TITLE PAGE

Protocol Title: A randomized, double-blind, single ascending dose study to determine the safety and tolerability, pharmacokinetics and pharmacodynamics of GSK3772847 administered subcutaneously in healthy participants

Protocol Number: 209635 / Amendment 2

Compound Number or Name: GSK3772847

Study Phase: Phase 1

Short Title: A study to evaluate the safety and tolerability, Pharmacokinetics and Pharmacodynamics of GSK3772847 administered subcutaneously in healthy participants

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s):

IND: 134366

Approval Date: 02-JUL-2020

PPD

From: PPD
Sent: Thursday, July 2, 2020 8:01 PM
To: PPD
Subject: FW: Prot-209635-sponsign

From: Courtney Crim PPD
Sent: 02 July 2020 14:13
To: PPD
Subject: RE: Prot-209635-sponsign

I approve.

Courtney

Courtney Crim, M.D.
Group Director
Respiratory TAU

From: PPD
Sent: Thursday, July 02, 2020 8:52 AM
To: Courtney Crim PPD
Subject: Prot-209635-sponsign
Importance: High

Dear Courtney,

To approve the clinical protocol indicated below, reply to this email and state your approval.

PROTOCOL NUMBER: 209635

DOCUMENT IDENTIFIER: 2020N427367_02

AMENDMENT NUMBER: 02

PROTOCOL TITLE: A randomized, double-blind, single ascending dose study to determine the safety and tolerability, pharmacokinetics and pharmacodynamics of GSK3772847 administered subcutaneously in healthy participants

Name of Sponsor Signatory: Courtney Crim, M.D

Title of Sponsor Signatory: Director, Clinical Development, Clinical Science, Respiratory, GlaxoSmithKline

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	*02-JUL-2020*	*2020N427367_02*
Amendment 1	*12-Jun-2020*	*2020N427367_01*
Original Protocol	*17-Mar-2020*	*2020N427367_00*

Amendment [2] 02-JUL-2020

Overall Rationale for the Amendment:

Amendment to reduce age range from 18 – 65 to 18 – 50 to ensure older populations, potentially more at risk of COVID-19 are not recruited into the study and to update secondary pharmacodynamics endpoint to specify nominal day as maximum timepoint.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 5.1 Inclusion Criteria	Change in inclusion from "18 to 65 years of age, inclusive" to "18 to 50 years of age, inclusive."	Reduced age range to ensure older populations, potentially more at risk of COVID-19, are not recruited into the study.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Updated secondary endpoint for pharmacodynamics (PD) of GSK3772847 from "Maximal decrease in free and increase in total soluble ST2 levels in serum up to a maximum of 89 days post dose" to "Maximal decrease in free and increase in total soluble ST2 levels in serum up to Day 85 visit"	To provide clarity by specifying nominal day as maximum timepoint.
Section 1.1 Synopsis Section 4.1 Overall Design	Clarified participant time in study from "16 weeks and 5 days" to "17 weeks and 4 days" Clarified participant time in study from "up to 89 days" to "up to 95 days"	Updated to clarify a participant's maximum time in study due to visit window extensions.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double-blind, single ascending dose study to determine the safety and tolerability, pharmacokinetics and Pharmacodynamics of GSK3772847 administered subcutaneously in healthy participants

Short Title: A study to evaluate the safety and tolerability, PK and PD of GSK3772847 administered subcutaneously in healthy participants

Rationale:

GSK3772847 is a human immunoglobulin G2 sigma isotype (IgG2σ) antibody that binds Domain 1 of the cell-surface interleukin-33 receptor (IL-33R). Inhibition of IL-33 signalling via blockade of the IL-33 receptor (Suppressor of tumorigenicity 2 [ST2], also known as Interleukin-1 receptor like-1 [IL-1RL1]) presents a potential novel treatment for severe asthma as an add-on to standard of care. Agents targeting this mechanism could be expected to have effects on both type 2 (T2)-driven and non-T2-driven disease.

The purpose of this study is to evaluate the safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending doses of GSK3772847 administered subcutaneously (SC) to healthy participants. It will establish the bioavailability of the SC formulation and evaluate the safety (in particular injection site tolerability) of the SC route.

GSK3772847 has been administered intravenously at doses up to and including 10mg/kg both as single and repeated doses (207597 [GlaxoSmithKline Document number 2017N316832_02 and 207972 [final report pending]). This is the first study to evaluate the PK and PD of GSK3772847 via the subcutaneous (SC) route. Participants will be randomized to receive doses of either 70 (Cohort 1) or 140 mg (Cohort 2, 3 and 4) GSK3772847 or placebo SC. Placebo is included to allow a valid evaluation of adverse events attributable to treatment versus those independent of treatment. The dose selection is based on credible doses for future clinical development and are expected to reduce free sST2 by greater than 90% at peak effect. Recovery to near baseline levels is expected within the study duration. GSK3772847 will be administered in one of 3 injection sites: upper arm, thigh or abdomen. This will allow evaluation of PK and PD via the 3 most common sites for SC administration.

Cohorts of healthy Japanese (Cohort 3) and Chinese (Cohort 4) participants will also be included to enable us to evaluate PK and PD in these populations. To minimise the number of comparisons the impact of injection site will only be evaluated in cohorts 1 and 2 only. Cohorts 3 and 4 will utilise only the upper arm injection site based on the ease of administration by a health care professional (HCP).

PK will be evaluated by non-compartmental analysis. In addition, data from this study will be included in a population-PKPD analysis together with the historic IV data to enable development an appropriate model to describe the PK and PD. This will be reported separately from the main clinical study report (CSR).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single dose of GSK3772847, compared with placebo administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	. • Occurrence of adverse events (AE's) and serious adverse events (SAE's) (including injection site reactions)
• To assess the pharmacokinetics (PK) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants (Cohorts 1 and 2 also summarised by injection site)	• PK parameters, including but not limited to, Area under the plasma-concentration time curve (AUC), maximum plasma concentration (Cmax), time to Cmax (Tmax) and terminal half-life (t1/2) of GSK3772847 per cohort
Secondary	
• To evaluate the pharmacodynamics (PD) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• Maximal decrease in free and increase in total soluble ST2 levels in serum up to Day 85 visit
• To assess the immunogenicity of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• occurrence of anti-GSK3772847 antibodies
• To assess potential changes in Cytochrome P450 3A4 (CYP3A4) enzyme activity following a single dose of GSK3772847 in healthy participants including cohorts of Japanese and Chinese participants.	• Plasma 4β-Hydroxycholesterol (4βOH) cholesterol/cholesterol ratio as an endogenous marker for CYP3A4 activity pre-treatment and following a single dose of GSK3772847
Other	
• To further assess the safety and tolerability of a single dose of GSK3772847, compared with placebo administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• 12-lead electrocardiogram (ECG) measurements • Clinical chemistry laboratory tests • Vital signs
• To evaluate the pharmacodynamics (PD) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• Free and total soluble ST2 levels in serum • Blood eosinophil levels
• To assess the pharmacokinetics (PK) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• GSK3772847 levels in serum

Overall Design:

This is a single centre, randomized, placebo-controlled, double-blind, ascending dose study in healthy participants.

Following a screening period (of up to 28 days), participants who meet the eligibility criteria will be assigned to one of four cohorts and will be randomly allocated within each cohort to receive a single dose of either GSK3772847 or placebo. All treatments will be administered subcutaneously by an HCP. The site of injection will be randomized to the upper arm, abdomen or thigh for cohorts 1 and 2 with cohorts 3 and 4 receiving injections in the upper arm only.

Before dosing in Cohorts 2, 3 and 4 can begin, blinded safety data (including injection site data from dosing to a minimum of 48 hours post-dose) will be reviewed in at least 20 subjects who have received a dose in Cohort 1 (see Section 9.6).

An interim analysis, to assess safety, tolerability, PK and PD, will be performed after a predefined number of participants from all four cohorts have reached 4 weeks post dose (see Section 9.5).

Disclosure Statement: This is a sequential safety, tolerability, PK and PD study with 4 cohorts that is participant and investigator blinded.

Number of Participants:

A total of 64 participants will be initially randomised for a total of 18 evaluable participants on GSK3772847 in cohorts 1 and 2, 6 Japanese participants in cohort 3 and 6 Chinese participants in cohort 4. Participants will be replaced if they withdraw from the study prior to completing all PK and sST2 assessments up to and including Day 29.

Intervention Groups and Duration:

Healthy participants who meet the eligibility criteria will be assigned to one of four cohorts and will be randomly allocated within each cohort to receive a single dose of either GSK3772847 or placebo detailed below.

In the event that all the participants from a given cohort cannot be dosed on the same day, the subgroup dosed must include participants randomized to each of the 3 injection sites.

Cohort 1: 18 participants 70mg GSK3772847 SC and 6 participants Placebo SC

Cohort 2: 18 participants 140mg (2 x 70mg) GSK3772847 SC and 6 participants Placebo SC

Cohort 3 (Japanese): 6 participants 140mg (2 x 70mg) GSK3772847 SC and 2 participants Placebo SC

Cohort 4 (Chinese): 6 participants 140mg (2 x 70mg) GSK3772847 SC and 2 participants Placebo SC

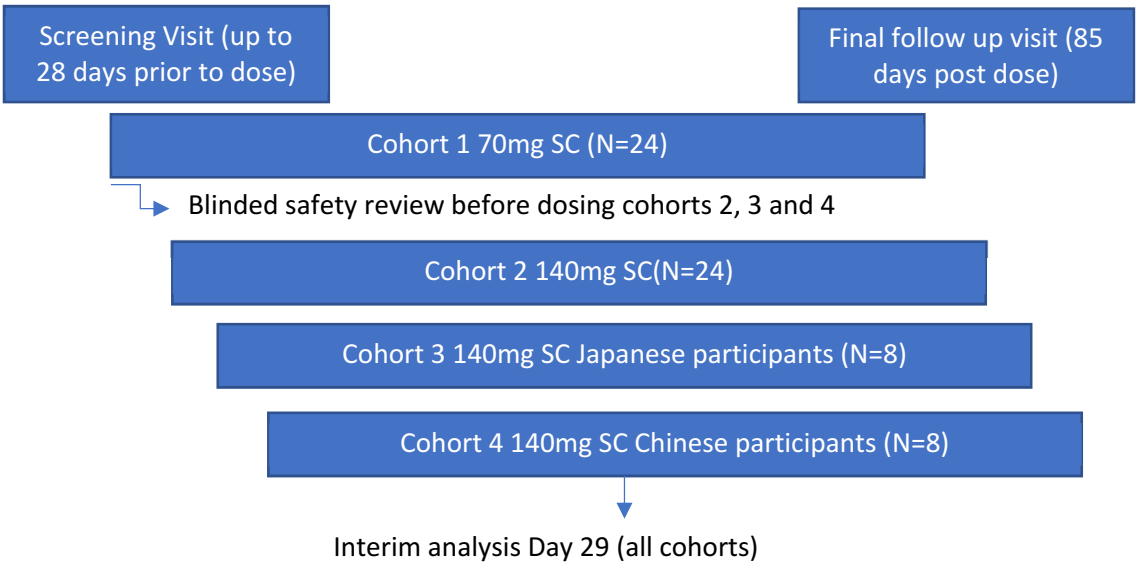
Each participant will:

- Be screened within 28 days prior to their first dose
- Stay within the clinic for 5 nights post dose
- Have follow up visits at days 9, 15, 29, 43, 57, 71 and at day 85
- The total duration a participant remains in the study is up to 17 weeks and 4 days (includes up to 28 days for screening, and up to 95 days post-dose follow up (includes 6 days in clinic)).

Data Monitoring or Other Committee: Yes

- A dose escalation committee will review blinded summary safety data (including injection site data obtained to 48 hours post-dose) of at least 20 participants from cohort 1 , as detailed in Section 9.6. The dose escalation committee will consist of the Principal Investigator and GSK Personnel.
- An interim analysis data review committee consisting of GSK personnel will review safety, PK and PD data of all participants from all cohorts, 4 weeks post dose as detailed in Section 9.5.

1.2. Schema



1.3. Schedule of Activities (SoA)

1.3.1. Screening Schedule of Activities

Table 1 Screening Schedule of Activities

Procedure	Screening up to 28 days before dose	Notes
Informed consent	X	
Inclusion and exclusion criteria review	X	
Demography and medical history	X	
Full physical examination including height and weight	X	
Alcohol/drug screen	X	
Urinary Cotinine Test	X	
Safety labs (haematology, clinical chemistry and urinalysis)	X	To be taken in non-fasted state Further details are given in Appendix 2
Hepatitis B and C and human immunodeficiency virus (HIV) screen	X	
12-lead ECG	X	
Vital signs	X	Supine blood pressure and heart rate
Concomitant medications	X	
Serious adverse events	X	
Pregnancy test	X	Serum at screening and urine dipstick test at all other visits

1.3.2. Treatment Period Schedule of Activities

Table 2 Treatment Period Schedule of Activities

Procedure	Day 0	Day 1 (Hours)					Day 2	Day 3	Day 4	Day 5	Day 6	Day 9	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85/Early withdrawal visit	Notes Time window for Outpatient visits: Day 9 ± 2 days, Day 15 ± 4 days, Days 29, 43 and 57 ± 7 days, Days 71 and 85 ± 10 days
		Pre-dose	0	2	4	8													
Clinic Visits																			
Admission to clinic	X																		Participants may remain in the clinic until day 6 with visits at days 6-8 as outpatient, at the investigator's discretion
Inclusion/Exclusion criteria review	X																		
Discharge from clinic											X								
Out-patient visit												X	X	X	X	X	X	X	
Study Intervention																			
Randomisation		X																	
SC dosing			X																
Safety Assessments																			
Safety labs (haematology, clinical chemistry and urinalysis)		X					X		X			X		X	X			X	WBC differentials MUST be blinded (see Appendix 2) To be taken in non-fasted state

Procedure	**Day 0**	**Day 1 (Hours)**					**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 9**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85/Early withdrawal visit**	**Notes Time window for Outpatient visits: Day 9 ± 2 days, Day 15 ± 4 days, Days 29, 43 and 57 ± 7 days, Days 71 and 85 ± 10 days**
		Pre-dose	**0**	**2**	**4**	**8**													
Alcohol/drug screen	X																		
Urinary Cotinine Test	X																		
12-lead ECG		X				X		X		X				X		X		X	When scheduled at the same timepoint, ECG's should be taken as close as possible to PK samples
Vital signs	X	X				X	X	X	X	X	X			X		X		X	Supine blood pressure and heart rate
Concomitant medications	◄==========►																		
SAE/AE Review	◄==========►																		Including injection site reactions
Local Injection site reaction evaluation					X		X	X											Targeted evaluation at 4 hours post-dose on Day 1 & 24 hours post-dose on Day 2 and 48 hours post-dose on Day 3. Spontaneous reporting at all other times.

Procedure	**Day 0**	**Day 1 (Hours)**					**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 9**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85/Early withdrawal visit**	**Notes Time window for Outpatient visits: Day 9 ± 2 days, Day 15 ± 4 days, Days 29, 43 and 57 ± 7 days, Days 71 and 85 ± 10 days**
		Pre-dose	**0**	**2**	**4**	**8**													
Pregnancy test	X													X		X		X	Serum pregnancy test at screening and urine dipstick test at all other visits
Brief Physical Examination																		X	See Section 8.2.1
Biomarker Collection																			
PK blood sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Day 1 samples ± 1 hours. Days 2-6 ± 2 hours relative to time of dosing
Free sST2 and total sST2 blood sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Samples should be taken within ± 2 minutes of PK
Immunogenicity blood sample		X											X	X		X		X	Collect pre-dose on Day 1
4βOH cholesterol/cholesterol plasma sample		X								X			X	X				X	All samples should be in non-fasted state for comparison with baseline.
Pharmacogenetic (PGx) blood sample				X															May be taken at any time post-dose

- 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 as the result of emerging pharmacokinetic/pharmacodynamic data from this study 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 Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- When scheduled at the same timepoints, vital signs should be conducted followed by ECG's prior to any blood draws.

2. INTRODUCTION

2.1. Study Rationale

GSK3772847 is a human immunoglobulin G2 sigma isotype (IgG2σ) antibody that binds Domain 1 of the cell-surface interleukin-33 receptor (IL-33R). Inhibition of IL-33 signalling via blockade of the IL-33 receptor (Suppressor of tumorigenicity 2 [ST2], also known as Interleukin-1 receptor like-1 [IL-1RL1]) presents a potential novel treatment for severe asthma as an add-on to standard of care. Agents targeting this mechanism could be expected to have effects on both type 2 (T2)-driven and non-T2-driven disease.

The purpose of this study is to evaluate the safety and tolerability, PK and PD of single ascending doses of GSK3772847 administered subcutaneously (SC) to healthy participants. It will establish the bioavailability of the SC formulation and evaluate the safety (in particular injection site tolerability) of the SC route.

GSK3772847 has been administered intravenously at doses up to and including 10mg/kg both as single and repeated doses (207597 [GlaxoSmithKline Document Number 2017N316832_02 and 207972 [final report pending]). This is the first study to evaluate the PK and PD of GSK3772847 via the subcutaneous (SC) route. Subjects will be randomised to receive doses of either 70 mg (Cohort 1) or 140 mg (Cohort's 2, 3 and 4) GSK3772847 or placebo SC. Placebo is included to allow a valid evaluation of adverse events attributable to treatment versus those independent of treatment. The dose selection is based on credible doses for future clinical development and are expected to reduce free sST2 by greater than 90% at peak effect. Recovery to near baseline levels is expected within the study duration. GSK3772847 will be administered in one of 3 injection sites: upper arm, thigh or abdomen. This will allow evaluation of PK and PD via the 3 most common sites for SC administration.

Cohorts of healthy Japanese (Cohort 3) and Chinese (Cohort 4) participants will also be included to enable us to evaluate PK and PD in these populations. To minimise the number of comparisons the impact of injection site will be evaluated in cohorts 1 and 2 only. Cohorts 3 and 4 will utilise only the upper arm injection site.

PK will be evaluated by non-compartmental analysis. In addition, data from this study will be included in a population-PKPD analysis together with the historic IV data to enable development of an appropriate model to describe the PK and PD. This will be reported separately from the main clinical study report (CSR).

2.2. Background

Severe asthma represents approximately 5-10 % of the asthma population and is associated with a greater frequency of asthma exacerbations, decreased health-related quality of life and greater symptom burden [Aburuz, 2007;Chung, 2014;Moore, 2007]. Current biologic agents approved for the management of patients with severe asthma have demonstrated efficacy for T2-driven disease (i.e., eosinophilic and/or elevated

serum immunoglobulin E [IgE]) however, there is no currently approved therapy that targets non-T2-driven asthma.

GSK3772847 (formerly CNTO 7160 which was in-licensed from Janssen) is a human IgG2σ monoclonal antibody (mAb) that binds to the extracellular domain of interleukin-33 receptor (IL-33R) and neutralizes IL-33-mediated IL-33R signalling. The IL-33R gene codes for both a soluble form (sST2) and a membrane-bound "long" form (ST2L or IL-33R). Soluble ST2 exists in the serum and is elevated in severe asthmatics during an exacerbation [Smithgall, 2008; Oshikawa, 2001].

IL-33R is expressed on immune cells, such as mast cells, basophils, eosinophils, and T helper cell type 2 (Th2) cells and has been shown to be upregulated on macrophages, neutrophils, and dendritic cells. It is also expressed on non-immune cells such as endothelial, epithelial and smooth muscle cells and fibroblasts. IL-33 has been shown to be released after endothelial or epithelial cell damage during trauma, physicochemical / microbarometric stress or infection [Arshad, 2016]. IL-33R signalling causes downstream production of Type 2 cytokines. The engagement of IL-33R with its ligand IL-33 contributes to Th2-mediated pathologies and allergic responses [Yagami, 2010;Smithgall, 2008]. , but has also been shown to promote Th1- and Th17-mediated responses [Arshad, 2016;Smithgall, 2008].. Inhibition of IL-33 signalling via blockade of the IL-33R may result in down regulation of immune cell responses and therefore presents a potential novel treatment for severe asthma on top of standard of care [Arshad, 2016].

The findings from the completed toxicology package comprising of IV and SC repeat dose studies (26 weeks in dosing duration and the enhanced pre and post-natal (ePPND) study), with the associated target engagement and pharmacokinetic data support the administration of GSK3772847 by IV and SC routes of administration for the proposed clinical use and is detailed in the Investigators Brochure [GlaxoSmithKline document number 2017N316832_02].

To date there have been three clinical studies conducted with GSK3772847 all using the IV formulation. This will be the first study to use the SC formulation. The SC formulation is being developed as this route of administration provides an easy to administer, cost effective dosage regimen which is generally preferred by patients.

Janssen conducted a Phase I randomized, double-blind, placebo-controlled, IV single ascending dose study in healthy participants and multiple ascending dose study in participants with asthma and participants with atopic dermatitis (Janssen Study CNTO7160ASH1001; (GSK study 208736, GlaxoSmithKline Document Number 2017N344518_00])). A summary of the data from this study is included in the investigator brochure [GlaxoSmithKline document number 2017N316832_02].

Study 207597 was a double-blind, parallel group, multicentre, stratified study evaluating the efficacy, safety and tolerability, PK and PD profiles of repeat doses of 10 mg/kg GSK3772847 given intravenously every 4 weeks (Weeks 0, 4, 8 and 12) compared with placebo in participants with moderately severe, uncontrolled asthma. The study used an inhaled steroid (ICS) titration design to evaluate whether GSK3772847 maintains

protection of asthma control. A summary of the data from this study is included in the investigator brochure [GlaxoSmithKline document number 2017N316832_02].

Study 207972 is a 28-week Phase IIa (planned n=46), multi-center, randomized, double-blind, placebo-controlled, parallel group study in moderate to severe asthma patients with allergic fungal airway disease (AFAD). This study was terminated early due to challenges in identifying suitable participants. The clinical phase has completed but the study has not yet reported.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK3772847 is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2017N316832_02].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3772847 may be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2017N316832_02].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3772847]		
Cardiovascular (CV) There is evidence to suggest that the IL-33/ST2 pathway may be protective in the cardiovascular system. Components of the IL-33/ST2 pathway are expressed in a number of cellular components of the heart and blood vessels in rodents and human patients. Increased circulating levels of soluble ST2 are markers of a poor prognosis in patients with hemodynamic stress (e.g. hemodynamic-hypertrophy, chamber dilation, fibrosis; ischemic- apoptosis and infarct volume). The effect was abolished in rodents with genetic knockout of ST2. Atherosclerotic plaque development was significantly reduced in ApoE -/- mice given exogenous IL-33 while plaques were larger in mice treated with soluble ST2 (which binds and blocks IL-33).	**Non-clinical:** No GSK3772847-related changes noted in (non-GLP) IV and SC 4 week monkey study at doses ≤100 mg/kg/week, or in the good laboratory practice (GLP) 3 or 6 month IV repeat dose toxicity study at doses ≤100 mg/kg/week) Also, no CV related changes noted in pregnant monkeys or infants of dams administered GSK3772847 (up to the age of 6 months) noted at doses 100 mg/kg/week. However, it should be noted that the animals in toxicity studies are healthy and, therefore, are unlikely to detect the potential target related CV liability. **Clinical**: In Janssen study CNTO7160ASH1001, several episodes of sinus tachycardia on telemetry were reported in a 20-year-old male healthy volunteer, between 1 and 9 hours post-dose (10 mg/kg), accompanied on one occasion by mild vertigo and malaise (no chest pain).	Exclude participants with abnormal, clinically significant finding(s) from 12-lead ECG at Screening/Visit 1 (Section 5.2 includes examples of types of abnormal and clinically significant ECGs Participants who meet protocol-defined QTc stopping criteria specified in Section 7.2 will be withdrawn from the study. CV events will be monitored in all clinical trials.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Troponin I, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were normal pre dose and Day 5, also normal ECG and vital signs including temperature. The event was considered by the investigator to be likely related to the investigational product. No specific cause was identified. Data on this event was reviewed by GSK (Internal Cardiac Safety Panel and CMO), and was not considered to impact further clinical development. During 12 hours post-dose telemetry monitoring in Part 1 of Janssen study CNTO7160ASH1001, 6 out of 60 completed subjects were assessed to have abnormal findings by the investigator. These events of sinus tachycardia (4 subjects on GSK3772847 and 1 subject on placebo) and idioventricular rhythm (1 subject on GSK3772847) were recorded as adverse events. In Part 2 of the Janssen study CNTO7160ASH1001, there were four reports of non-sustained ventricular tachycardia. Of these reports, one participant received placebo and two received GSK3772847 at 3 mg/kg and one received GSK3772847 at 10 mg/kg. The events were non-symptomatic, and a monomorphic pattern (i.e., not Torsades de pointes), which is	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	a pattern thought not to be indicative of increased risk for sudden ventricular tachycardia and sudden death. Heart rate (HR) analysis did not identify any safety concern (no pattern of increased HR suggestive of an increase in sympathetic tone). All 4 participants had normal results from exercise test and echocardiogram. Dosing was continued as planned, and the dose escalated to 10 mg/kg. In the phase IIa study 207597, CV findings included ventricular tachycardia in 4% of placebo and 1% of GSK3772847 participants (all cases were asymptomatic NSVT and deemed by the investigator as not related to study drug). The iSRC reviewed all cardiovascular safety data at three separate points during the study (following the 12 week visit of the 35th, 70th, and 105th subjects). There were no significant findings (cardiac or otherwise) at any point during the study that warranted early study termination.	
Increased risk of infections & immunosuppression Studies in mice indicate a potential role for IL-33 in infection control. IL-33 was shown to activate neutrophils in BALB/c mice subjected to cecal	**<u>Preclinical</u>**: No GSK3772847-related changes in clinical signs, white blood cell count or no microscopic changes (inflammatory cell infiltrates) in any tissues indicative of infection observed in monkey 4 week IV/SC IV 3 or 6 month toxicity at	Appropriate inclusion/exclusion criteria will be implemented in clinical protocols, to include: exclusion of participants with a known, pre-existing parasitic infestation within 6 months prior to Screening; exclusion of participants with the presence of hepatitis B surface antigen

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ligation and puncture thus preventing polymicrobial sepsis. Similarly, IL-33 is thought to stimulate neutrophil recruitment from the bone marrow to the periphery in response to fungal infection. Mice infected with flu virus and administered an IL-33 inhibitor exhibited a lower number of clusters of differentiated CD90+ and cluster of differentiated CD25+ innate lymphoid cells with consequent impaired lung function compared to phosphate buffered saline treated controls. IL-33 has also been shown to be produced in the helminth infected cecum of parasite infected mice and is shown to be important in expulsion of the parasite.	doses ≤100 mg/kg/week. Also no GSK3772847 related changes in in clinical signs, white blood cell counts in pregnant monkeys or infants of dams administered GSK3772847 (up to the age of 6 months) noted at doses 100 mg/kg/week **Clinical**: Safety data from Janssen study CNTO7160ASH1001 Single Ascending Dose (SAD) has shown the most frequent adverse events reported as infections, including nasopharyngitis, rhinitis, gastroenteritis and upper respiratory tract infection. The frequency of these events was similar in GSK3772847 and placebo groups (18/45 [40%] of participants administered GSK3772847 versus 6/24 [40%] administered placebo). Safety data from Part 2 of the Janssen study CNTO7160ASH1001 have shown the System-organ class (SOC) with the most frequent adverse events reported was 'Infections and infestations'. The number of asthma participants experiencing infections and infestations was similar between the group receiving GSK3772847 (9/18 [50%]) and the group receiving placebo (4/6 [66.7%]). The frequency	(HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment; exclusion of participants with Immunodeficiency (a known immunodeficiency such as human immunodeficiency virus infection); Participants who develop an infection will be requested to seek medical advice, and subject to close monitoring. Exclude patients with ongoing or recurrent infections. EU Regulatory guidance on development of asthma drugs request that agents that interact with the immune system should be investigated for their effect on the host response to infection and tumours. The incidence of infections will be monitored in clinical studies. Incidence of tumours and development of paradoxical immune responses (e.g. idiopathic thrombocytopenic purpura, autoimmune thyroiditis, multiple sclerosis-like syndrome) will be monitored in clinical trials via adverse event review.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of infection events in participants with atopic dermatitis was greater in participants in the GSK3772847 group compared with the placebo group (6/11 [54.5%] versus 1/4 [25%]). The most frequently-reported infection was nasopharyngitis. In the phase IIa study 207597, the number of participants experiencing infections and infestations was similar between the group receiving GSK3772847 (15/83 [18%]) and the group receiving placebo (16/82 [20%]). Among the most frequently reported adverse events (≥3%) were nasopharyngitis (5% in both groups), influenza (GSK3772847 1% and placebo 5%) and upper respiratory tract infection (5% and 1%), and cough (4% and 1%). One participant (1%) receiving placebo had an on-treatment SAE of pneumonia.	
Increased risk of hyper-sensitivity, anaphylaxis, cytokine release syndrome (CRS) Therapy with other mAbs has been associated with hypersensitivity reactions which may vary in severity and time of onset.	**Nonclinical**: Two maternal deaths at 20 mg/kg/week that occurred following 14 or 17 weekly doses were noted in the pre and post-natal cynomolgous monkey development study. These were considered to be due to a delayed-ADA mediated infusion reaction. Animals are not considered predictive for ADA-mediated	If a hypersensitivity or anaphylactic reaction occurs appropriate therapy should be given immediately. Agents to treat reaction should be available immediately. Guidance on reactions is given in Section 8.3.6. This is a single dose study and all participants will be dosed in the clinic by an appropriately qualified HCP.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	adverse reactions in humans, including infusion reactions, hypersensitivity reactions or anaphylaxis. **Clinical**: Not observed in Janssen study CNTO7160ASH1001 in healthy volunteers following single doses up to 10 mg/kg, and multiple doses in asthma and atopic dermatitis patients at doses up to 10 mg/kg (3 doses, once every two weeks [q2W] over four weeks). Based on in vitro cytokine release data and safety experience in Janssen study CNTO7160ASH1001 the risk of CRS is considered negligible. No cases of GSK3772847-related hypersensitivity, anaphylaxis or CRS occurred in study 207597 where participants received either GSK3772847 10 mg/kg or placebo every 4 weeks for a total of 4 doses over 12 weeks.	
Possible interaction with live virus or bacterial vaccines As GSK3772847 is an immunomodulator, there is a possibility that the subject will not mount an adequate immune response to a vaccine or even cause the infection the vaccine should protect against.	**Non-clinical**: In the monkey 13-week toxicity study no GSK3772847-related changes in the T cell dependent B cell response (IgM or IgG) was observed at doses ≤100 mg/kg/week. No changes in lymphocyte sub populations, T-helper cell sub populations or T cell dependent B cell response in infants. This data is	In the study, participants should not be vaccinated with live or attenuated vaccines within 4 weeks prior to receiving IP or up to 6 months after dose administration of GSK3772847. However, vaccines containing killed bacteria or inactivated virus will be permitted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Vaccination will also drive a systemic immune response to the pathogen antigen that runs the risk of causing some immunomodulation of the lung immune responses. This has been best studied in murine models where eosinophilic lung inflammation has been suppressed by systemic toll-like receptor activation.	indicative that healthy adult and infant monkeys were able to mount a response against the antigen challenge during GSK3772847 administration at doses where near complete inhibition of IL-33 was anticipated. Based on this data GSK3772847 is considered unlikely to blunt/inhibit the generation of a response to vaccinations. **Clinical**: Not observed in Janssen study CNTO7160ASH1001 in healthy volunteers following single doses up to 10 mg/kg, and multiple doses in asthma and atopic dermatitis patients at doses up to 10 mg/kg (3 doses, once every two weeks over four weeks). Not observed in study 207597, where participants with asthma received either GSK3772847 10 mg/kg or placebo every 4 weeks for a total 4 doses over 12 weeks.	
Potential of embryofetal development effects	Non-clinical: In the enhanced pre- and post-natal monkey study, there was no evidence of GSK3772847-related effects on pregnancy or on the survival, growth, and development of foetuses and infants. GSK3772847 was detected in maternal milk on PPD28 at 1000-fold lower than serum concentration values at the same interval.	FRP will be included in clinical studies. Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. To minimize the probability of pregnancy exposure:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical: Females of reproductive potential were included in Part 2 of Janssen study CNTO7160ASH1001 and no pregnancies were reported. Females of reproductive potential were included in protocol 207597 and no pregnancies were reported.	• FRP will be required to have established, proper of a highly effective method for avoiding pregnancy at screening to ensure there a minimum of 1 month of effective contraception prior of first dose, and to utilize one form of highly effective contraception throughout the study until follow-up. • Pregnancy testing will be performed prior to dosing, at regular intervals during treatment, until follow-up as documented in the clinical protocol. A positive pregnancy test will require immediate cessation of treatment.
Gastrointestinal disorders • Nausea • Vomiting	**Clinical:** In Part 2 of Janssen study CNTO7160ASH1001, the incidence of gastrointestinal disorders was greater in participants in the GSK3772847 groups compared with the placebo groups: 6/18 (33.3%) participants in the asthma cohort and 3/11 (27.3) participants in the atopic dermatitis cohort as compared with 0 participants in either the asthma cohort or atopic dermatitis cohort placebo groups. Gastrointestinal disorders events included nausea (1/18 participants in the asthma cohort, 2/11 participants in the atopic dermatitis cohort), vomiting, diarrhoea.	The incidence and severity of nausea and vomiting will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In the phase IIa study 207597, the number of participants experiencing nausea was 1% in both groups while the number of participants experiencing vomiting was 1% in the GSK3772847 group and 0 in the placebo group.	
Skin and subcutaneous tissue disorders • Contact dermatitis	**Clinical:** In Part 2 of Janssen study CNTO7160ASH1001, the incidence of contact dermatitis was greater in participants in the GSK3772847 groups compared with the placebo groups. In the asthma cohort, the number of participants with contact dermatitis was 4/18 (22.2%) in the combined GSK3772847 groups versus 1/6 (16.7%) in the placebo group. In the atopic dermatitis, the number of participants with contact dermatitis was 3/11 (27.3%) in the combined GSK3772847 versus 0/4 (0%) in the placebo group. No cases of contact dermatitis were reported in the phase IIa study 207597.	The incidence and severity of contact dermatitis will be monitored.
Study Procedures		
Risk associated with blood draws	Fainting, mild pain, bruising, irritation or redness at phlebotomy site, may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.

2.3.2. Benefit Assessment

There is no clinical benefit for healthy participants taking part in this study. However, participants will undergo a medical evaluation during screening (including physical examination, electrocardiogram (ECG), vital signs and laboratory assessments), which may provide important health information.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the proposed measures to be taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK3772847 are considered justified and adequately mitigated.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single dose of GSK3772847, compared with placebo administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	. • Occurrence of adverse events (AE's) and serious adverse events (SAE's) (including injection site reactions)
• To assess the pharmacokinetics (PK) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants (Cohorts 1 and 2 also summarised by injection site)	• PK parameters, including but not limited to, Area under the plasma-concentration time curve (AUC), maximum plasma concentration (Cmax), time to Cmax (Tmax) and terminal half-life (t1/2) of GSK3772847 per cohort
Secondary	
• To evaluate the pharmacodynamics (PD) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• Maximal decrease in free and increase in total soluble ST2 levels in serum up to Day 85 visit
• To assess the immunogenicity of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• occurrence of anti-GSK3772847 antibodies
• To assess potential changes in Cytochrome P450 3A4 (CYP3A4) enzyme activity following a single dose of GSK3772847 in healthy participants including cohorts of Japanese and Chinese participants.	• Plasma 4β-Hydroxycholesterol (4βOH) cholesterol/cholesterol ratio as an endogenous marker for CYP3A4 activity pre-treatment and following a single dose of GSK3772847
Other	
• To further assess the safety and tolerability of a single dose of GSK3772847, compared with placebo administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• 12-lead ECG measurements • Clinical chemistry laboratory tests • Vital signs
• To evaluate the pharmacodynamics (PD) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• Free and total soluble ST2 levels in serum • Blood eosinophil levels
• To assess the pharmacokinetics (PK) of a single dose of GSK3772847 administered subcutaneously in healthy participants including cohorts of Japanese and Chinese participants.	• GSK3772847 levels in serum

4. STUDY DESIGN

4.1. Overall Design

This is a single centre, randomized, placebo-controlled, double-blind, ascending dose study in healthy participants.

Following a screening period (of up to 28 days), participants who meet the eligibility criteria will be assigned to one of four cohorts and will be randomly allocated within each cohort to receive a single dose of either GSK3772847 or placebo. All treatments will be administered subcutaneously by a health care professional (HCP). The site of injection will be randomized to the upper arm, abdomen or thigh for cohorts 1 and 2 with cohorts 3 and 4 receiving injections in the upper arm only.

- Cohort 1: 18 participants will be randomly allocated to receive GSK3772847 70 mg SC and 6 will receive placebo SC.

- Cohort 2: 18 participants will receive GSK3772847 140 mg SC and 6 will receive placebo SC.

- Cohort 3: 6 Japanese participants will receive GSK3772847 140 mg SC and 2 will receive placebo SC.

- Cohort 4: 6 Chinese participants will receive GSK3772847 140 mg SC and 2 will receive placebo SC.

Each participant will:

- Be screened (within 28 days of dosing)
- Be admitted to the unit the day prior to dosing (Day 0) and be discharged after completion of assessments on day 6
- Attend follow up visits on days 9, 15, 29, 43, 57, 71 and 85 (for time windows see SoA Section 1.3)

Before dosing in Cohorts 2, 3 and 4 can begin, blinded safety data (including injection site data from dosing to a minimum of 48 hours post-dose) will be reviewed in at least 20 subjects who have received a dose in Cohort 1 see Section 9.6.

An interim analysis, to assess safety, tolerability and PK, will be performed after a predefined number of participants from all four cohorts have reached Day 29 as detailed in Section 9.5

A participant will be considered having completed the study if they complete the final visit.

The total duration a participant remains in the study is up to 17 weeks and 4 days (includes up to 28 days for screening and up to 95 days post-dose follow up (includes 6 days in clinic)).

4.2. Scientific Rationale for Study Design

This is a single centre, randomized, placebo-controlled, double-blind, ascending dose study in healthy participants to determine the safety (in particular injection site tolerability), PK and PD of GSK3772847 via the SC route. A total of 64 participants will be initially randomized for a total of 18 evaluable participants on GSK3772847 and 6 on placebo in cohorts 1 and 2, 6 Japanese participants in cohort 3 on GSK3772847 and 2 on placebo and 6 Chinese participants on GSK3772847 and 2 on placebo in cohort 4. Placebo is included to allow a valid evaluation of adverse events attributable to treatment versus those independent of treatment. SC GSK3772847 will be administered on a single occasion and participants will be followed up for over 3 half-lives (85 days) to ensure sufficient PK and PD information is gathered and to ensure that GSK3772847 PK has reached low enough levels to have insignificant pharmacological effects.

A healthy subject population is considered to be suitable for the evaluation of GSK3772847 PK comparability as all treatments will be administered to the same population and any differences would therefore be detected appropriately. Healthy subjects are considered to be a suitable population for biopharmaceutical PK comparability studies and the data can be extrapolated to other populations [CPMP/EWP/QWP/1401/98].

PK will be evaluated by non-compartmental analysis. In addition, data from this study will be included in a population-PKPD analysis together with the historic IV data to enable development an appropriate model to describe the PK and PD. This will be reported separately from the main clinical study report (CSR).

4.3. Justification for Dose

Doses of 70 and 140mg SC have been selected based on a preliminary population PK/PD model built using data from the IV FIH study (Janssen Study CNTO7160ASH1001; (GSK study 208736, GlaxoSmithKline Document Number 2017N344518_00). This model accounts for both the linear elimination pathway and for target mediated elimination via interaction with the target (ST2). These doses are expected to deliver exposures and ST2 suppression suitable for progression into later phase studies and are lower than the 10mg/kg IV dose utilised in studies 207597 [GlaxoSmithKline Document Number 2017N316832_02 and 207972 [final report pending]. The fraction of drug absorbed into the systemic circulation (F) after SC dosing was set at 0.8 based on precedented data for similar monoclonal antibodies. This value represents a credible estimate for the upper end of absorption and so the predicted exposures and safety margins are considered to be relatively conservative. The rate of absorption was similarly set to reflect precedence and predicts a T_{max} from approximately 3 to 10 days. Safety margins were calculated against both the 26 week IV and 4 week SC toxicity studies. The predicted exposures are given in the table below and show that the exposures are expected to be significantly below those in these key toxicity studies

Table 3 Predicted clinical exposures and safety margins for study 209635 following single SC dosing of 70mg and 140mg.

DOSE	Median AUC (0-Day85) (µg.day/mL)	Exposure margin vs 26 week IV tox study[a]	Exposure margin vs 4 week SC tox study[b]	Median C_{max} (µg/mL)	Exposure margin vs 26 week IV tox study[a]	Exposure margin vs 4 week SC tox study[b]
70 mg	272	141x	52.1x	7.89	936x	287x
140 mg	570	67x	24.8x	16.0	460x	141x

a. Margins calculated against mean maximum serum concentration (Cmax) and AUC(0-t) on week 26 in study 5002200 "GSK3772847A: A 26-Week (Once weekly) Intravenous Infusion Toxicity Study in Cynomolgus Monkeys"

b. Margins calculated against mean maximum serum concentration (Cmax) and AUC(0-t) on week 4 in study P32464G. "The Toxicokinetics of GSK3772847A in Cynomolgus Monkeys Following Once Weekly Subcutaneous Injection of GSK3772847A During a 4-Week Toxicity Study"

Sentinel dosing is not required as GSK3772847 has been dosed to over 160 participants in two completed studies (first time in human study CNTO7160ASH1001 and phase 2a study 207597 [GlaxoSmithKline Document Number 2017N316832_02) predominately at a significantly higher dose (10 mg/kg by intravenous injection).

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

AGE
1. Between 18 and 50 years of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. A participant with a clinical abnormality or laboratory parameter(s) not specifically listed in the exclusion criteria that is outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor (if required), agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or results.
GEOGRAPHIC ANCESTRY – JAPANESE PARTICIPANTS ONLY
3. Japanese Participants are eligible based on meeting all of the following: • Healthy male and female participants born in Japan • are descendants of four ethnic Japanese grandparents and two ethnic Japanese parents • holding a Japanese passport or identity papers • being able to speak Japanese • have lived outside Japan for less than 10 years at the time of screening.
GEOGRAPHIC ANCESTRY – CHINESE PARTICIPANTS ONLY
4. Chinese Participants are eligible based on meeting all of the following: • Healthy male and female participants born in mainland China • are descendants of four Chinese grandparents and two Chinese parents • holding a Chinese passport or identity papers • being able to speak Chinese • have lived outside China for less than 10 years at the time of screening.
WEIGHT
5. Body weight 35-150 kg and body mass index (BMI) within the range 18-32 kg/m2 (inclusive).
SEX
6. Male and Female Participants – see Appendix 4 Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
- Is not a woman of childbearing potential (WOCBP)
- OR
- Is a WOCBP and using an acceptable contraceptive method as described in Appendix 4 during the intervention period (at a minimum until after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive (Appendix 2) pregnancy test ([urine] as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
-

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

INFORMED CONSENT
7. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

MEDICAL CONDITIONS (INCLUDES LIVER)
1. Alanine transaminase (ALT) >2x upper limit of normal (ULN)
2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
4. Ongoing or recurrent infections
5. QT interval corrected for heart rate by Fridericia's formula (QTcF) >450 msec or any of the following abnormal and clinically significant ECG findings:

- Sinus bradycardia <45bpm

**Note: Sinus bradycardia <45bpm should be confirmed by two additional readings at least 5 minutes apart.*

- Sinus tachycardia ≥110bpm

**Note: Sinus tachycardia ≥110 should be confirmed by two additional readings at least 5 minutes apart.*

- Multifocal atrial tachycardia (wandering atrial pacemaker with rate >100bpm)
- Evidence of Mobitz II second degree or third degree atrioventricular (AV) block
- Pathological Q waves (defined as wide [>0.04 seconds] and deep [>0.4mV (4mm with 10mm/mV setting)] or >25% of the height of the corresponding R wave, providing the R wave was >0.5mV [5mm with 10mm/mV setting], appearing in at least two contiguous leads.

**Note: prior evidence (i.e., ECG obtained at least 12 months prior) of pathological Q waves that are unchanged are not exclusionary; and the investigator will determine if the subject is precluded from entering the study.*

- Evidence of ventricular ectopic couplets, bigeminy, trigeminy or multifocal premature ventricular complexes.
- For subjects without complete right bundle branch block: QT interval corrected for heart rate by Fridericia's formula (QTc[F]) ≥450 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects with complete right bundle branch block: QTc(F) ≥480 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).

**Note: All potentially exclusionary QT measurements should be confirmed by two additional readings at least 5 minutes apart.*

- ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)

**Note: prior evidence (i.e., ECG obtained at least 12 months prior) of ST-T waves that are unchanged are not exclusionary and the investigator will determine if the subject is precluded from entering the study.*

- Clinically significant conduction abnormalities (e.g., Wolff-Parkinson-White syndrome or bifascicular block defined as complete left bundle branch block or complete right bundle branch block with concomitant left fascicular block)
- Clinically significant arrhythmias (e.g., atrial fibrillation with rapid ventricular response, ventricular tachycardia)

PRIOR/CONCOMITANT THERAPY
6. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of study medication and until study completion, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
7. The participant has been 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). 8. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

DIAGNOSTIC ASSESSMENTS & OTHER EXCLUSIONS
9. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention. 10. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention. **NOTE**: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. 11. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. **NOTE**: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing. 12. A positive test for HIV antibody. 13. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months. 14. A positive pre-study drug/alcohol screen. 15. Any history of substance abuse or a positive test for drugs of abuse at screening or admission

16. Known, pre-existing parasitic infestations within 6 months prior to Screening
17. Vaccinated with live or attenuated vaccines within 4 weeks prior to receiving IP and up to 6 months after dose administration of GSK3772847
18. A positive highly sensitive pregnancy test (urine or serum as required by local regulations) at screening.
19. Positive urinary cotinine test indicative of smoking history at screening or each in-house admission to the clinical research unit or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.
20. Participants with allergy or intolerance to a monoclonal antibody or biologic or to any components of the formulation used in this study.
21. A vulnerable subject. Defined as individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.
22. Subjects who work for the Sponsor, CRO, or one of the study centres

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until after the final follow up.
- Participants will be required to be in a non-fasted state for ALL clinical laboratory tests and 4βOH cholesterol/cholesterol samples

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 8 hours before all ECG assessments.
- Participants will abstain from alcohol for 24 hours before dose and for 24 hours prior to the collection of all safety, pharmacokinetic and pharmacodynamic samples.
- Use of tobacco products of any kind is not allowed as outlined in the exclusion criteria

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in

light recreational activities during studies (e.g., walking, watching television, reading).

5.4. Screen Failures

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

Participants who fail eligibility may be rescreened once (restriction for rescreening not applicable for reserves). If rescreening is performed, participants must be assigned a different unique subject identification number for the rescreening, and all screening procedures must be repeated (unless agreed otherwise by the investigator and GSK medical monitor).

In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the subject will be considered a screen failure.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

ARM Name	GSK3772847 Injection, 70 mg and 140 mg arms	Placebo to Match
Intervention Name	GSK3772847 Injection, 70 mg, SC	Formulation buffer solution for injection
Type	Biologic	N/A
Dose Formulation	The GSK3772837 Injection is a solution for injection that formulated with phosphate buffer, L-arginine hydrochloride, sucrose, polysorbate 80, and water for injection.	The placebo to match GSK3772847 is supplied as solution for injection with the same GSK3772847 Injection formulation but without the active drug substance.

Unit Dose Strength(s)	70 mg/mL (1 mL nominal volume) in a 3 mL glass vial. Dosage levels vary per cohort.	1 mL nominal volume in a 3 mL glass vial. number of injections to match active dose.
Dosage Level(s)	<u>For 70 mg dose</u> The dose can be administered using a single 1 mL injection <u>For 140 mg dose</u> The dose can be administered using two x 1 mL injections	To match active (i.e. the same volume and number of injections as the participants on GSK3772847 in that cohort)
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo
IMP and NIMP	IMP	NIMP
Sourcing	Provided centrally by GSK	Provided centrally by GSK
Packaging and Labelling	Study intervention supplied by GSK as a sterile, preservative-free liquid in a 3 mL type 1 untreated borosilicate clear glass vial with a 13-mm fluorinated-polymer coated grey rubber stopper and a 13-mm aluminium seal. Each vial will be labelled as required per country requirement.	Placebo supplied as a sterile, preservative-free liquid in a 3 mL type 1 untreated borosilicate clear glass vial with a 13-mm fluorinated-polymer coated grey rubber stopper and a 13-mm aluminium seal. Each vial will be labelled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

- GSK3772847 must be prepared by an unblinded pharmacist or other appropriately licensed and authorized personnel.

- Unblinded site staff will be responsible for receipt, storage and labelling, and accountability of investigational product.

- GSK3772847 should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If visibly opaque particles, discoloration, or other foreign particles are observed, the solution should not be used.

- Detailed instructions for storage conditions, dose preparation, and administration will be provided in the unblinded site staff reference manual. Required storage conditions and expiration date are indicated on the label.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Because the likely difference in colour between the GSK3772847 and placebo solutions, an unblinded pharmacist or other qualified individual will prepare the GSK3772847 or placebo injections and apply a tape to cover the colour. Further details will be described in the study reference manual (SRM).

- Further guidance and information for the final disposition of unused study intervention are provided in the study reference manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

- On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 4 arms of the study, according to the randomization schedule generated prior to the study under the guidance of the Statistics Department at GSK. Participants will also be randomised to one of 3 injection sites for cohorts 1 and 2.

Each participant will be dispensed blinded study intervention, labelled with [his/her] unique randomization number, throughout the study.

- A replacement schedule will be generated for any participant who is randomized, receives treatment and withdraws prior to Day 29. Replacement participants will be allocated to the same randomized treatment, but with a different randomization number.

- Participants will be randomized in a 3:1 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study intervention and will endeavour to ensure that there are no differences in time taken to dispense following randomization.

- Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.2. Blinding

This will be a double blind (GSK Statistics & Programming and GSK Clinical Pharmacology Modelling & Simulation (CPMS) open) study. All study staff involved in the clinical assessments (which includes the investigator, sub-investigators other site staff), and the participant will be blinded to the treatment allocated to individual participants. Statistics & Programming and CPMS will be unblinded after the dose escalation committee review to enable reporting of the D29 data. See Section 9.5 . An unblinded qualified site staff member will be required to prepare the study treatment for dosing as described in the Study Reference Manual. The unblinded site staff member is not permitted to communicate the participants treatment allocation with blinded site staff.

The dose escalation committee (DEC) will review blinded summary data (including injection site data from up to 48 hours post-dose) as detailed in Section 9.6.

The interim analysis data review committee (DRC) will review data detailed in Section 9.5. Details of the committee are given in Section 10.1.5.2.

The following will also apply:

- The Investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the Investigator.
- Investigators have direct access to the participant's individual study treatment.
- In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making

such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.

- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and event or condition which led to the unblinding (i.e. the primary reason) will be recorded in source documentation and in the eCRF.

In the event of unblinding the Medical monitor/GSK team should be contacted to determine whether subject withdrawal is required. Should a participant's treatment assignment be unblinded and the Medical monitor/GSK team determine that the participant must be withdrawn from IP, the participant must be followed-up as per protocol until the completion of the Safety Follow-up assessments.

A participant whose treatment assignment is inadvertently unblinded (either to investigative staff or the participant themselves) will be permitted to remain in the study. Accidental unblinding will be recorded as a protocol deviation and the participant will be subject to review as to their inclusion in analyses as per the procedures set out in Section 9.3.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention 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 intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention Compliance

- Participants will receive study intervention 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 intervention 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 intervention.
- Used vials should NOT be discarded before the unblinded monitor has conducted a visit.

6.5. Concomitant Therapy

Details for concomitant medications are detailed in Section 5.2. Any use of prohibited medications (including the use of paracetamol/acetaminophen) will be reviewed on a case-by-case basis by the medical monitor.

6.6. Dose Modification

The decision to proceed to the next dose level of 140mg will be made by the Dose Escalation Committee (DEC) and the investigator based on blinded safety data (including injection site data obtained 48 hours post dose) from at least 20 participants from cohort 1.

Details of the DEC are given in Section 9.6.

6.7. Intervention after the End of the Study

As this is a healthy participant study, no intervention will be given to participants following the end of study.

7. DISCONTINUATION CRITERIA

Participants who meet any of the below criteria should, where possible, continue to be followed up until the completion of all safety, PK and PD follow-up assessments, at day 85:

- Liver Chemistry: protocol-defined liver chemistry stopping criteria
- QTc: protocol-defined stopping criteria
- Pregnancy: Positive pregnancy test (see Appendix 4)
- Hypersensitivity or anaphylactic reactions (see Section 8.3.6)

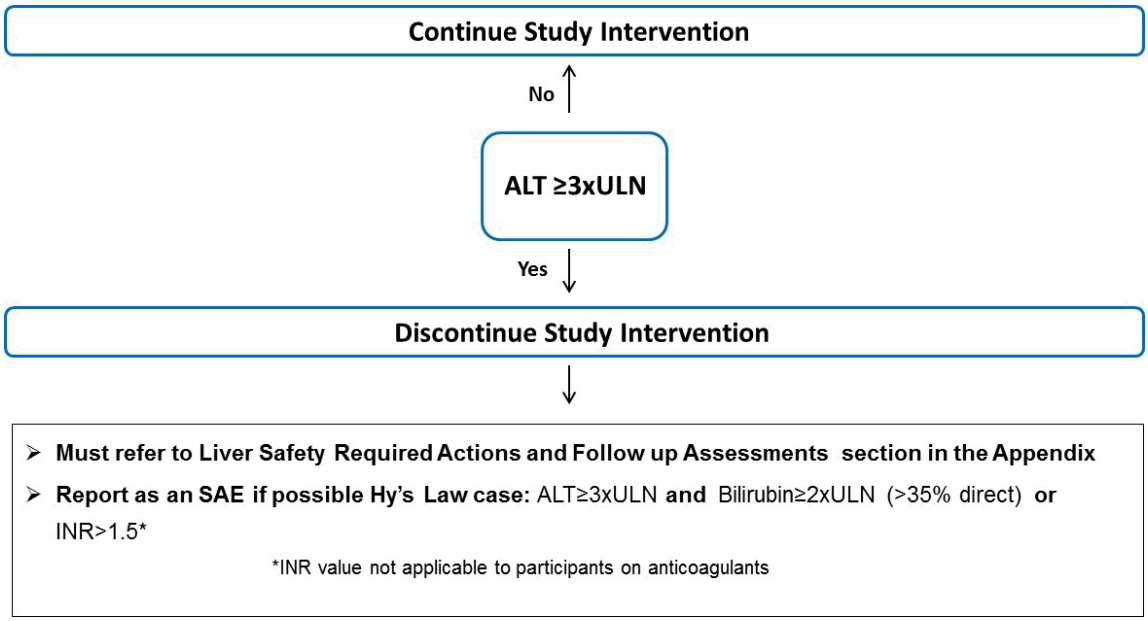
7.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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

- a participant meets one of the conditions outlined in the algorithm
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



- Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.
- Refer to Appendix 6 for required Liver Safety Actions and Follow up Assessments

7.2. QTc Stopping Criteria

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

- QTcF>500 msec,
- Change from baseline: QTcF >60 msec
- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period.

7.3. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See 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.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.4. 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 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.

Discontinuation of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- 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.
- Study procedures and their timing are summarized in the SoA (Section 1.3)
- 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3)

8.1. Efficacy Assessments

Not applicable

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

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

8.2.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse

8.2.3. Electrocardiograms

- 12-lead ECG's will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Refer to Section 7.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

8.2.4. Targeted Injection Site Reaction Examination

A targeted visual assessment of the injection site is to be conducted at 4, 24- and 48-hours post-dose. Any injection site reactions will be recorded in the CRF.

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) 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.
- 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 aetiology 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 (Section 1.3).
- Clinical safety laboratory data for white blood cell differentials must be blinded post-dose (see Appendix 2). Further details for laboratory requisition orders can be found in the study reference manual.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The definitions of device-related safety events, (adverse device effects (ADEs) and serious adverse device effects (SADEs)), can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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 intervention or the study, or that caused the participant to discontinue the study (see Section 7).

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

- All SAEs will be collected from the signing of the informed consent form until the final follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from Day 0 until the final follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. 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 after the conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- 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 3.
- 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.

8.3.3. 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 Section 8.3.6), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.3.4. 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 intervention 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 intervention 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.
- For all studies except those utilizing medical devices 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 SAEs) 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the final follow up at Day 85.
- 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 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Adverse Events of Special Interest

Participants will be monitored for injection site reactions during the study as indicated in the SoA (Section 1.3).

Injection site reaction guidance

Injection-related reactions occurring subsequent to administration of monoclonal antibodies can be characterised as either acute or delayed.

- Acute reactions occur within 24 hours, but usually within 10 minutes to 4 hours after receiving the drug
- Delayed reactions can occur from 24 hour to 14 days, but usually occur after 5-7 days

Both acute and delayed reactions can be further characterised as mild, moderate or severe, depending on the accompanying signs and symptoms.

Acute Reactions:

Acute reactions can be IgE-mediated Type I hypersensitivity (anaphylactic) reactions or non-allergic (anaphylactoid) reactions. Symptoms of a true allergic IgE-mediated anaphylactic reaction include bronchospasm or wheezing, hypotension, laryngeal or pharyngeal swelling, and urticaria.

Non-allergic reactions make up the overwhelming majority of acute infusion reactions. Symptoms generally include headache, nausea, fever, chills, dizziness, flushing, pruritus, and chest or back pain.

Delayed Reactions:

Delayed reactions may also occur in patients who receive monoclonal antibodies. Both Type III (immune complex) and Type IV (cell mediated) hypersensitivity should be considered. Delayed hypersensitivity reactions need to be clearly delineated from infusion reactions so collection and evaluation of non-acute clinical symptoms following administration of a therapeutic protein should be completed. Symptoms of a delayed reaction may include myalgia, arthralgia, fatigue, fever, headache, skin rash and pruritus.

8.4. Treatment of Overdose

For this study, any dose of GSK3772847 greater than 70mg (cohort 1) or 140mg (cohorts2-4) within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3772847 can no longer be detected systemically (at least 12 weeks).
3. Obtain a plasma sample for PK analysis immediately after dose of study intervention and where possible continue to sample as per the SoA (Section 1.3).
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.

8.5. Pharmacokinetics

Whole blood samples of approximately 3 mL will be collected for measurement of serum concentrations of GSK3772847as specified in the SoA (Section 1.3). The timing of PK

samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. The actual date and time (24-hour clock time) of each sample will be recorded.

Detailed instructions for processing, storage and shipment will be provided in the appropriate Study Reference Manual.

8.6. Pharmacodynamics

8.6.1. Soluble ST2

Whole blood samples of approximately 3mL will be collected during this study for the purposes of measuring free and total sST2 levels. Samples will be collected at the time points indicated in the SoA (Section 1.3). The timing of the collections may be adjusted on the basis of emerging PK or PD data from this study or other new information in order to ensure optimal evaluation of the biomarker endpoints. The actual date and time of each sample collection will be recorded.

Detailed instructions for processing, storage and shipment will be provided in the appropriate Study Reference Manual

8.6.2. Blood eosinophils

Blood eosinophil levels will be collected as part of routine safety laboratory sample collection. The timing of collection is detailed in the SoA (Section 1.3).

Detailed instructions will be provided in the study reference manual.

8.7. Genetics

Information regarding genetic research is included in Appendix 5.

Genetic sampling is optional. Participants can refuse genetic sampling but will still be allowed to participate in the study.

8.8. Biomarkers

8.8.1. 4βOH cholesterol/cholesterol

- Whole blood samples of approximately 3 mL will be collected for measurement of 4β hydroxycholesterol/cholesterol ratio as specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.

- Detailed instructions for processing, storage and shipment will be provided in the Study Reference Manual.

8.9. Immunogenicity Assessments

- Serum samples of approximately 2mL will be collected and tested for the presence of antibodies that bind to GSK3772847, as specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.
- The presence of anti-GSK3772847 antibodies will be assessed using a tiered approach including screening assay, a confirmation assay and calculation of titre.
- Detailed instructions for processing, storage and shipment will be provided in the Study Reference Manual.

8.10. Health Economics or Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis

The primary objective of this study is to evaluate the safety, tolerability and the pharmacokinetics of GSK3772847 administered subcutaneously. There are no formal hypothesis tests associated with this objective and no formal significance tests.

The information acquired from this study will be used to quantify the effects of GSK3772847 on safety and tolerability via the SC route where the main focus will be on injection site reactions and to assess the pharmacokinetics across the 3 injection sites and doses. In addition, PK will be evaluated in Japanese and Chinese participants.

An interim analysis will be performed after the minimum number of participants specified in Section 9.5 have reached 4 weeks post dose in Cohorts 1-4. The purpose of this interim analysis is to assess safety, tolerability and PK to inform on the properties of GSK3772847 dosed via the SC route.

9.2. Sample Size Determination

The study comprises:

- Cohort 1: 18 subjects on GSK3772847 70mg and 6 subjects on Placebo
- Cohort 2: 18 subjects on GSK3772847 140mg and 6 subjects on Placebo
- Cohort 3: 6 Japanese subjects on GSK3772847 140mg and 2 Japanese subjects on Placebo

- Cohort 4: 6 Chinese subjects on GSK3772847 140mg and 2 Chinese subjects on Placebo

This design will ensure that we have an adequate understanding of the tolerability of GSK3772847 when dosed subcutaneously and will enable estimation of the key PK parameters (AUC and C_{max}) with adequate precision (1 SE expected to be ~7% of the geometric mean for each dose (n=18) assuming a CV no greater than 30%, based on precedence with comparable mAbs). In addition, the sample size for the critical evaluations of dose and injection site comparisons are in line with appropriate guidance where the minimum number of subjects should not be smaller than 12 (NB in this context the injection sites are combined across both doses).

A total of 64 participants will be initially randomised for a total of 18 evaluable participants on GSK3772847 in cohorts 1 and 2, 6 Japanese participants in cohort 3 and 6 Chinese participants in cohort 4. Participants will be replaced if they withdraw from the study prior to completing all PK and sST2 assessments up to and including D29. It is anticipated that the number of such participants will be low (<10%), meaning that up to 72 participants would be randomised to achieve the required number evaluable.

An evaluable participant is one who receives a dose of GSK3772847 and has PK and sST2 data up to and including Day 29.

9.3. Populations for Analyses

The following populations (as defined below), will include participants who are randomized and replaced because they withdraw prior to D29.:

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized. A participant who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error provided they have not performed any study assessments. If a participant is a screen or run in failure but has been randomized and dosed and continues in the study, then they will be included in this population. They will be footnoted as a protocol deviation. If they were not dosed (but randomized in error), they will be excluded from the population.
PK/PD	All randomized subjects who received at least one dose of study treatment, and for whom at least one pharmacokinetic sample was obtained, analyzed and was measurable. Displays will be based on the treatment to which the participant actually received

Population	Description
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to FPFV and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modelling and Simulation (CPMS) department within GlaxoSmithKline. Plasma GSK3772847 concentration-time data will be analysed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (C_{max}), time to Cmax (T_{max}), area under the plasma concentration-time curve [$AUC_{(0-t)}$, and $AUC_{(0-\infty)}$] and apparent terminal phase half-life ($t_{½}$).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Respiratory Clinical Statistics, GlaxoSmithKline.

Free and total sST2 data will be presented in graphical and/or tabular form and will be summarised descriptively.

The PK and sST2 data are planned to be incorporated into a multi study population PKPD analysis. This will be reported separately from the main clinical study report (CSR).

9.4.2. Primary Endpoint(s)

The following primary safety endpoints will be summarised descriptively by treatment group and cohort: Incidence and frequency of AEs and SAEs, including injection site reactions.

Adverse events (AEs) will be coded using the standard GSK dictionary, Medical Dictionary for Regulatory Activities (MedDRA), and grouped by body system. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal AEs, non-fatal SAEs, adverse events of special interest (AESIs) and AEs leading to withdrawal.
Deaths and SAEs, if applicable, will be documented in case narrative format.

The PK parameters, including but not limited to, Area under the plasma-concentration time curve (AUC), maximum plasma concentration (Cmax), time to Cmax (Tmax) and terminal half-life (t1/2) of GSK3772847 will be summarised and listed per cohort. Cohorts 1 and 2 will also be summarised by injection site.

9.4.3. Secondary Endpoint(s)

Maximal decrease from baseline in free sST2 and maximal increase from baseline in total soluble sST2 levels in serum will be analysed. sST2 will be log transformed prior to analysis. An Analysis of Variance (ANCOVA) will be fitted to each cohort separately with the baseline value included as a covariate along with treatment. Treatment differences and 95% CIs will be presented.

Incidence and prevalence of anti-GSK3772847 antibodies and Plasma 4βOH cholesterol/cholesterol ratio (pre-treatment and following dosing of GSK3772847) will be listed and summarised by cohort (and injection site for cohorts 1 and 2) over time.

9.4.4. Other Endpoint(s)

12-Lead ECGs, clinical laboratory safety tests, vital signs, blood eosinophil levels, free and total soluble sST2 levels in serum and GSK3772847 levels in the serum will be listed and summarised by cohort (and injection site for cohorts 1 and 2) over time.

Further details will be included in the RAP.

9.5. Interim Analyses

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

An interim analysis will be performed after the following minimum number of participants have reached Day 29. Assuming a 10% dropout, this corresponds to:

- Cohort 1: at least 22 individuals (out of a total of 24 randomised)
- Cohort 2: at least 22 individuals (out of a total of 24 randomised)
- Cohort 3: at least 7 individuals (out of a total of 8 randomised)
- Cohort 4: at least 7 individuals (out of a total of 8 randomised)

The purpose of this interim analysis is to assess safety, tolerability and PK to inform on the properties of GSK3772847 dosed via the subcutaneous route and allow the project to move forward to the next phase of development but will not affect progression of this study since all subjects will have finished dosing.

Data reviewed will be PK, sST2 (both free and Total), and AE and SAE data. The PK free and total sST2 concentrations will be summarised and plotted up to 4 weeks. Cohorts 1 and 2 will also be summarised by injection site.

The interim analyses will be performed by GSK Clinical Statistics and programming and only the responsible statistician (and Quality control [QC] statistician), programmer and the CPMS representative will have access to individual participant data. The findings of the interim analyses will be shared with the DRC as detailed in the Interim Analysis Review Charter, (see Appendix 1, Section 10.1.5.2).

Analyses will also be conducted by CPMS as part of a multi-study population PKPD analyses to inform on the PK and PD properties of GSK3772847. These analyses will not have any impact on this study and will be reported separately.

9.6. Dose Escalation Committee

The Dose Escalation charter will describe the procedures related to DEC operations in greater detail.

For details on the dose escalation committee structure, refer to Section 10.1.5

The dose escalation committee (DEC), comprised of members from the GSK Study Team (namely safety and clinical) and the Investigator(s), will review blinded available data from at least 20 participants in cohort 1 before initiating dosing in cohorts 2,3 and 4. Dose escalation may occur only after review of individual injection site data.

The decision to proceed to dosing in cohorts 2,3 and 4 will be made by the Dose Escalation Committee based on assessment of the injection site data at 70 mg dose level as detailed in the Dose Escalation Charter.

Data may be reviewed in an unblinded fashion by a subset of the DEC (namely safety and clinical) should a significant safety concern arise during the blinded review.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 (e.g., 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

10.1.2. 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.

10.1.3. Informed Consent Process

- The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. 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 tick box will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

- 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 centre.
- 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

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. Committees Structure

10.1.5.1. Dose Escalation Committee Structure

During the dose escalation data review blinded study safety data will be reviewed by the dose escalation committee for the purposes outlined in the dose escalation charter (DEC). The dose escalation committee (DEC), comprised of members from the GSK Study Team (namely safety and clinical) and the Investigator(s)

Further details of interim analysis data review the dose escalation committee are found in the dose escalation charter.

10.1.5.2. Interim Analysis Data Review Committee (DRC)

During the Interim Analysis data will be reviewed by the DRC for the purposes outlined in the data review charter. The DRC will be composed of a predefined subset of the study team, including but not limited to GSK Clinical Statistics and the responsible statistician, programmer and the CPMS representative, Lead Physician, Clinical Scientist and Safety.

Further details of interim analysis data review committee are found in the interim data review charter.

10.1.6. Dissemination of Clinical Study Data

- 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 protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the

data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. 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 (e.g., 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.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the (Electronic) case report form (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.
- Quality tolerance limits (QTLs) will be pre-defined in the Integrated Project Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study, and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.1.8. Source Documents

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

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

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 intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be conducted by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel

Pregnancy Testing:

Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1, Inclusion Criteria

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count	***RBC Indices*:**	***WBC count with Differential (see footnote 3):***	
	RBC Count	MCV	WBC	
			Neutrophils	
	Haemoglobin	MCHC	Lymphocytes	
	Haematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
		Magnesium		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥ 1+])			
Other tests	• hsCRP			

Laboratory Assessments	Parameters
Other Screening Tests	• HIV • Hepatitis B • Hepatitis C (Hep C antibody) • FSH and estradiol (as appropriate) • Alcohol, cotinine and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; hsCRP = highly sensitive C-reactive protein; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; UACR = urinary albumin-creatinine ratio; WBC = white blood cell, pH= hydrogen ion concentration.

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6 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.
3. WBC differentials will be reviewed at screening only, in order to confirm participant eligibility. At all other times the site must order haematology test with blinded differentials.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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.

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

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., 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.

10.3.2. 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 (e.g., 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:

- Results in death
- Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

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

Results in persistent or significant 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 (e.g. sprained ankle) which may

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

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention 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 intervention 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.

10.3.4. 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 (see next section) 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 medical monitor 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 medical monitor. • 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. • 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. • Contacts for SAE reporting can be found in study reference manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the 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, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.

10.4.2. Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
• Sexual abstinence • *Note: 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 intervention. 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.*
• **ACCEPTABLE METHODS[d]**
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with

spermicide (double-barrier methods)[c]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. e. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. 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 male participants who receive study intervention.
- 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.
- The female 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.
- The initial 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 for medical reasons will be reported as an AE or SAE.

- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will be withdrawn from the study

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention 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 deoxyribonucleic acid (DNA) analysis
- DNA samples may be used for research related to GSK3772847. They may also be used to develop tests/assays including diagnostic tests) related to GSK3772847. 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 analysed for genetic effects on response. This may include, but not be limited to, an investigation as to whether polymorphisms from IL33 and IL1RL1 gene regions associate with IL33 or soluble ST2 expression levels or associate with efficacy or safety responses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3772847 or study interventions 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 GSK3772847 (or study interventions of this class) continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin <2xULN and</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥2xULN or</td></tr>
</table>

Liver Chemistry Stopping Criteria	
INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody

10.7. Appendix 7: COVID-19 Measures

COVID-19 pandemic may impact the conduct of the clinical study. Challenges may arise from quarantines, site closure, travel limitations or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for the site if impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

The site will follow its pre-defined COVID-19 measures for testing participants, providing PPE to participants and staff and infection control.

These measures will remain in place until the site is able to resume normal working activities.

10.7.1. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, the site should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up when clinical trial site visits are not possible. For the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.7.2. Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which (at the discretion of the Investigator) may include collection of blood and urine samples and measurement of vital signs, ECG's and weight. It is the responsibility of the investigator to inform the CRO and GSK when this occurs and to document in source notes.

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary.
- Additional unscheduled safety assessments such as blood or urine sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- The assessments conducted at Day 9, 15, 29, 43, 57, 71 and 85 may be completed by a home health nurse to alleviate the burden on subjects of frequent visits to the study site
- If visits to a site/home are not feasible, then the medical evaluation of safety may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. The CRO will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and the CRO and GSK should be notified as soon as possible by the investigator that the service is required.
- As part of this model, study visits are completed using the vendors platform, which should be a software interface that connects participants to their investigators and study teams through either a study-issued smartphone or participant's own device (BYOD) model in addition to providing a data collection platform. This technology may be used in combination with visits from mobile study personnel (e.g. mobile nurses) to participants' homes for various lab collections and designated study procedures.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary. Provision of a study-issued smartphone or the vendors platform on a participant's own device allows for study participants to report AEs at any time. Participants can also request a timely secure videoconference with the investigator and/or site staff.
- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

10.7.3. Data Management/Monitoring:

- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by national legislation and the clinical site. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
BYOD	Bring Your Own Device
CI	Confidence Interval
CV	Cardiovascular
Cmax	maximum serum concentration
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical Study Report
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
DoR	Delegation of Responsibility
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
EW	Early Withdrawal
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GLP	Good laboratory practice
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
HCP	Health care professional
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG2σ	human immunoglobulin G2 sigma isotype
IgG	Immunoglobulin G
IL-33R	Interleukin-33 receptor
IL-1RL1	Interleukin-1 receptor like-1
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous

Kg	Kilogram
mAb	monoclonal antibody
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg (μg)	Microgram
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
min	Minute
mIU	Milli international units
mL	Milliliter
μL	Microlitre
mm	Millimeter
mV	Millivolt
msec	Millisecond
PD	Pharmacodynamic
PGx	Pharmacogenetic
PI	Principal Investigator
PK	Pharmacokinetic
PPE	Personal Protective Equipment
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
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SDV/SDR	Source Data Verification/Source Document Review
SGPT	Serum Glutamic-Oxaloacetic Transaminase
SoA	Schedule of Activities
SRM	Study Reference Manual
ST2	Suppressor of tumorigenicity 2
sST2	Soluble ST2
ULN	Upper Limit of Normal
VT	Ventricular Tachycardia
WBC	White Blood Cell
WOCBP	Woman of childbearing potential
w/v	Weight/volume
4βOH	4β-Hydroxy

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

10.9. Appendix 9: Protocol Amendment History

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

Amendment [1] 12-JUN-2020

Overall Rationale for the Amendment:

An amendment to include a COVID-19 measures appendix, increase outpatient visit windows and define sample collection window for Free sST2 and total sST2 blood samples.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA) Table 2	Increase in visit windows from "Day 9 and 15 ± 2 days, thereafter ± 4 days" to "Day 9 ± 2 days, Day 15 ± 4 days, Days 29, 43 and 57 ± 7 days, Days 71 and 85 ± 10 days	To increase flexibility of participant outpatient visits from Day 15 to 85.
	Define sample collection window for Free sST2 and total sST2 blood sample from "samples must be taken at the same time as PK" to "samples should be taken within ± 2 minutes of PK"	To provide clarity on the defined window for Free sST2 and total sST2 blood sample collection windows.
Section 10. Supporting documentation and operational considerations	Inclusion of "Appendix 7: COVID-19 measures"	To outline measures that may be applicable if the site is impacted by the COVID-19 pandemic, including allowing home health nursing and telemedicine for outpatient visits.

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