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

Number of Participants:

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

Treatment Groups and Duration:

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

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

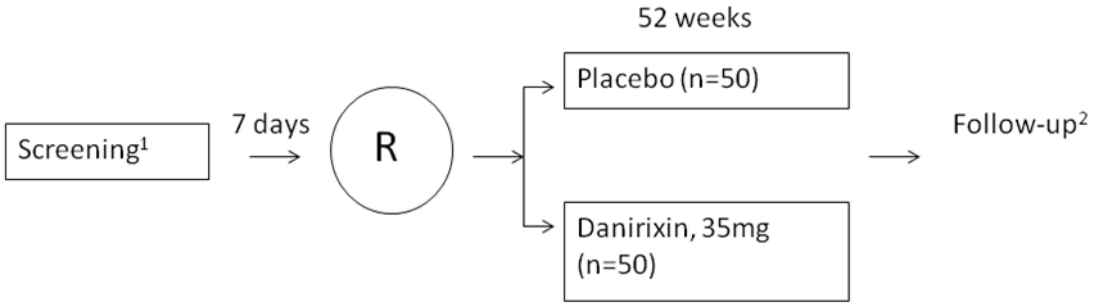
5. STUDY DESIGN

5.1. Overall Design

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

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

Figure 1 Study Schematic



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

5.2. Number of Participants

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

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

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all planned study visits including the last study visit and the last scheduled procedure shown in the Schedule of Activities (Table 1).

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

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, parallel-group design. This is a well established design to evaluate the efficacy and safety of an investigational drug. With the use of an enriched population, it is anticipated that one year of treatment will be sufficient to detect a trend in altering disease progression. Danirixin has already been clinically investigated over one year treatment duration (GlaxoSmithKline Document Number 2013N180289_03 Study ID 200163).

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

5.5. Dose Justification

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

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

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

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

In the previous clinical studies, danirixin was administered as a free base tablet, whereas the danirixin formulation to be used in this study will be a hydrobromide salt tablet. The hydrobromide tablet has approximately twice the bioavailability of the free base tablet in healthy elderly participants (GlaxoSmithKline Document Number 2015N248339_00, Study ID 201037). Thus the danirixin (hydrobromide tablet) 35mg BID dose for investigation in this study is expected to provide steady-state systemic exposure approximately equivalent to the 75mg BID (free base tablet) used in Study 200163. Predicted steady-state exposures and multiples of blood *ex vivo* CXCL1-induced CD11b pharmacology at the proposed danirixin doses are presented in Table 2.

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

Dose (mg)	Predicted# steady-state median (5th, 95th percentile)			Cavg multiple of IC50*	Cmin multiple of IC50*
	AUC(0-24) steady-state (ug.h/mL)	Cavg (ng/mL)	Cmin (ng/mL)		
35	9.59 (4.70, 19.3)	399 (196, 806)	192 (47.6, 630)	5.1	2.4

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

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

6. STUDY POPULATION

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

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

6.1. Inclusion Criteria

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

Age

1. Participant must be 40 to 76 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

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

numerous previous studies of COPD participants and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ and produces SGRQ scores equivalent to the original SGRQ instrument [Jones, 1992].

9.1.3. CAT

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

9.1.4. COPD Exacerbations

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

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

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

The date of onset and the date of resolution will be recorded in the source documents and the eCRF based on the Investigator's judgement.

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

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

Participants will complete a Global Rating of Change in COPD (overall disease) question at every visit following randomization (or Early Withdrawal (EW) Visit). Response

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

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.4 (Appendix 4) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

- COPD exacerbations

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE). These events will be recorded on the DRE page in the participant's CRF within 72 hours after the investigator

becomes aware of the event. These DREs will be monitored by the Safety Review Team (SRT) on a routine basis as described in Section 12.3 (Appendix 3).

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

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

9.2.7. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 60 hours after the last dose of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 12.5 (Appendix 5).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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9.2.8. Medical Device Incidents (Including Malfunctions)

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

The definition of a Medical Device Incident can be found in Section 12.8 (Appendix 8).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Section 12.4 (Appendix 4).

9.2.8.1. Time Period for Detecting Medical Device Incidents

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

9.4.3. Electrocardiograms

For participant screening and pre-dose on Day 1, triplicate ECG measurements should be collected. For all subsequent ECG assessments, single measurements are to be collected. 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 10 minutes.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Section 12.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered abnormal and clinically significant during participation in the study or within 3 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the SoA (Table 1).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the CRF.

9.4.5. Pneumonia

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

- Increased cough
- Increased sputum purulence (colour) or production
- Auscultatory findings of adventitious sounds (e.g. egophony, bronchial breath sounds, rales, etc.)

- Dyspnea or tachypnea
- Fever (oral temperature > 37.5 ^{o}C)
- Elevated white blood cell count (WBC) (> 10 x 10^9/L or > 15% immature forms)
- Hypoxemia (Hb O_2 saturation < 88% or at least 2% lower than baseline value)

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

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

9.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

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

See Section 12.6 (Appendix 6) for Information regarding genetic research. Details on procedures for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

Collection of samples for biomarker research is also part of this study. The following samples for biomarker research will be collected from all participants in this study as specified in the SoA:

- peripheral venous blood samples for the preparation of serum and plasma

Samples will be tested for biomarkers that are indicative of inflammation (i.e. CRP), extracellular matrix turnover and remodelling to evaluate their association with the

EMA	European Medicines Agency
Emax	Maximum response achievable
eMDI	Electronic metered dose inhaler
EW	Early Withdrawal
FDA	Food and Drug Administation (United States)
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FSH	Follicle Stimulation Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HBsAG	Hepatitis B surface antigen
HCRU	Healthcare Resource Utilization
hCG	Human chorionic gonadotrophin
HDPE	High density polyethylene
Hep B	Hepatitis B
Hep C	Hepatitis C
hsCRP	High sensitivity C-reactive protein
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to treat

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

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine hCG testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease

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

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

Definition of SAE

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

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

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

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

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

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

a Informed consent may be signed prior to screening visit in the case that any changes in medications are necessary
b Agreeing to genetic sample consent is not required for study participation
c Smoking status/history assessed at screening; smoking status re-checked at Visit 2
d Includes substance usage, past and present medical conditions and family history of premature CV disease
e Hepatitis B (HBsAg) and Hepatitis C (HepC antibody) testing is required. If testing otherwise performed within 3 months prior to the first dose of study treatment, testing at screening is not required. Hepatitis C RNA testing is optional; however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease.
f Participant's clinical status should be reviewed
g Pregnancy testing is only required for women of child bearing potential (WOCBP). A positive urine pregnancy test requires confirmation with a serum pregnancy test.

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

Weight

4. Body weight ≥ 45 kg

Sex

5. Male or female

   a. Male participants:

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

   b. Female participants:

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

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

   OR

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

Informed Consent

6. Capable of giving signed informed consent as described in Section 12.3 (Appendix 3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

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

options will be on a 7 point Likert scale ranging from much better to much worse. Asking at each Visit allows for early detection of response as well as continued response.

9.2. Adverse Events

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

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

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

- All SAEs will be collected from the time the informed consent is signed by the participant until the follow up visit at the time points specified in the SoA (Table 1).
- All AEs will be collected from the start of study treatment (randomization visit) until the follow-up visit at the time points specified in the SoA (Table 1).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs must be reported immediately and not more than 24 hrs to the sponsor, as indicated in Appendix 4 (Section 12.4). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4 (Section 12.4).

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

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

- The method of documenting Medical Device Incidents is provided in Section 12.8 (Appendix 8).

9.2.8.2. Follow-up of Medical Device Incidents

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

9.2.8.3. Prompt Reporting of Medical Device Incidents to Sponsor

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

9.2.8.4. Regulatory Reporting Requirements for Medical Device Incidents

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

observed clinical responses or to help understand the underlying biological responses to danirixin.

In addition, with the participant's consent, samples will be stored and may be used to investigate additional biomarkers thought to play a role in COPD disease progression or to evaluate their association with observed clinical responses to danirixin

Samples also may be used for research to develop methods or support identification of prognostic/diagnostic biomarkers associated with clinical outcomes in COPD and related diseases.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

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

10.1. Sample Size Determination

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

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

IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IVIVT	In vitro In vivo Translation
IWRS	Interactive Web Response System
kg	Kilogram
L	Liter
LABA	Long acting β2 receptor agonist
LAMA	Long acting muscarinic receptor antagonist
LH	Leutinizing Hormone
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin count
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MM	Medical monitor
MSDS	Material Safety Data Sheet
msec	Millisecond
NOAEL	No observed adverse effect level
O_2	Oxygen
PK	Pharmacokinetics
PR	PR interval; duration in milliseconds from the beginning of the P wave to onset of ventricular depolarization (R)
PRO	Patient Reported Outcome
PTS	Platform Technology and Science
QRS	QRS interval; duration in milliseconds of the QRS complex
QT	QT interval; duraction in milliseconds between the start of the Q wave and the end of the T wave
QTcF	QT interval corrected for heart rate (Friderica formula)
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SABA	Short-acting β2 Receptor Agonist
SAE	Serious Adverse Event

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.

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

5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

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

Reference

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