Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3772847, compared with placebo, administered intravenously every 4 weeks for 12 weeks (Week 0 – Week 12, 4 doses in total) in participants with severe asthma.	Primary – Proportion of participants with loss of asthma control over Weeks 0-16 where 'loss of asthma control' is defined as at least one of the following: • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation) or • Pre-bronchodilator Forced expiratory volume in 1 second (FEV1) decrease from baseline (measured at the end of Run-in) >7.5 % or • Inability to titrate inhaled corticosteroid according to the pre-defined schedule (Section 5.1) or • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥0.5 point.
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • Time to loss of asthma control. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule • The incidence, mean rate, and total number per participant of hospitalisations or Emergency Room (ER) visits during the study treatment period. • Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16. • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16. • Proportion of St. George's Respiratory

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period (Visit window ± 3 days)**										**Follow-up Period[2] (± 3 days)**			**Notes**
Visit	**0**	**1**	**2[3]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (ETP or EW)**	**12**	**13**	**14**	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	**-4~-2**	**-2**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	
Study Day	**-28~-14**	**-14**	**1**	**8**	**15**	**29**	**43**	**49**	**71**	**85**	**99**	**113**				
Pregnancy test[1]	X[2]		X[3]			X[3]		X[3]		X[3]		X	X	X	X	1. Test for women with child bearing potential. 2. Serum pregnancy test at V0/V1. 3. Test to be performed pre-dose during the treatment period.
[HIV, Hep B and Hep C screen]		X														A confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. If test has been performed within 3 months prior to first dose of study treatment, testing at screening is not required.
Randomization Criteria			X													
Spirometry		X	X		X	X	X	X	X	X	X	X				Test to be performed pre-dose during the Treatment period
Reversibility		X														
12-lead ECG		X	X[1]			X[1]		X[1]		X[1]		X				1. Test to be performed pre-dose and post-dose within 30 mins after end of infusion.

Objectives	Endpoints
participants with severe asthma.	hospitalisation). • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • Time to loss of asthma control. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule • The incidence, mean rate, and total number per participant of hospitalisations or Emergency Room (ER) visits during the study treatment period. • Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16. • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16. • Change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16. • Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF over each four weeks of the 16 week treatment period. • Change form baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period. • Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period. • Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the16 week treatment period. • Change from baseline in fractional exhaled nitric oxide (FeNO) at each week measured.
• To evaluate the safety and tolerability of GSK3772847, compared with placebo	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs).

randomization criteria (Section 6.3) will be randomized in a 1:1 ratio to enter a double-blinded Treatment Period and receive the following study treatment every 4 weeks for 12 weeks (Week 0, 4, 8 and 12) while initially remaining on the open label background therapy of FP/Sal 500/50 mcg BID at Randomization:

- GSK3772847 administered intravenously or
- Placebo administered intravenously

At Visit 4 (i.e. two weeks after Randomization) the open label background therapy will be switched from FP/Salmeterol 500/50 mcg BID to FP 500 mcg BID for 2 weeks. This will mark the beginning of the FP titration period. Every two weeks for the next six weeks the dose of FP will be reduced by approximately 50 % (i.e. FP 250 mcg BID at Visit 5 for 2 weeks, FP 100 mcg BID at Visit 6 for 2 weeks, then FP 50 mcg BID at Visit 7 for 2 weeks) until complete FP discontinuation at Visit 8, provided that the participant does not meet any of the loss of asthma control criteria. If any of the pre-defined criteria for loss of asthma control are met during the Treatment Period, participants will be withdrawn from the investigational product (IP) and should resume regular treatment for their asthma, as determined by the investigator.

For participants who receive all four doses of blinded study treatment, an End of Treatment Period (ETP) Visit will be performed 4 weeks after the final dose of the blinded study treatment is administered at Week 12. Participants should resume regular treatment for their asthma, as determined by the investigator, after protocol defined study assessments are completed. Three Follow-up visits will be performed 4, 8, and 12 weeks (Week 20, Week 24, and Week 28) after the ETP Visit for safety assessments.

For participants who discontinue IP early, but have not withdrawn consent to participate in the study, an early withdrawal (EW) visit will be performed 4 weeks after the last dose of blinded study treatment. These participants should continue in the study and complete all assessments at the remaining protocol-defined visits until their EW visit. Participants should resume regular treatment for their asthma, as determined by the investigator. Three Follow-up visits will then be performed 4, 8, and 12 weeks after the EW visit for safety assessments.

Participants who discontinue IP early and withdraw consent to participate in the study should complete as many assessments planned for the EW visit as possible.

To evaluate the safety and tolerability of repeat dose of GSK3772847, a placebo arm will be included to allow the absolute effect of GSK3772847 to be assessed. The treatment duration of 12 weeks is supported by pre-clinical study data. Dosing frequency of IP every 4 weeks with endpoints assessments scheduled 4 weeks post final IP dose are determined by the available target engagement pharmacodynamic findings. Upon completing the 16 week Treatment Period (or after IP discontinuation), participants should resume regular treatment for their asthma, as determined by the investigator and will be followed up for an additional 12 weeks before a final safety evaluation. This Follow up Period will ensure that sufficient PK samples are taken to fully characterise the pharmacokinetics, pharmacodynamics, and anti-drug antibody responses in this population.

An inhaled short acting beta$_2$–receptor agonist, salbutamol/albuterol will be provided to all participants to use as needed to relieve asthma symptoms from Screening (Visit 1) to end of the Treatment Period. Both safety and efficacy parameters will be assessed regularly in the clinic to minimise any potential risks to the participants. Participants' safety will also be assured by having withdrawal criteria (Section 8.1) in case of loss of asthma control.

5.5. Dose Justification

The dosing regimen of 10 mg/kg IV at Week 0 then Weeks 4, 8 and 12 was selected based on the observed evidence of target suppression following single doses in healthy participants (CNTO7160ASH1001). In summary, administration of a single 10 mg/kg dose led to significant (>95%) suppression of serum free sST2 and sustained elevations of total sST2 up to at least 28 days after dosing. Therefore, the selected regimen should deliver significant target suppression throughout the treatment period, including at trough, and allow determination of the impact of targeting this pathway on the primary endpoint (measured over 0-16 weeks).

Simulations of exposure were generated using a preliminary Michaelis Menten (MM) population PK model using the single dose data from 0.03-10 mg/kg up to 28 days. Safety margins were estimated by comparing the mean clinical exposures (predicted or observed) against the mean observations in the 3-month GLP toxicology study in cynomolgus monkeys (T-2013-007). Area under the curve (AUC) margins were calculated by comparing the predicted clinical exposures from 0-28 weeks (end of study) to the observed exposure from 0-92 days (13 weeks) when the main study animals were removed from study. Predicted exposures throughout the study and follow up period are significantly lower than those observed in study T-2013-007 as shown in Figure 1

period is the past week. A score of <0.75 indicates well-controlled asthma and a score ≥1.5 indicates poorly controlled asthma [Juniper, 2006]. A change of ≥0.5 in score suggests a clinically important change in score [Juniper, 2005].

9.1.1.2. St. George's Respiratory of Life Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well established instrument, comprising 50 questions designed to measure Quality of Life in patients with diseases of airway obstruction, measuring symptoms, impact, and activity. The questions are designed to be self-completed by the participant [Jones, 1992] with a recall over the past 4 weeks. Higher scores indicate worse health status, and a change of 4 points is considered a clinically relevant change [Jones, 2005].

9.1.2. Daily Diaries

Participants will be issued with a PEF/e-Diary device at Visit 1 for twice daily use (in the morning upon waking and in the evening just before going to bed) throughout the study. The device will be provided by a third-party vendor. Information on the device and its use are documented in the SRM and the third-party vendor manual. Participants will be instructed on how to use the device in order to record results for the following in the eDiary each day from Visit 1 onwards:

- Morning and evening peak flow (best of three).
- Daytime asthma symptom score using a 5-point scale
- Inhalations of rescue medication usage over the previous 24-hours
- Frequency of awakening due to asthma symptoms requiring rescue medication use
- Morning and Evening use of FP/Sal and FP during the run-in and treatment periods

Section 9.1.2 describes the assessments and questionnaires recorded on the eDiary device, as well as the alerts that can be triggered based on recorded results. The data from the eDiary device will be automatically transmitted to a centralized server. The Investigator and designee(s) will be provided with access to the transmitted eDiary data via a vendor-provided portal and should review the data on an ongoing basis to check for the incidence of alerts as well as subject compliance with eDiary use.

Participants will also be issued with a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study (please refer to the SRM for further details). Participants must also use this paper worksheet to record all healthcare contacts that occur during their participation in the study. This paper worksheet will be used to assist participant recall in discussions with the Investigator, for site staff to then enter as appropriate in the electronic case report form (eCRF).

9.1.2.1. Night-time Awakening, Daytime Asthma Symptom Questions

Every morning upon waking (from the morning after Visit 1 onwards), participants will answer a question on the occurrence of night-time awakenings due to asthma symptoms. The participant's response to the question on the occurrence of night-time awakenings

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

9.2.2. Method of Detecting AEs and SAEs

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

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

Participants will be issued with a paper Medical Problems/Medications Taken worksheet to record any medical problems experienced and medications used during the study (See Section 9.1.2).

9.2.3. Follow-up of AEs and SAEs

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

9.2.4. Regulatory Reporting Requirements for SAEs

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

3. Obtain a serum sample for PK analysis within 7 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

Vital signs should be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2) prior to conducting spirometry. Blood pressure (systolic and diastolic) and pulse rate will be measured in the supine position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

9.4.3. Electrocardiograms

All sites will use standardised ECG equipment provided by a centralized external vendor. A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs. Recordings will be made at the time-points defined in the Schedule of Activities (SoA) table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.

For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8).

The Investigator, a designated sub-Investigator or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The Investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

All ECGs will be electronically transmitted to an independent cardiologist and evaluated. The independent cardiologist, blinded to treatment assignment, will be responsible for providing measurements of heart rate, QT intervals and an interpretation of all ECGs

collected in this study. A hard copy of these results will be sent to the Investigator. The Investigator must provide his/her dated signature on the confirmed report, attesting to his/her review of the independent cardiologist's assessment.

Details of the cardiac monitoring procedures will be provided by the centralized cardiology service provider.

9.4.4. Continuous ambulatory ECG (Holter)

Continuous ECG monitoring (Holter) assessments have been added to the protocol to allow for a quantitative assessment of abnormal rhythm events. Holter monitors will be provided by a third party vendor to each site. The device should be connected and electrodes attached to the participant as per the vendor's instructions.

data from this study or other new information in order to ensure optimal evaluation of the biomarker endpoints.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 6. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx and genetic assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx and genetic assessments (i.e., approval of Appendix 6).

In some cases, approval of the PGx and genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx and genetic assessments is being deferred and the study, except for PGx and genetic assessments, can be initiated. When PGx and genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx and genetic assessments will not be conducted.

9.8. Biomarkers

9.8.1. Exploratory Biomarkers

Blood (serum) and sputum (Section 9.8.1.1) samples will be collected during this study and may be used for the purposes of measuring asthma biomarkers or endotypes of asthma, as well as response to GSK3772847. Biomarkers will include, but not be limited to, serum total IgE, Eosinophilic Cationic Protein (ECP) and Type-2 chemokines (e.g. CCL13, CCL17) as well as sputum cell counts (e.g. percentage eosinophils). Samples may also be used to identify factors that may influence the development of asthma and/or medically related conditions. Samples will be collected at the time points indicated in the SoA.

9.8.1.1. Sputum Sub-Study

At selected sites only, consenting participants who are randomized at Visit 2 will be entered into the Sputum sub-study. In a subset of approximately 50% of eligible participants sputum samples will be collated as specified in the SoA.

Details of the sputum collection and processing methodology will be provided in the SRM.

9.8.2. Immunogenicity Assessments

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3772847, as specified in the SoA. 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 a screening assay, a confirmation assay and calculation of titre.

Instructions for the collection and handling of biological samples will be provided in the SRM.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary null hypothesis (H_0) for this study is that the ratio of the proportions of subjects with loss of asthma control from randomization to Week 16 between GSK3772847 and placebo is unity.

$$H_0: \frac{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ GSK3772847}{Proportion\ with\ loss\ of\ asthma\ control\ \ at\ Week\ 16\ on\ Placebo} = 1$$

The alternative hypothesis (H_1) for this study is that the ratio of the proportions of subjects with loss of asthma control from randomization to Week 16 between GSK3772847 and placebo is not unity.

$$H_1: \frac{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ GSK3772847}{Proportion\ with\ loss\ of\ asthma\ control\ \ at\ Week\ 16\ on\ Placebo} \neq 1$$

The hypothesis will be tested by calculating the posterior probability that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.5 and 0.2 (i.e. a 0%, 25%, 50% and 80% reduction) and supported by an estimate of the ratio with a 95% credible interval. A non-informative prior will be used.

Although the success of the study will be assessed by calculating posterior probabilities of the treatment effect reaching various thresholds and not statistical significance, a frequentist analysis will also be performed testing the above hypothesis.

10.2. Sample Size Determination

The study will randomize 74 participants per treatment arm with the aim of having 70 evaluable participants per arm. For the purpose of this study an evaluable participant is defined as a participant who completes the Week 16 clinic visit whilst remaining on IP or who withdraws from IP having met the primary endpoint. See Section 10.4.1 for how subjects who withdraw early from IP for reasons other than loss of asthma control are handled in the analysis.

hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HR	Heart rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
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
iSRC	Independent Safety Review Committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	Interactive Web Response System
ITT	Intent to Treat
Kg	Kilogram
LABA	Long-Acting Beta-2-Agonists
LTRA	Leukotriene Receptor Antagonist
mAb	monoclonal antibody
MAO	Monoamine oxidase
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg (μg)	Microgram
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered Dose Inhaler
mg	Milligram
min	Minute
mIU	Milli international units
mL	Milliliter
μL	Microlitre
mm	Millimeter
mV	Millivolt
MSDS	Material Safety Data Sheet
msec	Millisecond
NOAEL	No Observed Adverse Effect Level
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association

Laboratory Assessments	**Parameters**			
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	CPK
	Albumin	Phosphorus	GGT	Chloride
		Carbon Dioxide		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, leukocyte, nitrite, urobilinogen by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum/urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology (HIV antibody, hepatitis B surface antigen HBsAg, and hepatitis C virus antibody) • "All study-required laboratory assessments will be performed by a central laboratory The results of each test must be entered into the eCRF.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. Abbreviations: RBC= Red Blood Cell Count, WBC= White Blood Cell Count, MCV= Mean corpuscular volume, MCH= mean corpuscular haemoglobin, MCHC= mean corpuscular haemoglobin concentration, RDW= Red cell distribution width, AST= Aspartate Aminotransferase, ALT= Alanine Aminotransferase, SGPT= Serum Glutamic-Oxaloacetic Transaminase, CPK= creatine phosphokinase, GGT= Gamma-glutamyltransferase, hCG= human chorionic gonadotropin, HIV= Human Immunodeficiency Virus

assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	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 (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

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

Objectives	Endpoints
	Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16. • Change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16. • Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF over each four weeks of the 16 week treatment period. • Change form baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period. • Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period. • Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the16 week treatment period. • Change from baseline in fractional exhaled nitric oxide (FeNO) at each week measured.
• To evaluate the safety and tolerability of GSK3772847, compared with placebo administered intravenously every 4 weeks for 12 weeks (Week 0-12, 4 doses in total) in participants with severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs. • Change between post-dose and pre-dose in vital signs. • Change from baseline in 12-lead electrocardiogram (ECG) measurements. • Change between post-dose and pre-dose in 12-lead ECG measurements • Change from baseline in 24 hours Holter measurements. • Change from baseline in clinical laboratory tests (haematology and chemistry). • Incidence of and titres of anti- GSK3772847 antibodies.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with severe asthma.	• Serum concentrations of GSK3772847.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with severe asthma.	• Free and total soluble ST2 levels in serum.

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period (Visit window ± 3 days)**										**Follow-up Period[2] (± 3 days)**			**Notes**
Visit	**0**	**1**	**2[3]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (ETP or EW)**	**12**	**13**	**14**	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	**-4~-2**	**-2**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	
Study Day	**-28~-14**	**-14**	**1**	**8**	**15**	**29**	**43**	**49**	**71**	**85**	**99**	**113**				
24 hrs Holter		X	X[1]			X[1]				X[1]						Holter monitor needs to be returned to clinic at end of 24-hour recording (i.e. the next day). 1. Place the Holter 30-60 mins prior to dosing.
Vital signs		X	X[1]	X	X	X[1]	X	X[1]	X	X[1]	X	X	X	X	X	1. Test to be performed pre-dose prior to spirometry and post-dose prior the 12 –lead ECG.
Double blind Study Treatment (IP)			X			X		X		X						
FP/Sal (500/50) dispensing		X	X													
FP (mcg) dispensing					500	250	100	50								
Genetic blood sample – Pre dose			X													Pharmacogenetic sample may be drawn any time from Visit 2 onwards. Informed consent for optional substudies e.g.genetics must be obtained before collecting a sample
ACQ-5		X	X													After randomization, ACQ5 will be completed by the participants every 7 days.
SGRQ			X			X		X		X		X				

Objectives	Endpoints
administered intravenously every 4 weeks for 12 weeks (Week 0-12, 4 doses in total) in participants with severe asthma.	• Change from baseline in vital signs. • Change between post-dose and pre-dose in vital signs. • Change from baseline in 12-lead electrocardiogram (ECG) measurements. • Change between post-dose and pre-dose in 12-lead ECG measurements • Change from baseline in 24 hours Holter measurements. • Change from baseline in clinical laboratory tests (haematology and chemistry). • Incidence of and titres of anti- GSK3772847 antibodies.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with severe asthma.	• Serum concentrations of GSK3772847.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with severe asthma.	• Free and total soluble ST2 levels in serum.
Exploratory	
• To compare the effect of GSK3772847 with placebo on biomarkers in serum and sputum.	• Changes from baseline in induced sputum biomarkers (subset). • Changes from baseline in exploratory serum markers.

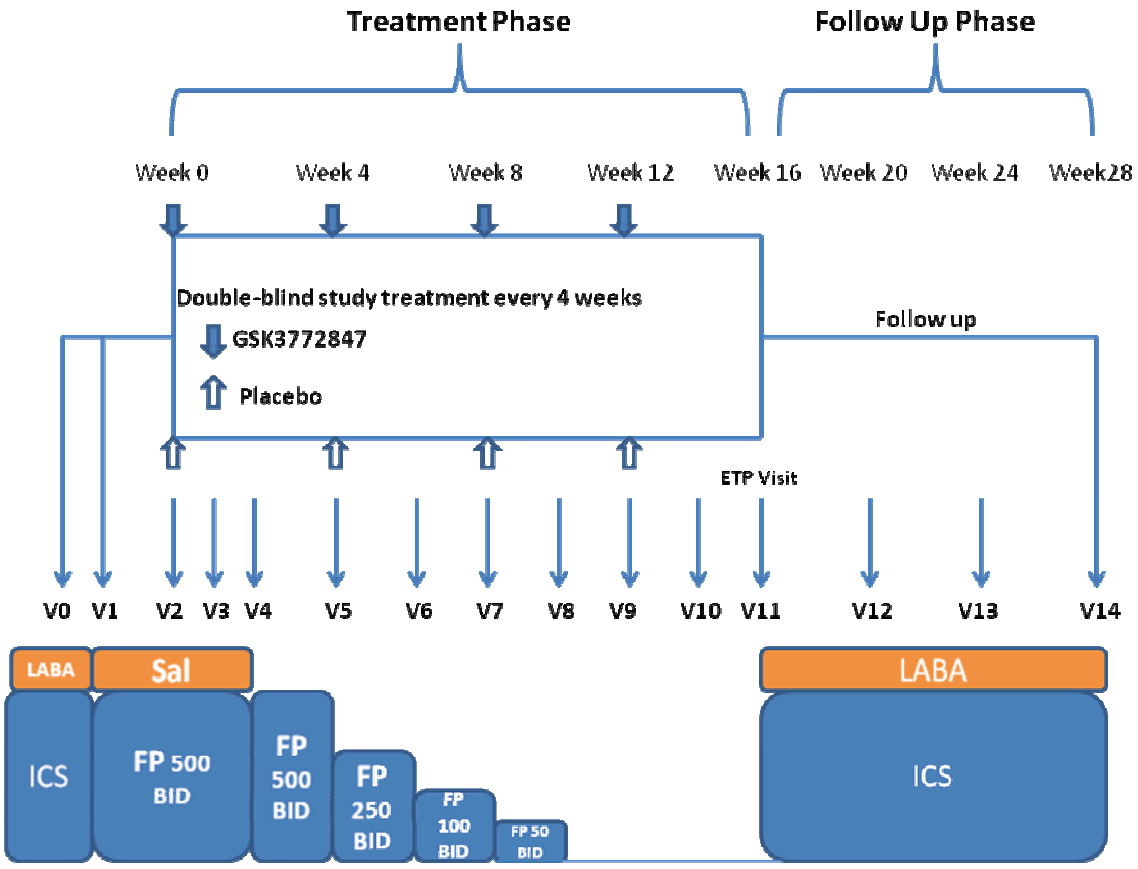
5. STUDY DESIGN

5.1. Overall Design

This is a Phase IIa, multicenter, randomized, placebo-controlled, double-blind, stratified, parallel group study.

There will be a 2-week Run-in period following Screening (Visit 1). Eligible participants will be randomized at the end of the Run-in period (Visit 2). **Randomization will be stratified based on participants' baseline peripheral blood eosinophil count aiming for at least 30% of participants with eosinophil count <150 cells/µL, which is measured at Screening.**

When required, a pre-screening visit (Visit 0) can be scheduled up to 2 weeks prior to Screening (Visit 1). The pre-screening visit (Visit 0) can also occur on the same day as the Screening visit (Visit 1). Participants who meet the eligibility criteria at Screening (Visit 1) will withdraw their regular ICS/ long-acting beta-2-agonists (LABA) treatment for asthma and enter a two-week Run-in period during which they will receive open label background therapy of fluticasone propionate (FP)/salmeterol (Sal) 500/50 mcg BID. At the end of the Run-in period at Visit 2 (Week 0), participants who meet pre-defined



Following randomization participants will return to the clinic at least every 2 weeks for scheduled FP dose titration and assessment of asthma control until the last dose of blinded study treatment (Visit 10).

Albuterol/salbutamol will be provided for symptomatic relief to be used on an as needed basis from Screening through to the ETP visit.

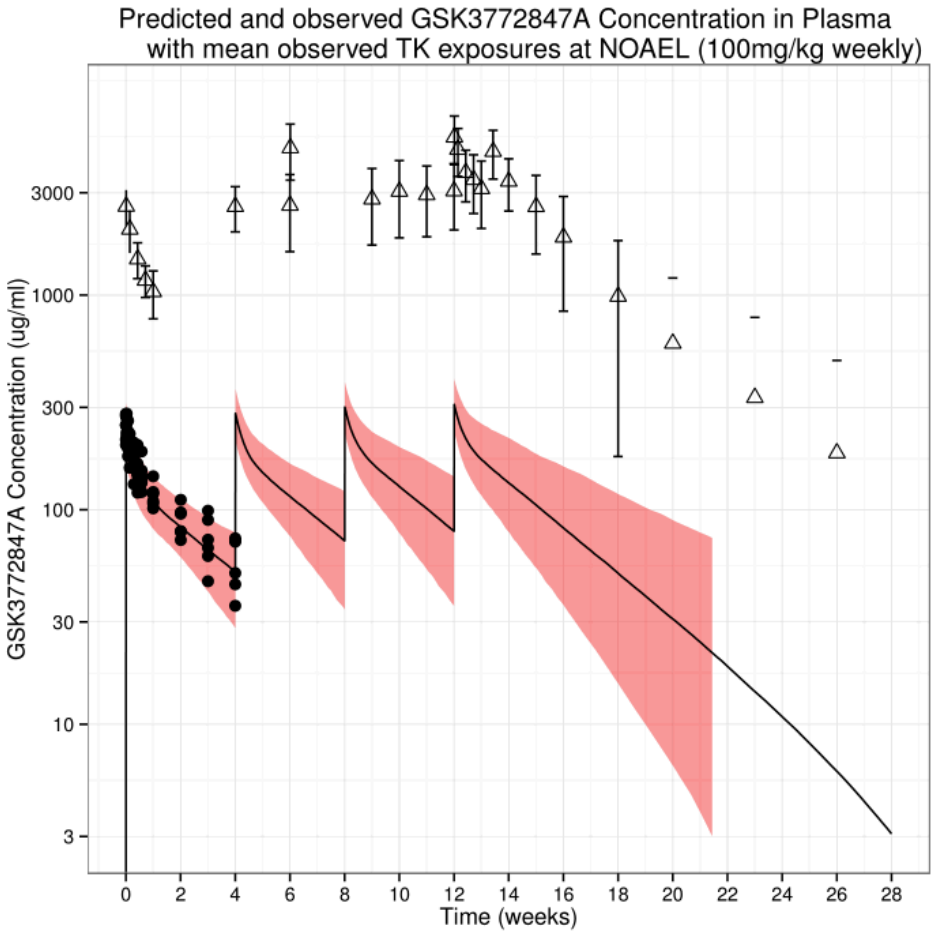
The maximum total duration of the study is approximately 33 weeks.

An independent Safety Review Committee (iSRC) will periodically review unblinded safety data to protect and maintain participant safety whilst maintaining scientific validity. Members of the iSRC will be independent of the project. The data will include, but not necessarily be limited to SAEs, Holters, and ECGs. Details are described in the iSRC Charter.

5.2. Number of Participants

Approximately 300 participants with severe persistent asthma who are maintained on high-dose ICS/LABA will be screened to ensure 148 randomized (74 on GSK3772847, 74 on placebo) participants and 140 evaluable participants. For the purpose of this study an evaluable participant is defined as a participant who completes the Week 16 clinic visit whilst remaining on IP or who withdraws from IP having met the primary endpoint. **High-dose ICS is defined as fluticasone propionate 500 mcg twice daily (i.e. 1000 mcg total daily dose) or equivalent**.

Figure 1 **Predicted clinical exposures at 10mg/kg at weeks 0, 4, 8 and 12 using a preliminary MM population PK model against observed exposures in study CNTO7160ASH1001 (part 1 single dose) and observed exposures at the No Observed Adverse Effect Level (NOAEL) (100 mg/kg weekly) in the 3-month GLP toxicology study in cynomolgus monkeys (T-2013-007).**



- Open Triangles: Observed mean and SD of exposures through main study and recovery phase (post week 13) in toxicology study T-2013-007.
- Solid circles: Observed clinical exposures in part 1 of study CNTO7160ASH1001.
- Solid line and shade region: median and 95% prediction interval for clinical exposures using a preliminary MM population PK model.

The anticipated exposure margins of the dosing regimen of 10 mg/kg IV at Week 0 then Weeks 4, 8 and 12 over the 3-month GLP toxicology study in cynomolgus monkeys (T-2013-007) are summarised in Table 1.

will be either 'Yes' (i.e. Did you wake up due to asthma symptoms (i.e. wheezing, coughing, shortness of breath, or chest tightness) or 'No' (i.e. they did not experience at least one night-time awakening due to asthma symptoms). If 'Yes', participants will be asked to respond either 'Yes' or 'No' to the question on rescue medication (i.e. when you woke up due to your asthma symptoms did you use any rescue bronchodilator?).

On the evening of Visit 1 (just before going to bed) and every evening there-after, participants will answer a question on daytime asthma symptoms. These questions will be answered on a 5-point scale (0 to 4) with '0' representing no daytime asthma symptoms and '4' representing very severe daytime asthma symptoms. Please describe the severity of your asthma symptoms (i.e. cough, wheeze, chest tightness, shortness of breath) today [0=no asthma symptoms, 1=mild asthma symptoms, 2= moderate asthma symptoms, 3=severe asthma symptoms, 4= very severe asthma symptoms].

9.1.2.2. Morning and Evening Home PEF

Participants will conduct PEF measurements using the PEF/eDiary device each morning and each evening. Three measurements for each session will be recorded by the participants in the eDiary. Assessments will be performed:

- After completing all other eDiary assessments
- Prior to albuterol/salbutamol use
- Prior to FP/Sal and FP use

9.1.2.3. Alerts

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions for the participant to contact the investigator if any of the alert criteria are met. An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with Baseline (last 7 days of run-in).
- A symptom score of 3 for at least two of three successive days.
- An increase from baseline of ≥4 puffs /day of albuterol/salbutamol use on 2 consecutive days.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.

9.1.3. Pulmonary Function Test

Spirometry equipment and a device to measure FeNO (see Section 9.1.4) will be provided to all sites by a third-party vendor. Spirometry data from this study will be analysed by a third-party vendor. Details on performing the spirometry assessments, including information on the equipment provided and its use as well as specific

- 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.

9.2.5. Cardiovascular and Death Events

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

The CV eCRFs are presented as queries in response to reporting of certain CV Medicinal Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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

9.2.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the last follow-up visit.
- If a pregnancy is reported, the investigator should inform GlaxoSmithKline (GSK) within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the Investigator on the AE/SAE eCRF pages.

The dose of GSK3772847 considered to be an overdose has not been defined. There are no known antidotes and GlaxoSmithKline does not recommend a specific treatment in the event of a suspected overdose. The Investigator will use clinical judgement in treating the symptoms of a suspected 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 for 16 weeks after the last dose.

9.4.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

9.5. Pharmacokinetics

- Whole blood samples of approximately 3 mL will be collected for measurement of serum concentrations of GSK3772847as specified in the SoA. 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.
- Samples will be used to evaluate the PK of GSK3772847. Samples collected for analyses of serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Instructions for the collection and handling of biological samples will be provided in the SRM

9.6. Pharmacodynamics

Pharmacodynamic (PD) Biomarkers

Blood (serum) samples 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. The timing of the collections may be adjusted on the basis of emerging PK or PD

In addition to testing the hypothesis in the overall population, the study will randomize a sufficient number of participants to evaluate trends in pre-defined subgroups (e.g. eosinophil strata).

The true proportion of participants that would experience a loss of asthma control on each treatment is unknown. However in a similar study of Dupilumab compared with placebo, the proportion of participants with loss of control were 6% and 44% for Dupilumab and placebo respectively. Table 4 gives the power to detect a statistically significant difference (at the two-sided 5% level) between the two treatments assuming the true proportion with loss of control on placebo is 44% and the true proportion with loss of control on active is 6%, 11%, 19% and 22% [Fleiss, 2003].

Table 4 Table of Power Achievable for Different Treatment Comparisons using N=70 per arm calculated using PASS

True proportion on Placebo	True proportion on GSK3772847	Reduction	Power
44%	6%	86%	> 99%
44%	11%	75%	> 99%
44%	19%	57%	90%
44%	22%	50%	80%

Assuming the true proportion with loss of control on placebo is 44%, then with 70 evaluable participants per arm, the study will have at least 80% power to detect a statistically significant difference between treatments assuming the true proportion with loss of control on GSK3772487 is at most 22% (Table 4).

With 70 evaluable participants per arm and assuming the true proportion with loss of control on placebo is 44%, the smallest observed difference that would lead to rejection of the null hypothesis (minimum detectable effect) is 31% corresponding to a proportion with loss of control on GSK3772847 of 28%.

There is a single primary endpoint so no adjustments are required for multiplicity.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who were randomized. A subject 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.
Modified Intent-to-treat	All randomized subjects who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually

OCS	Oral Corticosteroid
PEF	Peak Expiratory Flow
PD	Pharmacodynamic
PGx	Pharmacogenetic
PK	Pharmacokinetic
prn	As needed
PSVT	Paroxysmal supraventricular tachycardia
q2W	Every two weeks
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
RDW	Red cell distribution width
RNA	Ribonucleic acid
SABA	Short-Acting Beta-2-Agonists
SAD	Single Ascending Dose
SAE	Serious Adverse Event
Sal	Salmeterol
SGPT	Serum Glutamic-Oxaloacetic Transaminase
SGRQ	St. George's Respiratory Questionnaire
SRM	Study Reference Manual
ST2	Suppressor of tumorigenicity 2
sST2	Soluble ST2
ULN	Upper Limit of Normal
US	United States
VT	Ventricular Tachycardia
WBC	White Blood Cell
WOCBP	Woman of childbearing potential
w/v	Weight/volume

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF.

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

Phase II liver chemistry increased monitoring criteria with continued therapy

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

References

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