseline in NETs formation in participants with COPD following 14 days treatment with danirixin hydrobromide (HBr) 35mg twice daily | • Reduction in sputum NETs (quantified by Histone-elastase complexes) |
| **Secondary** | |
| • To assess the change from baseline in NETs formation in participants with COPD following 14 days treatment with danirixin HBr 35mg twice daily | • Reduction in sputum NETS (quantified by Deoxyribonucleic acid [DNA]-elastase complexes)<br>• Reduction in sputum NET area quantification by microscopy |
| • To further characterize the safety of danirixin HBr 35mg twice daily compared with placebo in | • Adverse events<br>• Vital Signs<br>• ECG |

| Objectives | Endpoints |
|---|---|
| participants with COPD | • Spirometry<br>• Clinical Laboratory Assessments (hematology, clinical chemistry, urinalysis) |
| • To assess the effects of danirixin HBr 35mg twice daily on NETosis-associated biomarkers in sputum and peripheral blood | • Change from baseline in sputum resistin levels<br>• Change from baseline in the ratio of sputum NETs to sputum neutrophils<br>• Change from baseline in sputum elastase activity<br>• Change from baseline in peripheral blood neutrophil NET formation (DNA release, microscopy) |
| • Characterise the population pharmacokinetic (PK) profile of approximately 14 days of dosing of danirixin HBr 35mg twice daily in participants with COPD | • Model specific PK parameters of danirixin (e.g., oral clearance, oral steady-state volume of distribution). |

Further exploratory analyses related to the above endpoints may be performed.

**Overall Design:**

This is a double blind (sponsor unblind), parallel group study, with two groups randomized to 14 days of treatment with either danirixin 35mg HBr or matching placebo. The target population will be individuals with COPD who have evidence of existing elevated sputum NETosis.

There will be no Independent Data Monitoring Committee.

**Number of Participants:**

Approximately 50 participants will be screened to randomize 24 evaluable participants (18 in the treatment arm and 6 in the placebo arm). If a subject prematurely discontinues the study or is unable to complete all study assessments, additional subjects may be enrolled as replacement subjects at the discretion of the sponsor in consultation with the investigator. Additional subjects may be enrolled to improve the statistical properties of the end of study decision criteria (i.e., the probability of a positive outcome) based on the observed variability at an interim analysis. It is expected that the dropout rate in the study should be <10% given the study duration. Enrolment is not expected to exceed a maximum of 32 participants.

**Treatment Groups and Duration:**

The study will consist of a screening/baseline period of up to 30 days, a 2 week treatment period, and a 1-week follow-up visit. The study duration, including screening and follow-up, is not expected to exceed 2 months for participants in the study.

Study treatment will consist of two groups: danirixin 35mg HBr orally twice daily or matching placebo.

# 2. SCHEDULE OF ACTIVITIES (SOA)

| Procedure | Pre-Screening and Screening[1] | | Treatment Period (14 days) | | | Follow-up Phone call | Unscheduled visit [2] | Notes |
|---|---|---|---|---|---|---|---|---|
| | V0 | V1 | V2 | V3 | V 4 | V5 | | |
| **Day** | **Day -30 to -1** | | **D 1** | **D 7** | **D14** | **D 21** | **As required** | |
| **Assessment window** | | | | **±1d** | **±1d** | **± 3d** | **As required** | |
| Written, informed consent | X | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | Recheck clinical status before randomization. |
| Demography, Medical history | X | | | | | | | |
| Baseline COPD assessment test (CAT) score | X | | | | | | | |
| Adverse event (AE)/Serious adverse event ( SAE) review | X | ←========== | | | →| X | X | |
| Concomitant medication review | X | ←========== | | | →| X | X | |
| Full physical examination including height and weight | X | | | | | | X | |
| Vital signs | X | X | X | X | X | | X | |
| Volatile organic compound (VOC) measurement | X[3] | X[3,4] | X[5] | X[3] | X[3] | | X | |
| Spirometry | X | | X | | X | | X | |
| Induced Sputum Samples (including biomarker samples) | X | X [4] | X | X | X | | X | |
| Spirometry post-Sputum Induction | X | X [4] | X | X | X | | X | |
| Triplicate 12-lead ECG | | X | X | | X | | X | |
| Chest X-ray (historical within 1 year acceptable) | | X | | | | | | |
| HIV, Hepatitis B and C screening | | X[6] | | | | | | |
| Laboratory assessments (clinical chemistry including liver chemistries, haematology, biomarkers) | | X | X | | X | | X | |
| Pharmacokinetic (PK) sample | | | X[7] | X[8] | X[7] | | X | See footnotes for timings of PK sampling |
| Genetic sample | | | X[9] | | | | | Pre-dose (baseline) sample. |
| Urinary Pregnancy test (WOCBP only) | | X[10] | X[10] | | X[10] | | X[10] | |
| Urinalysis (including biomarker samples) | | X | X | | X | | X | |
| Randomization | | | X | | | | | All baseline assessments at V2 should be completed prior to randomization |
| Study treatment | | | X | ←→ | X | | | |

| Procedure | Pre-Screening and Screening[1] | | Treatment Period (14 days) | | | Follow-up Phone call | Unscheduled visit [2] | Notes |
|---|---|---|---|---|---|---|---|---|
| | V0 | V1 | V2 | V3 | V 4 | V5 | | |
| Dispense study medication | | | X | | | | | |
| Monitor IP compliance (via manual counting and App) | | | X | X | X | | | Digital App monitoring to begin at V2 |
| Collect IP | | | | | X | | | |

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed consent form (ICF).
- Safety assessments should be performed in the following order where applicable/ possible: vital signs, ECG measurements, blood samples and spirometry.

1. Screening visit is split into pre-screening on visit 0 and screening on visit 1 although the visits may be performed on the same day. This is to a) enable participants to potentially have more than one attempt at sputum induction for meeting eligibility and b) to only collect minimal screening data for subjects who fail on the basis of the elevated NETs since that is the key inclusion criteria that may not be known from medical records.
2. Unscheduled visits may be used to collect information related to adverse events, for follow up of any safety assessments, and also to complete assessments where participants were not able to perform these within the visit window for any reason. It is not necessary to carry out all of the assessments listed under an unscheduled visit at a single visit; the assessments performed should be driven by the need for the visit.
3. VOC measurement should be undertaken prior to sputum induction at these visits.
4. Sputum induction (and associated VOC measurement and safety spirometry) at visit 1 is only necessary if participant unable to give sample at visit 0. Where the participant is judged by the investigator to have a borderline sputum NETs level ( <0.5 units/ml) at visit 0, they will be invited to give a second sputum sample on visit 1 to re-assess eligibility.
5. VOC measurements should be undertaken at the following timepoints at this visits: prior to sputum induction,and 4 hours post dose
6. 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 Ribonucleic acid (RNA) testing is optional; however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enroll participants with positive Hepatitis C antibody due to prior resolved disease.
7. At visits 2 and 4, PK samples should be collected at the following time-points: pre-dose, 0.5, 1, 2 and 4 hours post-dose.
8. At visit 3 only a pre-dose PK sample should be collected.
9. Agreeing to genetic sample consent is not required for overall study participation. Informed consent for genetic sample must be obtained prior to taking sample.
10. Pregnancy testing only required for women of child bearing potential (WOCBP). A positive urine pregnancy test requires confirmation with a serum pregnancy test.

# 3. INTRODUCTION

The inflammation associated with chronic obstructive pulmonary disease (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 CXC chemokine receptor type 2 (CXCR2) chemokine receptor plays a pivotal role in neutrophil recruitment to the lung. For neutrophils, chemokine binding to the CXCR2 receptor 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.

Danirixin is a selective CXCR2 antagonist being developed as a potential anti-inflammatory agent for the treatment of COPD and influenza. Danirixin has demonstrated potent antagonism of CXCR2 activity both *in vitro* and *in vivo* in preclinical studies [GlaxoSmithKline Document No. YM2010/00163/08].

Clinical pharmacology studies in healthy volunteers demonstrated the pharmacodynamic activity of danirixin (inhibition of *ex vivo* CXCL1-induced CD11b expression on peripheral blood neutrophils). In a Phase IIa study in symptomatic participants with mild to moderate COPD at risk for exacerbation (GSK Study No. 200163) [GlaxoSmithKline Document No. 2013N180289_03], danirixin reduced respiratory symptoms as measured with E-RS:COPD, compared to placebo [Miller, 2016].

## 3.1. Study Rationale

The aim of this study is to better understand the mechanism of action of danirixin, and to understand whether danirixin impacts neutrophil function via effects on neutrophil extracellular traps (NETs) formation in sputum and in peripheral blood *in vivo*, since *in vitro experiments* have suggested that CXCR2 antagonism reduces NETs formation in peripheral blood neutrophils from COPD patients [Pedersen, 2017], with NETs formation being proposed as one mechanism for disease progression in COPD.

This study specifically aims to test the hypothesis that twice daily administration of danirixin HBr 35mg reduces NET formation in participants with COPD and is the first study of its kind in COPD. Reduction of NET formation has potential application in a host of chronic lung diseases, infections and autoimmune disease, thus supporting development of danirixin across a wide range of indications.

## 3.2. Background

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. There is a paucity of novel therapies that target these symptoms, and there are no currently available therapies that modify disease progression

in COPD. There are no licensed CXCR2 antagonists currently available, with one other compound (AZD5069) currently under development for indications other than COPD.

The current study is a mechanistic study to better understand the pharmacology of danirixin and to assess the effect of danirixin on neutrophil extracellular traps (NETs) formation (or NETosis). NETs consist of decondensed chromatin coated in antimicrobial and granular proteins that are extruded in the extracellular space by neutrophils as a defensive mechanism in response to microorganisms, soluble factors and host molecules [Pires, 2016].

Whilst NETs can have a protective role against bacterial dissemination [Brinkmann, 2004] excessive NETosis can cause host damage, with the lung being especially vulnerable to damage from NETs. For example, following infection with the H1N1 virus in animal models, NETs expressing MMP-9 were found entangled with alveoli, causing increased alveolar capillary damage and small airway obstruction, suggesting a link between these DNA lattices and lung damage [Narasaraju, 2011]. There is differential activation of NETosis pathways and responses in reaction to different pathogens and triggers [Delgado-Rizo, 2017] hence consideration of both the host microbiome and infectious species are important. COPD patients colonized with *Haemophilus Influenzae* appear more susceptible to NETosis [Dicker, 2017], therefore identification of host microbiome subspecies could be important for targeting patients for treatment with CXCR2 antagonists. Detection of the lung microbiome has been explored via breath analysis of volatile organic compounds (VOC),and may provide a non-invasive method to identify people with COPD who are colonized with *Haemophilus Influenzae* [Shafiek, 2015]

In addition to infectious disease, massive NET formation has also been reported in autoimmune diseases, inflammatory disease, and several lung diseases [Delgado-Rizo, 2017], including COPD, and could form one mechanism for disease progression [Grabcanovic-Musija, 2015; Dicker, 2017].

Blocking CXCR2 on neutrophils has been shown to decrease NET formation in some inflammatory *in vitro* and murine models [Marcos, 2010]. In peripheral blood neutrophils derived from COPD patients, in vitro treatment with CXCRs antagonists showed a reduction in NETs formation [Pedersen, 2017].

This study specifically aims to test the hypothesis that danirixin may reduce NET formation (NETosis) in participants with COPD, to improve our understanding of its pharmacology in humans, and the definition of target patient population for subsequent clinical trials.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK1325756 is provided in the Investigator's Brochure.

## 3.3. Benefit/Risk Assessment

More detailed information about the potential benefits and risks of danirixin may be found in the danirixin Investigator's Brochure [GlaxoSmithKline Document No. YM2010/00163/08].

### 3.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational Product (IP) GSK 1325756** | | |
| 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 twice daily dosing (BID) free base tablet.<br><br>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<br>No adverse events related to testicular effects have been observed in clinical studies to date. | Standard safety monitoring will be employed.<br><br>The potential risk of testicular injury has been conveyed in the informed consent.<br><br>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 area under the concentration curve from pre-dose to 24 hours post-dose (AUC[0-24] for the NOAEL of testicular effects is low. |
| 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 | Monitoring of peripheral blood neutrophil count.<br><br>Stopping criteria: in participants with a confirmed absolute neutrophil count ≤ 0.5 x $10^9$/L product will be discontinued and |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | (e.g., influenza viral load).<br><br>Secondary bacterial infections after viral infection have not been directly evaluated in nonclinical studies.<br><br>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.<br><br>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 201682, GlaxoSmithKline Document No. 2014N205875_00), decreased neutrophil counts have been observed in subjects receiving either placebo or danirixin; no instances of danirixin-related neutropenia have been reported in clinical studies to date. In healthy subjects, the data are confounded by the observation of low neutrophil counts before dosing or at follow-up, and were not dose-related, while in patients with influenza, neutrophil counts recovered while receiving danirixin, coincident with resolution of the viral infection. There have been no reports of neutrophil count decreases below the lower limit of normal in patients with COPD | neutrophil count will be monitored until return to normal.<br><br>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. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | who were treated with danirixin for one year.<br><br>These data support the conclusion that a causal association of neutropenia with danirixin cannot be definitively established. | |
| 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 elated 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.<br>Male participants with female partners of child-bearing potential must comply with the contraception requirements. |
| **Study Procedures** | | |
| Sputum Induction | During induction of sputum, the hypertonicity of saline, the rate and volume of administration can potentially cause bronchoconstriction and clinically important dyspnoea in some patients with COPD, with a resulting fall in forced expiratory volume in one second $FEV_1$ of >10%. | Participants will be dosed with bronchodilators prior to sputum induction and will have a post-induction spirometry measure at 15 minutes, and will be treated with bronchodilators if there is evidence of bronchospasm. |
| **Other** | | |
| None | | |

### 3.3.2. Benefit Assessment

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

### 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. To date no significant risks have been identified for danirixin from toxicology data or completed and ongoing clinical studies. While the potential for AEs related to testicular effects or impaired neutrophil response cannot be dismissed, no such effects have been observed in healthy subjects, or in subjects with COPD or influenza. Data regarding host response outcomes in COPD and influenza are limited, but no increase in infections have been observed to date.

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 the change from baseline in NETs formation in participants with COPD following 14 days treatment with danirixin HBr 35mg twice daily | • Reduction in sputum NETs (quantified by Histone-elastase complexes) |
| **Secondary** | |
| • To assess the change from baseline in NETs formation in participants with COPD following 14 days treatment with danirixin HBr 35mg twice daily | • Reduction in sputum NETS (quantified by Deoxyribonucleic acid [DNA]-elastase complexes)<br>• Reduction in sputum NET area quantification by microscopy |
| • To further characterize the safety of danirixin HBr 35mg twice daily compared with placebo in | • Adverse events<br>• Vital Signs<br>• ECG |

| Objectives | Endpoints |
|---|---|
| participants with COPD | • Spirometry<br>• Clinical Laboratory Assessments (hematology, clinical chemistry, urinalysis) |
| • To assess the effects of danirixin HBr 35mg twice daily on NETosis-associated biomarkers in sputum and peripheral blood | • Change from baseline in sputum resistin levels<br>• Change from baseline in the ratio of sputum NETs to sputum neutrophils<br>• Change from baseline in sputum elastase activity<br>• Change from baseline in peripheral blood neutrophil NET formation (DNA release, microscopy) |
| • Characterise the population pharmacokinetic (PK) profile of approximately 14 days of dosing of danirixin HBr 35mg twice daily in participants with COPD | • Model specific PK parameters of danirixin (e.g., oral clearance, oral steady-state volume of distribution). |
| **Exploratory** | |
| • To explore the relationships between NETs formation and lung microbiome composition | • Characterize sputum microbiome composition and diversity |
| • To explore volatile organic compound (VOC) profile in participants with COPD | • Characterize relationship between lung microbiome and exhaled volatile organic compounds (VOCs) in stable COPD<br>• To explore variability of exhaled VOCs |
| • To explore the effects of danirixin HBr 35mg twice daily on neutrophil activity and exploratory biomarkers | • Changes from baseline in ex-vivo neutrophil phagocytosis of bacteria by flow cytometry<br>• Changes in exploratory urine, sputum and blood biomarkers (e.g. plasma fibrinogen, serum C-reactive protein, serum IL-8 or sputum mucin) |
| • To explore the effects of an App on adherence to treatment with danirixin or placebo | • Characterize treatment adherence in relation to monitoring via App and explore relationship to PK parameters |

# 5. STUDY DESIGN

## 5.1. Overall Design

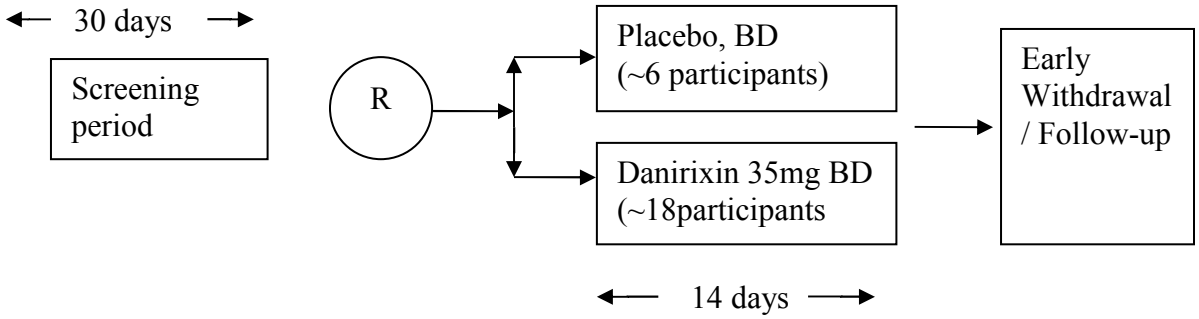
A study schematic is shown in Figure 1. This is a parallel group study. Following screening, participants will be randomized (3:1) to receive danirixin 35 mg or placebo. Study treatment will be administered twice daily for 2 weeks.

Based on the observed variability at an interim analysis, additional subjects may be enrolled to improve the statistical properties of the end of study decision criteria (i.e., the probability of a positive outcome). Outputs containing unblinded treatment assignments will be created for this interim analysis will only be made available to a limited number of GSK staff. Full details will be included in the study data dissemination plan. No Independent Data Monitoring Committee (IDMC) will be utilized for this study.

While the study is being conducted, core members of the study team will be unblinded (with the exception of those study team members who will directly interact with study sites, e.g. Operations and Science Leader and Data Quality Leader). There will be ongoing review of safety data and clinical outcomes. Only the study statistician will have access to individual participant treatment assignments, other core team members will review aggregate summaries by study treatments. A study charter will specify which team members will have access to unblinded data while the study is ongoing and the data to be included in the data reviews.

The danirixin safety review team will perform ongoing safety review and will meet at least once while the study is ongoing and as needed based on emerging data to review available safety information.

**Figure 1 Study Schematic**




*R=Randomization

Notes:

- Early Withdrawal visit to occur as soon as possible (ASAP) after decision to withdraw by either investigator or participant
- Follow up phone-call to occur within 7 days of last dose of study medication

## 5.2. Number of Participants

Approximately 50 participants will be screened to obtain approximately 24 subjects who are randomized and also complete the primary endpoint assessment at Day 14. It is anticipated that less than 10% of participants will drop out of the study given the short duration of treatment.

A maximum of 32 participants will be randomized such that approximately 24 evaluable participants complete the study. An evaluable participant is one that completes all assessments related to the primary endpoint at visits 0 - 4 (see Section 10.1 for further details).

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

## 5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

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

## 5.4. Scientific Rationale for Study Design

This study is designed as a mechanistic study to evaluate the effect of danixirin in reducing NET formation. NET formation has been studied across several human studies, however consensus has not been reached on identification of NETs, which relies upon detection of DNA. Presence of bacterial DNA can confound results from sputum, therefore detection of histone elastase complexes is increasingly recognised as a specific and robust assay for detection of NETosis, and is used as the primary endpoint. The duration of treatment, 2 weeks, is adequate to see treatment effect given that neutrophil lifespan is 1-2 days.

## 5.5. Dose Justification

One dose of danirixin is proposed for this study, 35mg twice daily. 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 in healthy volunteers
- Evidence of reduced respiratory symptoms in mild to moderate COPD participants in the Phase IIa study (200163)
- Relative bioavailability study comparing danirixin free base vs HBr

Analysis of the percent inhibition achieved across the pooled data from studies in healthy volunteers indicated that the maximum possible inhibition of CXCL1-induced CD11b activated neutrophil expression had been achieved following oral administration of danirixin at a nominal dose of 200 mg BID.

In Phase IIa COPD study (200163), a dose of danirixin (free base) 75 mg BID resulted in a reduction in respiratory symptoms compared to placebo.

The danirixin formulation to be used in this study (207551) will be a hydrobromide salt tablet. The hydrobromide tablet has approximately twice the exposure of the free base tablet in healthy elderly participants (GSK Study No. 201037). Based on the anticipated higher exposure from the hydrobromide tablet, the 35 mg twice daily dose was selected for this study to maximize the potential to see any impact on NET formation.

# 6. STUDY POPULATION

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

## 6.1. Inclusion Criteria

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

**Age**

1. Participant must be 50 to 75 years of age inclusive, at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2. Diagnosis of COPD with mild to moderate airflow obstruction (post-bronchodilator $FEV_1$/ Forced Vital Capacity (FVC) ratio <0.7 and FEV1% predicted (pred) ≥40% at screening) based on the Quanjer reference equations, with spirometry conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) current guidelines.
3. Elevated sputum neutrophil extracellular traps based on screening assay for histone-elastase complexes of >0.5 units/ml sputum. Two further screening samples can be submitted for analysis within 30day screening period if previous samples do not pass criteria.
4. Able to produce at least 1ml of sputum sample at the screening visit with nebulised saline induction
5. Current smokers and former smokers with a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent). Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1.

**Weight**

6. Body weight ≥45 kg

**Sex**

7. 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, corresponding to approximately 6 half-lives (which is the time needed to eliminate any teratogenic treatments after the last dose of study treatment and refrain from donating sperm during this period.

   **b. Female participants:**

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

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

   OR

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

**Informed Consent**

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

## 6.2. Exclusion Criteria

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

**Medical Conditions**

1. Primary clinical diagnoses of any of the following relevant lung diseases; asthma, sarcoidosis, tuberculosis, pulmonary fibrosis, severe bronchiectasis or lung cancer
2. Known alpha-1-antitrypsin deficiency
3. Pulse oximetry <88% at rest at screening. Participants should be tested while breathing room air.
4. Participants on long term oxygen therapy (defined as >15 hours/day of oxygen use)
5. Unstable co-morbidities (eg cardiovascular disease, active malignancy) which in the opinion of the Investigator would make the participant unsuitable to be enrolled in the study. This includes any abnormality identified on screening bloods or screening ECG which in the opinion of the Investigator would make the participant unsuitable for the study.

6. 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.
7. Current or chronic history of liver disease, or know hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
8. Participants with a known or suspected history of alcohol or drug abuse within the last 2 years

**Prior/Concomitant Therapy**

9. Antibiotic use concurrently or within 28 days preceding the screening visit, including current or planned chronic use of macrolide antibiotics during the study period for the prevention of COPD exacerbations. Examples of chronic use include daily or two-three times per week for at least 3 months
10. Systemic immunosuppressive medication, including current oral corticosteroids at a dose >5mg, concurrently or within 28 days preceding the screening visit.
11. Oral or injectable Cytochrome P450 (CYP) 3A4 or Breast Cancer Resistance Protein (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: Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan..
12. Current use of phosphodiesterase-4 inhibitors: Roflumilast, Crisaborole and Apremilast
13. Current use of Raloxifene
14. Current use of low molecular weight heparin

**Prior/Concurrent Clinical Study Experience**

15. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half lives, or twice the duration of the biological effect of the investigational product (whichever is longer).
16. Exposure to more than four investigational products within 12 months prior to the first dosing day.

**Diagnostic assessments**

17. Participants with a peripheral blood neutrophil count < 1.0 x $10^9$/L at screening
18. Diagnosis of pneumonia (chest X-ray or computed tomography [CT] confirmed) within the 3 months prior to screening
19. 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).

20. Abnormal and clinically significant 12-lead ECG finding at screening. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would preclude a participant 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 beats per minute (bpm);
    - sustained or non-sustained ventricular tachycardia (VT)
    - second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator has been implanted)
    - QT interval corrected for heart rate by Fridericia's formula (QTcF) ≥500 msec in participants with QRS <120 msec and QTcF ≥ 530 millisecond (msec) in participants with QRS ≥120 msec

**Other Exclusions**

21. Affiliation with a study site: study investigators, sub-investigators, study coordinators, employees of a study investigator, sub-investigator or study site, or immediate family members of any of the above that is involved with the study.

## 6.3. Lifestyle Restrictions

No restrictions are required.

### 6.3.1. Meals and Dietary Restrictions

No meal or dietary restrictions are required for participation in this study, but participants should have fasted for 6 hours prior to each visit. 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. Caffeine, Alcohol, and Tobacco

Participants should refrain from alcohol for 24 hours prior to each study visit, and avoid caffeine for 6 hours prior to each visit. Participants should avoid changes to their tobacco habit for the duration of the study, and, where applicable, try to refrain from smoking for 4 hours before each visit.

### 6.3.3. 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 SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) or have an exacerbation of COPD in the screening period (run-in failure) may be rescreened once. If rescreening is performed, subjects are assigned a different unique subject Identification (ID) number for the re-screening, and all the screening procedures must be repeated.

# 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

| | | |
|---|---|---|
| **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 HBr | 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 Labelling** | Study Treatment will be provided in a High-density polyethylene (HDPE) bottle with desiccant. Each bottle will be labelled as required per country requirement. | Study Treatment will be provided in a HDPE bottle with desiccant. Each bottle will be labelled as required per country requirement. |
| **Manufacturer** | GSK | GSK |

## 7.2. Dose Modification

No individual participant dose modifications or adjustments are allowed.

## 7.3. Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site.

Study treatment will be dispensed at study visit 2 (see SoA). Returned study treatment should not be re-dispensed to the participants.

## 7.4. Blinding

The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken by the investigator or treating physician in the case of an emergency, or if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The investigator is encouraged to discuss with the GSK Medical Monitor or appropriate GSK study personnel before the blind is broken. If GSK is not notified before the blind is broken, they must be notified as soon as possible after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

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.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual or other specified location.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## 7.6. Treatment Compliance

- When 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 danirixin or placebo will be assessed through querying the participant during the site visits and documented in the source documents and case report form (CRF). A record of the number of danirixin or placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the CRF.

  Compliance at each visit will be determined as follows:

  (# dispensed - # returned) x 100 / (# days since last visit)

- Participants estimated to have taken less than 80% or more than 120% of study treatment tablets at two consecutive visits will be considered noncompliant. All attempts should be made to improve the participant's compliance in taking study treatment at visit 3.
- Treatment compliance may additionally be assessed via a digital application (a medication adherence monitoring Platform) for all participants in the study. The Platform uses artificial intelligence on smartphones to confirm treatment ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions. Use of this platform will in no way supersede or replace the physician and/or prescribed medication protocol of the participants. Since the platform does not change the treatment protocol of the participants, but rather encourages adherence to the study treatment to the predefined protocol, use of this platform presents minimal risk to the participants. Consenting to use of the Platform is optional for participation in the study.

  The monitoring Platform requires that all participants take each dose of the study treatment while using a smartphone. The platform will be provided to participants preloaded on a smartphone, or participants can download the platform onto their own mobile device during V2.

When at home, participants will receive reminders within predefined windows to self-administer the study treatment using the front-facing webcam on their smartphone. The application on the smartphone will make an automated determination of whether the participant has properly ingested their treatment at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider

need to be available at the time the participant takes their treatment. Further information on the Platform in available in Appendix 9 .

## 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. long-acting muscarinic antagonist [LAMA], long-acting beta-agonist [LABA]) and long-acting bronchodilator combination therapies (e.g. LAMA/LABA) and long-acting bronchodilator/inhaled corticosteroid steroid combination (ICS) therapies (e.g. LABA/ICS, LAMA/LABA/ICS)

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

- Systemic immunosuppressive medication, including current oral corticosteroids at a dose >5 mg, concurrently or within 28 days preceding the screening visit.
- Acute or chronic use of antibiotics, including macrolides for the prevention or treatment 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 includeMethotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.
- Current use of phosphodiesterase-4 inhibitors: Roflumilast, Crisaborole and Apremilast
- Broad spectrum phosphodiesterase inhibitors (e.g. theophylline)
- Raloxifene
- Low molecular weight heparin

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

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

The use of rescue medications is allowable at any time during the study. 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

A participant who discontinues study treatment should return to the clinic only for safety assessments as part of an unscheduled visit (physical examination, 12-lead ECG, vitals, blood tests, urinalysis and concomitant medication review) and to return IP as detailed in the SoA and Section 9.4.

### 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.

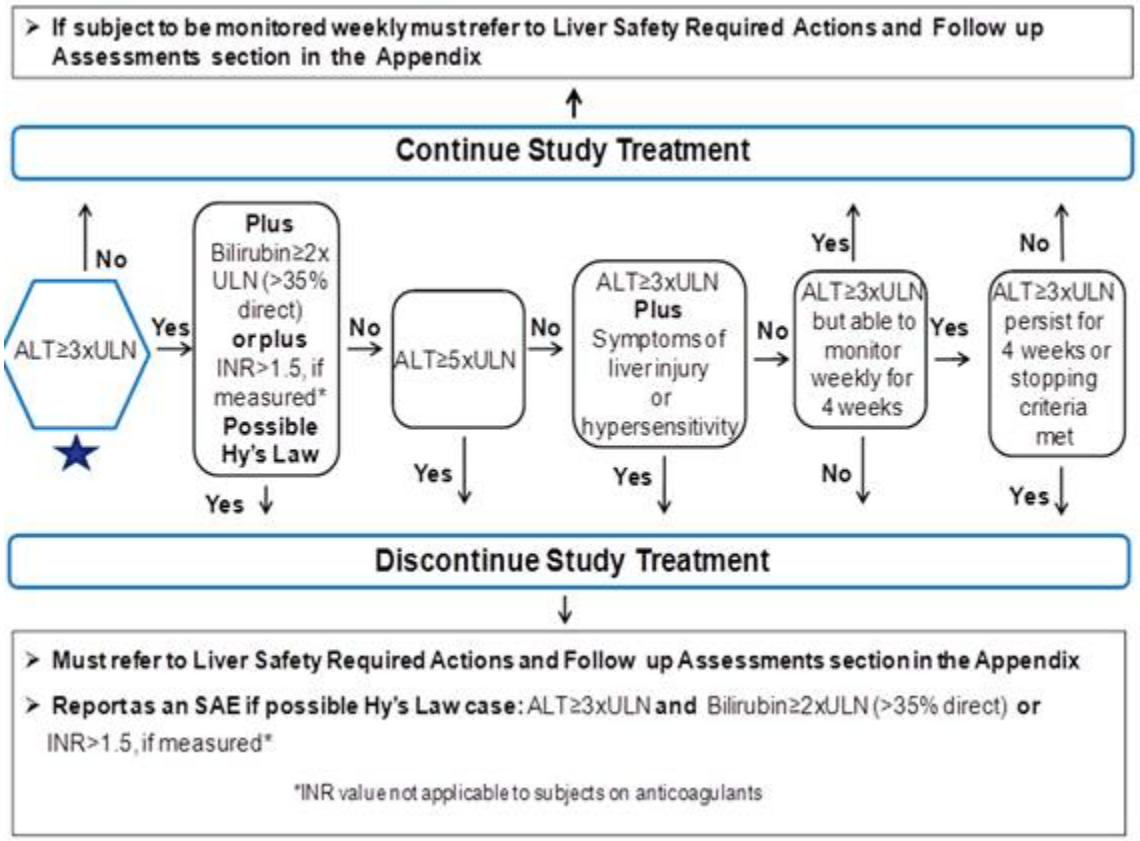
Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm

OR

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

**Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm**




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

### 8.1.2. 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 discontinue treatment and withdraw from the study. The neutrophil count should be monitored daily until it returns to within the baseline value, as detailed in Appendix 8.

### 8.1.3. 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 QT interval corrected for heart rate by Bazett's formula (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* QT

interval corrected for heart rate *(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 participants with underlying bundle branch block, follow the discontinuation criteria listed below:

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

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

### 8.1.4. Temporary Discontinuation

Withdrawal of study treatment requires withdrawal from the study.

### 8.1.5. Rechallenge

#### 8.1.5.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

## 8.2. Withdrawal from the Study

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

- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- **Any participant who experiences a COPD exacerbation (i.e., associated with antibiotic or steroid use) will be permanently discontinued from study treatment and should return to the clinic for follow-up if possible. Only the safety assessments scheduled for the follow-up visit should be conducted in these participants as described in the SoA (Section 2).**

## 8.3. Lost to Follow Up

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

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

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

# 9. STUDY ASSESSMENTS AND PROCEDURES

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

baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the 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. Induced Sputum samples

Participants should have pre-treatment with a short-acting bronchodilator prior to sputum induction where they have not conducted post-bronchodilator spirometry prior to sputum induction. Sputum induction will be performed using 3% saline given as 3 nebulisations [Singh, 2010]. Where 3% saline is insufficient to obtain a sufficiently large sputum sample, 4.5% saline will be administered as 3 nebulisations. This process may take from 10 to more than 20 minutes, depending on the participant and the concentration of salt. Sputum induction can be terminated at any time if participants are able to produce a sputum sample of sufficient volume. The participant should be monitored for 15 minutes following the procedure; if any respiratory distress or wheezing is present, a short-acting bronchodilator should be administered. Safety spirometry is required for 15 minutes after end of the procedure (see Section 9.4.5), and a short-acting bronchodilator should be administered if there is any evidence of bronchospasm.

A minimum of 1ml of sputum will be collected. Remaining sputum may be stored for future biomarker analysis (see Section 9.1.2)

### 9.1.2. Biomarkers

Sputum will be used to assess NET formation via a range of measures: Histone-elastase complexes, DNA-elastase complexes, NET area quantification by microscopy, ratio of sputum NETs to sputum neutrophils. Additionally, sputum will also be analyzed for resistin levels, elastase activity, microbiome composition and diversity and ex-vivo neutrophil phagocytosis of bacteria by flow cytometry, as samples permit.

Blood will be used for the assessment of NET formation in peripheral blood and to explore biomarkers associated with disease activity such as plasma fibrinogen and C-reactive protein (CRP).

Storage of biomarkers for future research is an optional part of this study, and participants will be asked for written consent for storage, which they can withdraw at any time. Blood, urine and sputum samples for biomarker research will be collected from participants in this study where possible as specified in the SoA.

Since collection of biomarkers is optional, separate collection procedures are not essential, i.e. sputum collection is through any remaining sputum from induction, and a further sputum induction is not necessary. Similarly, blood and urine will be collected for storage at the same time as taking clinical measurements for the study; where remnant

volumes are insufficient for storage, further attempts at collection are entirely voluntary for participants.

In addition, with the participant's consent, samples will be stored and analysis may be performed on biomarker variants thought to play a role in NETosis to evaluate their association with observed clinical responses to danirixin.

Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to danirixin, disease process, pathways associated with disease state, and/or mechanism of action of the study treatment.

### 9.1.3. Measurement of volatile organic compounds (VOCs)

Exhaled breath samples through normal tidal breathing will be collected via a ReCIVA (Owlstone Medical, Cambridge, UK) collection device, which connects a disposable face mask onto multiple sorbent tubes that bind VOCs. The sorbent tubes will be stored and later subject to analysis via one or more devices that measure patterns of exhaled VOCs, such as eNoses or Field asymmetric ion mobility spectrometry (FAIMS) devices, and may also be subject to gas chromatography mass spectrometry for comparison. Exhaled breath samples should be collected at the timepoints specified in the SoA, and samples should be collected prior to administration of bronchodilators and sputum induction (with the exception of the samples taken at 4 hours post dose). Further sampling considerations are detailed in the SRM.

## 9.2. Adverse Events

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

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

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4

### 9.2.2. Method of Detecting AEs and SAEs

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

### 9.2.3. Follow-up of AEs and SAEs

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

### 9.2.4. Regulatory Reporting Requirements for SAEs

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

### 9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will

be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

### 9.2.6. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 60 hours after the end of treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

## 9.3. Treatment of Overdose

For this study, any dose of danirixin greater than 70 mg within a 24-hour time period 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 if applicable, for at least 3 days following overdose.
3. Obtain a plasma sample for PK analysis 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 (with participants wearing no shoes) will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 9.4.2. Vital Signs

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

### 9.4.3. Electrocardiograms

- Triplicate 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 8.1.3 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 Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

### 9.4.5. Spirometry

Post-bronchodilator spirometry using $FEV_1$ and FVC measurements ($FEV_{1\%pred}$, and $FVC_{\%pred}$ and $FEV_1$/FVC will be calculated based on Quanjer reference equations [Quanjer, 2012]) will be at time points listed in the SoA. Spirometry assessments should be performed in accordance with ATS/ERS guidelines as outlined in the SRM.

## 9.5. Pharmacokinetics

Blood samples for pharmacokinetic analysis of danirixin (approximately 1ml) will be collected at the time points indicated in SoA. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Processing, storage and shipping procedures are provided in the SRM.

Blood analysis will be performed under the management of Platform Technology and Science (PTS)/In vitro In Vivo Translation (IVIVT)/Third Party Resourcing (TPR), GlaxoSmithKline. Concentrations of DNX will be determined in the blood samples using the currently approved analytical methodology.

Raw data will be stored at the bioanalytical site (detailed in the SRM).

Once the blood has been analyzed for DNX, any remaining blood may be analyzed qualitatively for other circulating metabolites and the results reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

## 9.6. Genetics

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

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

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the study reference manual.

### 9.7. Biomarkers

See Section 9.1.2 for information on biomarker collection and analysis.

### 9.8. Health Economics OR Medical Resource Utilization and Health Economics

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

## 10. STATISTICAL CONSIDERATIONS

### 10.1. Sample Size Determination

Approximately 50 subjects will be enrolled in the study to obtain approximately 24 subjects who are randomized and also complete the primary endpoint assessment at Day 14. Subjects who are withdrawn may be replaced. Subjects will be randomized at a ratio of 3:1 for Danirixin:placebo.

While the sample size has been determined by feasibility, consideration has been made regarding the probability of observing a reduction in sputum NETs (quantified by Histone-elastase complexes). Observational data from an external cohort of COPD patients (not yet published) was used to quantify variability of the measurement and used for simulations. Other *ex vivo* data [Pedersen, 2017] using another CXCR2 receptor antagonist and a different assay method had demonstrated a 40% reduction in median spontaneous NET formation.

Danirixin effect is modelled through a parameter, $\rho$, which indicates the extent Danirixin attenuates the true mean sputum NETs value under treatment with placebo. If $\rho = 1$, then there is no Danirixin effect; if $\rho < 1$, then Danirixin reduces the mean sputum NETs value by that amount (e.g. if $\rho = 0.7$ then Danirixin reduces mean sputum NETs by 30%.)

A mixture prior was utilized. One centred on no effect ($\rho = 1$), the other centred on an effect with $\rho = 0.7$, with both normally distributed with the same standard deviation (0.182, based on historical data). It was assumed that under the no effect case, the probability that $\rho$ is less than 0.7 is 5% and under the effect case, the probability that $\rho$ is greater than 1.0 is 5%. The mixture prior used equal weight for each scenario.

Based on this prior, the following probabilities for the study were estimated:

- The probability to observe a mean Danirixin sputum NETs value, which is lower than that observed in the historical data set, is 69.3%.

- The study has a 70% probability of success of being at least 50% certain, after the study, that the true mean sputum NETs values for Danirixin are lower than Placebo

These estimates are contingent on assumptions about Danirixin effects; the ones selected are *a priori* plausible but may change once data from the study is available. Changes to sample size may be made based on the accruing information about effect size and variability once sufficient data is available.

## 10.2. Populations for Analyses

- For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled | All participants who sign the ICF<br>This population will be used for tables/listings of reasons for withdrawal before randomization and listings of AEs and SAEs for non-randomized subjects. |
| Randomized | This population (also considered as the **Intent-to-Treat (ITT) Population)** will consist of all subjects randomized to treatment who receive at least one dose of study medication. This will constitute the primary population for all analyses. |
| Primary Completer | This population will consist of all subjects in the Randomized population who have completed the assessments supporting the primary endpoint (sputum NETs). |
| Safety | All participants in the Randomized population who take at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received. |

- Subjects who withdraw from the study and are replaced will be part of the Enrolled, Randomized and (if applicable) Safety populations.

- The primary analysis for the study (mean reduction in sputum NETs) will use the Primary Completer population.

## 10.3. Statistical Analyses

### 10.3.1. Efficacy Analyses

The Primary Completer population will be used for the primary analysis of sputum NETs.

A mixed effects model with repeated measures will be used for the sputum NETs data. The mean and corresponding 95% credible interval will be calculated for the Danirixin

treatment arm at Day 14. The posterior probability that the true mean reduction from baseline for the Danirixin treatment group in sputum NETs is greater than a 0%, 15%, 30% and 40% reduction will be calculated, as appropriate, depending on the observed data.

Additionally, the mean and corresponding 95% credible interval for the difference between Danirixin and placebo at Day 14 will be produced. The posterior probability that the true relative reduction from baseline in sputum NETs is greater than a 0%, 15%, 30% and 40% reduction will be calculated, as appropriate, depending on the observed data.

The existing reference data may be used to construct the prior distribution for the placebo arm instead of a non-informative prior. A non-informative prior will be utilized for the other parameters in the statistical model as appropriate to their distribution.

Other efficacy data will be presented in tabular and/or graphical format and summarized descriptively. Full details of the analyses to be performed on all efficacy endpoints will be described in the reporting and analysis plan (RAP).

### 10.3.2. Safety Analyses

The Safety population will be used for all safety analyses. Safety data will be presented in tabular and/or graphical format and summarized descriptively. Full details of the analyses to be performed on all safety endpoints will be given in the RAP.

### 10.3.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modelling & Simulation department within GlaxoSmithKline. Blood danirixin concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.2.or later. Calculations will be based on the actual sampling times recorded during the study. From the blood concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed blood concentration (Cmax), time to Cmax (tmax), area under the blood concentration-time curve [AUC(0-t)], time of last observed concentration (tlast). The RAP will describe the planned analyses in greater detail.

PK data from this study may be combined with historic data for the purposes of population PK modelling which would be the subject of a separate analysis plan and would be presented separately from the main clinical study report (CSR).

### 10.3.4. Other Analyses

Biomarker and exploratory analyses will be described in the RAP.

Population analyses for volatile organic compounds will be the subject of a separate analysis plan and presented separately from the main clinical study report (CSR).

### 10.3.5. Interim Analyses

An interim analysis of the primary endpoint may be performed at the discretion of the sponsor to make a determination whether to enrol additional subjects beyond the target of 24 evaluable participants, based on the determination of the posterior probability of a reduction in sputum NETs in the Danirixin arm.. All available data for evaluable subjects for sputum NETs using the histone elastase assay will be included in the analysis.

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

### 10.3.6. Data Management

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

- Management of clinical data will be performed in accordance with applicableGSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.

- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials andday/month of birth will not be collected or transmitted to GSK according to GSK.

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# 12. APPENDICES

## 12.1. Appendix 1: Abbreviations and Trademarks

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminot*ransferase* |
| *ASAP* | *As so*on as possible |
| ATS | American Thoracic Society |
| AUC(0-24) | Area under the concentration curve from pre-dose to 24 hours post-dose |
| BID | Twice daily dosing |
| BPM | Beats per minutes |
| CONSORT | Consolidated Standards of Reporting Trials |
| BCRP | Breast Cancer Resistance Protein |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| CT | Computed tomography |
| CV | Cardiovascular |
| CXCL1 | chemokine (C-X-C motif) ligand 1 |
| CXCR2 | CXC chemokine receptor type 2 |
| CYP3A4 | cytochrome P-450 isoenzyme 3A4 |
| DNA | Deoxyribonucleic acid |
| DNX | Danirixin |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ERS | European Respiratory Society |
| FAIMS | Field asymmetric ion mobility spectrometry |
| FDA | United States Food and Drug Administration |
| $FEV_1$ | The amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation also known as forced expiratory volume in one second |
| FSH | Follicle Stimulating Hormone |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GFR | Glomerular Filtration Rate |
| GSK | GlaxoSmithKline |
| Hep C | Hepatitis C |
| HBr | Hydrobromide |
| HBsAg | Hepatitis B Surface Antigen |
| HDPE | High-density polyethylene |
| IB | Investigator's Brochure |
| HIV | Human Immunodeficiency Virus |

| | |
|---|---|
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICS | Inhaled corticosteroid |
| ID | Identification |
| IDSL | Integrated Data Standards Library |
| IEC | Independent Ethics Committee |
| ITT | Intent-to-treat |
| IRB | Institutional Review Board |
| IVRS/IWRS | Interactive Voice/Web Response System |
| LABA | Long-acting beta-agonist |
| LAMA | Long-acting muscarinic antagonist |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSDS | Material Safety Data Sheet |
| NETs | Neutrophil extracellular traps |
| NETosis | NET formation |
| NOAEL | No observed adverse effect level |
| PK | Pharmacokinetic |
| Pred | Predicted |
| PTS-DMPK | Platform Technology and Science- Drug Metabolism and Pharmacokinetics |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected for heart rate by Bazett's formula |
| QTcF | QT interval corrected for heart rate by Fridericia's formula |
| RAP | Reporting and Analysis Plan |
| RNA | Ribonucleic acid |
| SABA | Short acting beta agonists |
| SAE | Serious Adverse Event |
| SAMA | Short acting muscarinic antagonists |
| SRM | Study Reference Manual |
| SRT | Safety Review Team |
| SoA | Schedule of Activity |
| SUSAR | Suspected unexpected serious adverse reactions |
| ULN | Upper Limit of Normal (reference range for laboratory) |
| VOC | Volatile organic compound |
| VT | Ventricular tachycardia |
| WOCBP | Woman of child bearing potential |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| NONE |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| ReCIVA |

## 12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 1 Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit<br>Fibrinogen | RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes | WBC count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry[1] | BUN | Potassium | Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT) | Total and direct bilirubin |
| | Creatinine | Sodium | Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) | Total Protein |
| | Glucose [non-fasting] | Calcium | Alkaline phosphatase | C-reactive protein |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Other Screening Tests | • Follicle-stimulating hormone (as needed in women of non-childbearing potential only)<br>• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]<br>• Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis | | | |

| Laboratory Assessments | Parameters |
|---|---|
| | C virus antibody) [if applicable]<br>The results of each test must be entered into the CRF. |

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

## 12.3. Appendix 3: Study Governance Considerations

### Regulatory and Ethical Considerations

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

### Financial Disclosure

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

### Informed Consent Process

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

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

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

## Data Protection

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

## Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will

generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

## Dissemination of Clinical Study Data

## Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

## Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in 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.<br>• 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).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• 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.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. |

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

the disease/disorder being studied, unless more severe than expected for the participant's condition.

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

## Definition of SAE

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

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

**a. Results in death**

**b. Is life-threatening**

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

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

**d. Results in persistent disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

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

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

## Definition of Cardiovascular Events

**Cardiovascular Events (CV) Definition:**

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

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

## Recording AE and SAE

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are

requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

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

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

## Reporting of SAE to GSK

**SAE Reporting to GSK via Electronic Data Collection Tool**

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

| **SAE Reporting to GSK via Paper CRF** |
| --- |
| • Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **SAE coordinator**.<br>• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.<br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.<br>• Contacts for SAE reporting can be found in the study reference manual. |

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

### Definitions

### Woman of Childbearing Potential (WOCBP)

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

**Women in the following categories are not considered WOCBP**

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

### Contraception Guidance

#### 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 2 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.
- In addition male participants must refrain from donating sperm for duration of study and for 60 hours after study completion or from last dose.

**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 2.

**Table 2 Highly Effective Contraceptive Methods**

| **Highly Effective Contraceptive Methods That Are User Dependent** [a]<br>*Failure rate of <1% per year when used consistently and correctly.* |
|---|
| Combined (estrogen- and progestogen-containing ) hormonal contraception associated with inhibition of ovulation[b]<br>• oral<br>• intravaginal<br>• transdermal |
| Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>• injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• bilateral tubal occlusion |
| Vasectomized partner<br>*(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<br>(*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 pregnancy test
- Additional pregnancy testing is not required during the treatment period, but is required 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.

## 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 treatment and will 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, COPD and related diseases, or neutrophil extracellular traps. They may also be used to develop tests/assays including diagnostic tests) related to danirixin and other CXCR2 antagonists, and COPD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to 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 continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

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

**Phase II liver chemistry stopping criteria and required follow up assessments**

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

| **Required Actions and Follow up Assessments** | |
|---|---|
| **Actions** | **Follow Up Assessments** |
| • **Immediately** discontinue study treatment<br>• Report the event to GSK **within 24 hours**<br>• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]<br>• Perform liver chemistry event follow up assessments<br>• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below)<br>• **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below)<br>• If restart/rechallenge **not allowed per protocol or not granted**, permanently | • Viral hepatitis serology[4]<br>• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend<br>• Obtain blood sample for pharmacokinetic (PK) analysis, up to 72 h after last dose[5]<br>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).<br>• Fractionate bilirubin, if total bilirubin ≥ 2xULN<br>• Obtain complete blood count with differential to assess eosinophilia<br>• 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<br><br>**MONITORING:**<br><br>**<u>For bilirubin or INR criteria:</u>**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**<br>• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline<br>• A specialist or hepatology consultation is recommended<br><br>**<u>For All other criteria:</u>**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs**<br>• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline | liver injury, or hypersensitivity, on the AE report form<br>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.<br>• Record alcohol use on the liver event alcohol intake case report form (CRF) page<br><br>**<u>For bilirubin or INR criteria:</u>**<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.<br>• 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].<br>• 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.<br>• Participant can continue study treatment<br>• Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline<br>• If at any time participant meets the liver chemistry stopping criteria, proceed as described above<br>• 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: Neutrophil Safety

| **Neutrophil Stopping Criteria:** Absolute neutrophil count (ANC) ≤ 0.5 x $10^9$ /L (peripheral blood) | |
|---|---|
| **Required Actions and Follow up Assessments** | |
| **Actions** | **Follow Up Assessments** |
| • **Immediately** discontinue study treatment<br>• Report the event to GSK **within 24 hours**<br>• Complete an SAE data collection tool if the event also meets the criteria for an SAE<br>• Monitor the participant until neutrophil count stabilizes or returns to within baseline (see **MONITORING** below)<br>• **Do not restart** participant with study treatment<br><br>**MONITORING:**<br>• Treatment of any suspected infections[1]<br>• Repeat CBC within **24 hrs**<br>• Monitor CBC daily until neutrophil count resolves, stabilizes or returns to within baseline | • Record the appearance or worsening of any clinical symptoms on the AE report form[1]<br>• Obtain blood sample for pharmacokinetic (PK) analysis within 12 hours after last dose[2]<br>• Record use of concomitant medications on the concomitant medications report form |

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.

## 12.9. Appendix 9: Medication Adherence Platform

After the device confirms proper treatment ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrolment. The captured data and video is reviewable through a roles and rules restricted system ensuring privacy of the information. All video images and data captured by the AiCure application will be held in encrypted format, both within the application itself and on the secure servers used to validate the Study; those servers are located in the U.S., and therefore your data will be stored and processed in the U.S. The system has been designed to support compliance with applicable regulations to protect the privacy and security of healthcare information, including the Data Protection Act 1998.

Phone numbers of the participants may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with participants, including automated messaging from the Platform device and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with participant names, nor will they be given access to participant medical records.

The Platform Provider will protect participants' personal information to the full extent required by law. However, information from this Study, including de-identified video recording(s) of participant performance of various actions, may be submitted to the Study site, and potentially to the U.S. Food and Drug Administration (FDA). Both information obtained by the application, and information in the participant Informed Consent, may be examined by the Study site or the Study site's representatives, and may also be reviewed by the FDA and other regulatory agencies, Institutional Review Board(s) and or Ethics Committee(s). A depersonalized version of the Study data may be generated and retained by the Platform Provider for use beyond the term of the trial. This will be utilized solely to improve the operation of the Platform, categorize adherence activity by disease state or other useful categories, and/or for regulatory filings by the Platform Provider to support future applications for the Platform Provider's product. Individuals who are not associated with the care and treatment of participants will not have access to participant identity or any medical records. The Platform Provider may also retain a copy of Study data in disaggregated (ie identifiable participant) format beyond the term of the trial for the above purposes where the relevant participant has provided express written authorization for the Platform Provider to do this. Any such authorization shall be entirely voluntary on the part of the participant and separate from participation in the Study.