TITLE PAGE

Protocol Title: A randomized, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma

Protocol Number: 207597/02

Short Title: A study to evaluate the effect of GSK3772847 in patients with moderately severe asthma.

Compound Number: GSK3772847

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Approval Date: 13-SEP-2017

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13 Sept 2017
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GlaxoSmithKline

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	*13-SEP-2017*
Amendment 1	*02-JUN-2017*
Original Protocol-2017N311825_00	*06-MAR-2017*

Amendment 2: 13-SEPTEMBER-2017

Overall Rationale for the Amendment: To add more information on the risk:benefit section and the study design justification sections. To address clarifications regarding the unblinding of treatment in case of emergency. To clarify that rechallenge is not allowed once the treatment discontinuation criteria are met. Also, a few typographical errors were corrected.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	In SoA Table 2, corrected Week 8 as Day 57, rather than Day 49.	Typographical error
Section 3.3.2 Benefit Assessment	Clarified that there is no marketed treatment for non T2-driven severe asthma.	To provide additional information on the risk:benefit assessment.
Section 3.3.2 Benefit Assessment	Included more information on the plan for monitoring the participants' asthma status.	To provide additional information on the risk:benefit assessment.
Section 3.3.2 Benefit Assessment	Included that ICS titration design is recommended per GINA guidelines to identify the lowest effective dose.	To provide additional information on the risk:benefit assessment.
Section 5.1 Overall study design	Corrected the visit of the last blinded study treatment in the parentheses as Visit 9, rather than Visit 10. The last dose of blinded study treatment is Visit 9 and not Visit 10.	Typographical error
Section 5.4 Scientific Rationale for Study Design	Clarified that loss of asthma control as a result of ICS titration could be completely compensated by re-establishment of the previous	To provide additional justification on the selected study design.

Section # and Name	Description of Change	Brief Rationale
	treatment regimen with the participant achieving the same level of asthma control that existed prior to study entry.	
Section 7.4 Blinding	Clarified that the investigator has the sole responsibility for unblinding in case of emergency and that the investigator should try to contact GSK prior to unblinding only if this does not delay emergency treatment of the participant	To be consistent with EMA guidelines on treatment unblinding in case of emergency
Section 8.1 Treatment discontinuation criteria	Removed the parentheses specifying at which visits abnormal ECGs would lead to treatment discontinuation. Abnormal ECGs at any visit would lead to treatment discontinuation. The visit numbers in the parentheses were included in error.	Typographical error
Section 8.1.3 Rechallenge	Clarified that rechallenge is not allowed after a participant has met any of the treatment discontinuation criteria	To clarify that rechallenge is not allowed if any of the treatment discontinuation criteria are met.
Section 10.3 Populations for Analysis	Removed the definition of the Safety population	The modified intention to treat population (mITT) is the same as the safety population.
Section 10.4 Statistical Analyses	Clarified that the efficacy analyses and the safety analyses will be performed on the mITT population	The modified intention to treat population is the same as the safety population.
Section 11 References	Included the reference on the paper by Matz J 2001 and McIvor RA, 1998.	To provide the reference paper on the updated information on loss of asthma control in Section 5.4.

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma.

Short Title: A study to evaluate the effect of GSK3772847 in patients with moderately severe asthma.

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.

At the time of writing this protocol, a two-part, single and multiple ascending dose first time in human (FTIH) study has completed dosing (final clinical study report is pending). The safety information from this study is included in the investigator brochure (GlaxoSmithKline Document Number 2017N316832_00). There are no efficacy data available to date.

The present study is the first GSK sponsored study with GSK3772847. It is a Phase IIa / proof of concept study to investigate efficacy, safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of GSK3772847 in participants with moderately severe asthma. The study will use an inhaled steroid titration design in order to evaluate whether GSK3772847 maintains protection of asthma control. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which changes in the level of asthma control were induced by medication withdrawal. This design may not reflect real world fluctuations in asthma control; however, studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on changes in asthma control in a relatively short period of time, before further investigations are conducted in longer term studies.

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 moderately 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: • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥0.5 point 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 • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation).
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with moderately severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • 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 who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • 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.

Objectives	Endpoints
	• 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 moderately severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28. • Change between post-dose and pre-dose in vital signs at weeks 0, 4, 8 and 12. • Change from baseline in 12-lead electrocardiogram (ECG) measurements at weeks 4, 8, 12 and 16. • Change between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12. • Change from baseline in 24 hours Holter measurements at weeks 4 and 12. • Change from baseline in clinical chemistry at weeks 2, 4, 8, 12, 16 and 28. • Change from baseline in hematology and cardiac markers at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28. • Incidence of and titres of anti- GSK3772847 antibodies at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with moderately severe asthma.	• Serum concentrations of GSK3772847 at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with moderately severe asthma.	• Free and total soluble ST2 levels in serum at weeks 2, 4, 8, 12, 16, 20, 24 and 28.

Overall Design:

This is a Phase IIa, multicenter, randomized, placebo-controlled, double-blind, stratified, parallel group study in participants with moderately severe asthma.

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.

Number of Participants:

Approximately 300 participants with moderately severe 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. High-dose ICS is defined as fluticasone propionate 500 mcg twice daily (i.e. 1000 mcg /day) or equivalent. For the purpose of this study an evaluable participant is defined as a participant who completes the Week 16 clinic visit whilst remaining on investigational product (IP) or who withdraws from IP having met the primary endpoint.

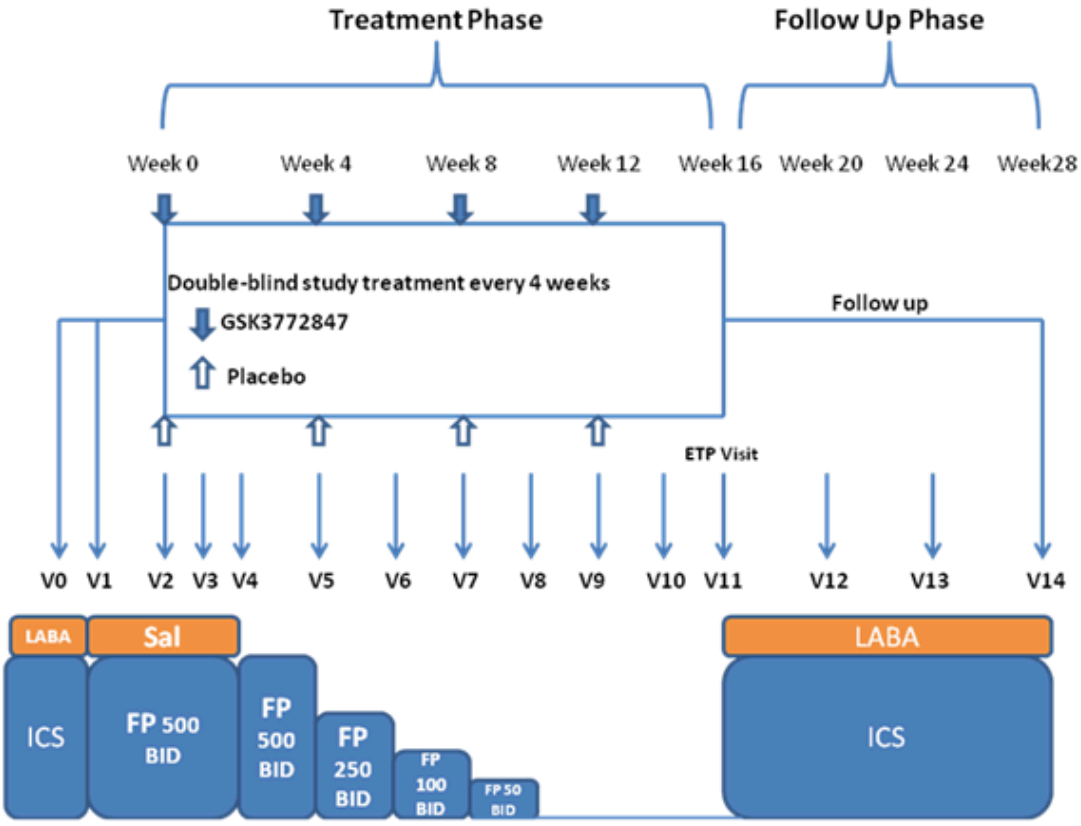
Treatment Groups and Duration:

When required, a pre-screening visit (Visit 0) can be scheduled for signing the informed consent, up to 2 weeks prior to Screening (Visit 1). The pre-screening visit can also occur on the same day as the Screening visit. Participants who meet the eligibility criteria at Screening (Visit 1) will withdraw their regular ICS/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 twice daily (BID). At the end of the Run-in period at Visit 2 (Week 0), participants who meet pre-defined randomization criteria will be randomized in a 1:1 ratio to enter a double-blind 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, two weeks after Randomization, the open label background therapy will be switched from FP/Sal 500/50 mcg BID to FP 500 mcg BID for 2 weeks. Visit 4 will be the beginning of a six week 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 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.

An End of Treatment Phase (ETP) Visit will be performed 4 weeks after the final dose of the blinded study treatment is administered at Week 12. 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. 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/EW Visit for safety assessments.



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 9). 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.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period**										**Follow-up Period[2] (± 3 days)**			**Notes**
			± 2 days			**± 3 days**										
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**	**57**	**71**	**85**	**99**	**113**				
Informed consent (ICF)	X															
Genetic ICF	X															
ICF for sputum	X															
Inclusion and exclusion criteria		X														
Randomisation Criteria			X													
Demography	X															
Full physical exam including height and weight		X														
Medical history (includes substance abuse)		X														Substances [Drugs, Alcohol, tobacco] and family history of premature CV disease]): [including cardiovascular medical history]

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
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**	**57**	**71**	**85**	**99**	**113**				
Laboratory																
Laboratory assessments		X[1, 2]	X[1]	X	X[1]	X[1]	X	X[1]	X	X[1]	X	X[1]			X[1]	Haematology (including eosinophil count) and cardiac markers measured at all clinic visits. 1. Clinical chemistry (including liver chemistry). 2. Routine urinalysis at screening (Visit 1)
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.

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
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**	**57**	**71**	**85**	**99**	**113**				
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
Sputum sample collection			X					X				X				Pre-dose collection and in a sub-set of participants (~50 %) at selected sites; also collected for EW participants
PK, target engagement and immunogenicity assessments			X	X	X	X		X		X		X	X	X	X	See SoA Table 2 for details
Exploratory Biomarkers			X					X				X				Pre dose collection
Efficacy																
Spirometry		X	X		X	X	X	X	X	X	X	X				Test to be performed pre-dose during the Treatment period
Reversibility		X														
FeNO			X	X	X	X	X	X	X	X	X	X				Test to be performed pre-dose
Review loss of asthma control criteria				X	X	X	X	X	X	X	X	X				It will include review of data to determine loss of asthma control. See Section 9.1.5.
Dispense eDiary		X														

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
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**	**57**	**71**	**85**	**99**	**113**				
Collect eDiary												X				
Review eDiary			X	X	X	X	X	X	X	X	X	X				
Safety																
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.
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.
Dispense paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X		
Review paper Medical Problems/Medications Taken worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period**										**Follow-up Period[2] (± 3 days)**			**Notes**
			± 2 days			**± 3 days**										
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**	**57**	**71**	**85**	**99**	**113**				
AE/SAE review	X[1]	X[1]	←==========→										X	X	X	1. At V0 and V1 collect only SAEs considered as related to study participation.
Concomitant medication review	X	X	←==========→										X	X	X	
Questionnaires																
ACQ-5		X	X													After randomization, ACQ5 will be completed by the participants every 7 days.
SGRQ			X			X		X		X		X				
Study Treatment																
Double blind Study Treatment (IP)			X			X		X		X						Patients will remain in the clinic for monitoring for at least 2 hours after the end of infusion.
FP/Sal (500/50) dispensing		X	X													
FP (mcg) dispensing					500	250	100	50								
Dispense albuterol (as needed)		X	X	X	X	X	X	X	X	X	X	X				

SoA Table 2: Timings of PK, target engagement and immunogenicity samples

Procedure	Treatment Period										Follow-up[2] (± 3 days)			Notes
	± 2 days			± 3 days										
Visit	**2[1]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (ETP or EW)**	**12**	**13**	**14**	1. Visit 2 = Day 1 (first dose of IP). 2. FU period to start 4 weeks after ETP or EW visit.
Week	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	
Study Day	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**				
Double blind Study Treatment (IP)	**X**			**X**		**X**		**X**						
PK sample	X[2]	X	X	X[3]		X[3]		X[1]		X	X	X	X	1. Pre dose and post dose. 2. Post dose only. 3. Pre dose only. <u>Pre-dose samples</u> within 2 hours from the planned dosing time. <u>Post-dose samples</u> as soon as possible after end of infusion but must be taken within 4 hours.
Free and total sST2	X[1]	X	X	X[3]		X[3]		X[1]		X	X	X	X	
Immunogenicity sample	X[3]		X	X[3]		X[3]		X[3]		X	X	X	X	

3. INTRODUCTION

3.1. Study Rationale

GSK3772847 is a human immunoglobulin G2 sigma isotype (IgG2σ) antibody that binds Domain 1 of the cell-surface receptor 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.

At the time of writing this protocol, a two-part, single and multiple ascending dose first time in human (FTIH) study has completed dosing (final report is pending). The safety information from this study is included in the investigator brochure (IB [GlaxoSmithKline Document Number 2017N316832_00]). There are no efficacy data available to date.

The present study is the first GSK sponsored study with GSK3772847. It is a Phase IIa / proof of concept study to investigate efficacy, safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of GSK3772847 in participants with moderately severe asthma. The study will use an inhaled steroid titration design in order to evaluate whether GSK3772847 maintains protection of asthma control. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which changes in the level of asthma control were induced by medication withdrawal [Bel, 2014; Wenzel, 2013; Nair, 2009]. This design may not reflect real world fluctuations in asthma control; however, studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on changes in asthma control in a relatively short period of time, before further investigations are conducted in longer term studies.

3.2. 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 [Chung, 2014; Aburuz, 2007; 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 signaling. 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].

In a 3-month good laboratory practice (GLP) toxicology study, GSK3772847 was administered to cynomolgus monkeys as a weekly 15-minute IV infusion (20 or 100 mg/kg) and was found to be well-tolerated at both doses.

Janssen (Study CNTO7160ASH1001) have conducted a Phase I randomized, double-blind, placebo-controlled, intravenous (IV) single ascending dose study in healthy participants and multiple ascending dose study in participants with asthma and participants with atopic dermatitis. The study has completed dosing. The final clinical study report is still pending. There are no efficacy data available to date.

More information about the non-clinical and clinical studies is available in the GSK3772847 IB (GlaxoSmithKline Document Number 2017N316832_00).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks and reasonably expected adverse events of GSK3772847 may be found in the IB (GlaxoSmithKline Document Number 2017N316832_00).

3.3.1. 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 GLP 3 month IV repeat dose toxicity study at doses ≤100 mg/kg/week) or subcutaneous (SC) administration. 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). 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	Exclude participants with existing clinically significant organic heart disease (e.g. Coronary artery disease [CAD], New York Heart Association (NYHA) Class III/IV heart failure) and abnormal, clinically significant findings from 12-lead ECG and 24-hour holter monitoring (Section 6.2 and Section 6.3). CV events will be monitored (including ECG and Holter monitoring) as specified in Section 2. All cardiac-related AEs will be reviewed by an independent safety review committee (iSRC). Protocol-defined stopping criteria are specified in Section 8.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. The abnormalities were considered clinically significant and recorded as treatment emergent 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 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.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Dosing was continued as planned, and the dose escalated to 10 mg/kg.	
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 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+ inate 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.	**Preclinical**: 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 or IV 3 month toxicity 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	Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening are excluded from participation in the study (Section 6.2) Participants who develop an infection will be requested to seek medical advice, and subject to close monitoring. 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 and routinely as part of the post marketing pharmacovigilance process. Exclude patients with ongoing or recurrent infections.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	similar between the group receiving GSK3772847 (9/18 [50%]) and the group receiving placebo (4/6 [66.7%]). The frequency 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	Close monitoring of infection AEs (including 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**: Not observed in studies to date. **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.	If a hypersensitivity or anaphylactic reaction occurs, infusion should be discontinued immediately and appropriate therapy instituted. Agents to treat reactions should be available immediately. Stopping & continuation criteria will be included in protocols. Painkillers can be prescribed for pain at site of injection. Patients developing hypersensitivity, anaphylactic reactions or anaphylactic shock will be withdrawn from the study. All doses in this trial will be administered in the clinic.
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	**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. This data is indicative that healthy monkeys were able to	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
cause the infection the vaccine should protect against. Steroid withdrawal is expected to augment a pro-inflammatory response in the lung of the patients that drives the asthma phenotype. 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.	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).	
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
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.	The incidence and severity of contact dermatitis will be monitored.

3.3.2. Benefit Assessment

Efficacy of GSK3772847 has not yet been demonstrated and there are no existent data from molecules with the same or similar mode of action. Taking part in this study may or may not improve a participant's health, and may or may not directly benefit a participant. This study will provide additional safety and efficacy information on GSK3772847.

Whilst the *in vivo* models of T2 asthma support a role for IL-33 pathway in eosinophilic asthma disease, it is clear that IL-33 plays a significant role in other types of immune responses and cell types including amplification of Th1 and Th17 responses in combination with other cytokines [Arshad, 2016; Smithgall, 2008]. Agents targeting this mechanism could be expected to have effects on both type 2 (T2)-driven and non-T2-driven disease. Currently available marketed biological treatments for the treatment of severe asthma are indicated for patients with T2-driven disease, refractory eosinophilic asthma, or patients with IgE-mediated asthma. There is currently no marketed treatment for non T2-driven severe asthma.

All study participants will receive open label salbutamol/albuterol to use as needed for asthma symptom relief from Screening to the end of the Treatment Period. Medical assessments are planned during the study to evaluate participants' health status. The assessments include physical examination, vital signs, electrocardiogram (ECG), Holter monitoring, and clinical laboratory evaluation including liver chemistry and blood chemistry panel at a number of clinic visits.

Participants will be monitored for changes in asthma control through daily use of an electronic Diary (eDiary) and twice-daily PEF measurements. The participants will use the eDiary to record asthma symptoms, rescue medication use, and nocturnal awakening due to asthma symptoms requiring rescue medication use. Alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions for the participant to contact the investigator and send the data as soon as possible. Data will also be transmitted automatically within 24 hours to the centralised server. Email notifications will be sent to the investigator as soon as the data is transmitted to the centralized server allowing the investigator to contact the participants in order to discuss the participants' symptoms and evaluate whether they experienced loss of asthma control. Participants' health status will also be evaluated by ACQ-5 and SGRQ during the study. With this built-in safety monitoring and the frequent visit schedule, a participant will be withdrawn from study treatment due to experiencing symptomatic or spirometric changes that meet one of the pre-defined loss of asthma control criteria and will be started on alternative standard of care therapy. The aim will be to retain participants in the study post withdrawal of study medication to follow-up for safety.

Potential participants must be clinically stable on their asthma regimen for at least 4 months prior to study entry. The Global Initiative for Asthma (GINA), 2016 Guidelines advocate attempting to discontinue LABA if possible and step-down therapy once adequate asthma control is met. During ICS titration, the lowest effective dose is determined at the dose, below which asthma control deteriorates. According to GINA 2016 Guidelines, during this process the patients' asthma status is closely monitored and a clear plan is provided to the patients with instructions on how asthma symptoms should

be documented by the patients and the action plan that should be followed if previous therapy needs to be resumed. Similarly, in this study, participants will have their asthma status documented at study entry, their symptoms and PEF will be monitored twice daily, scheduled visits will be arranged and they will have clear instructions as to what actions to take with any increase in asthma symptoms. Furthermore, a potential benefit to the subjects would be the ascertainment that asthma control might be maintained on a lower ICS dose than that which the subject received prior to study entry, with the potential for fewer or less severe ICS-related adverse events.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize the risk to the participants participating in the study, the balance of anticipated benefits and apparent risks associated with GSK3772847 continues to be acceptable. There is an opportunity to determine if there is a new drug that can be developed for patients with severe asthma who may benefit from the broad spectrum effects hypothesized for GSK3772847.

4. 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 moderately 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: • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥0.5 point 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 • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation).
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with moderately severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • 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 who have a significant asthma exacerbation (requiring OCS and/or hospitalisation).

Objectives	Endpoints
	• 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 administered intravenously every 4 weeks for 12 weeks (Week 0-12, 4 doses in total) in participants with moderately severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28. • Change between post-dose and pre-dose in vital signs at weeks 0, 4, 8 and 12. • Change from baseline in 12-lead electrocardiogram (ECG) measurements at weeks 4, 8, 12 and 16. • Change between post-dose and pre-dose in

Objectives	Endpoints
	12-lead ECG measurements at weeks 0, 4, 8 and 12. • Change from baseline in 24 hours Holter measurements at weeks 4 and 12. • Change from baseline in clinical chemistry at weeks 2, 4, 8, 12, 16 and 28. • Change from baseline in hematology and cardiac markers at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28. • Incidence of and titres of anti- GSK3772847 antibodies at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with moderately severe asthma.	• Serum concentrations of GSK3772847 at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with moderately severe asthma.	• Free and total soluble ST2 levels in serum at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
Exploratory	
• To compare the effect of GSK3772847 with placebo on biomarkers in serum and sputum.	• Changes from baseline in induced sputum biomarkers (subset) at weeks 8 and 16. • Changes from baseline in exploratory serum markers at weeks 8 and 16.

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. In order to achieve the stratification balance, as a result of participants' eosinophil count it may be necessary to withdraw participants from the study during the Run-in period.**

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 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

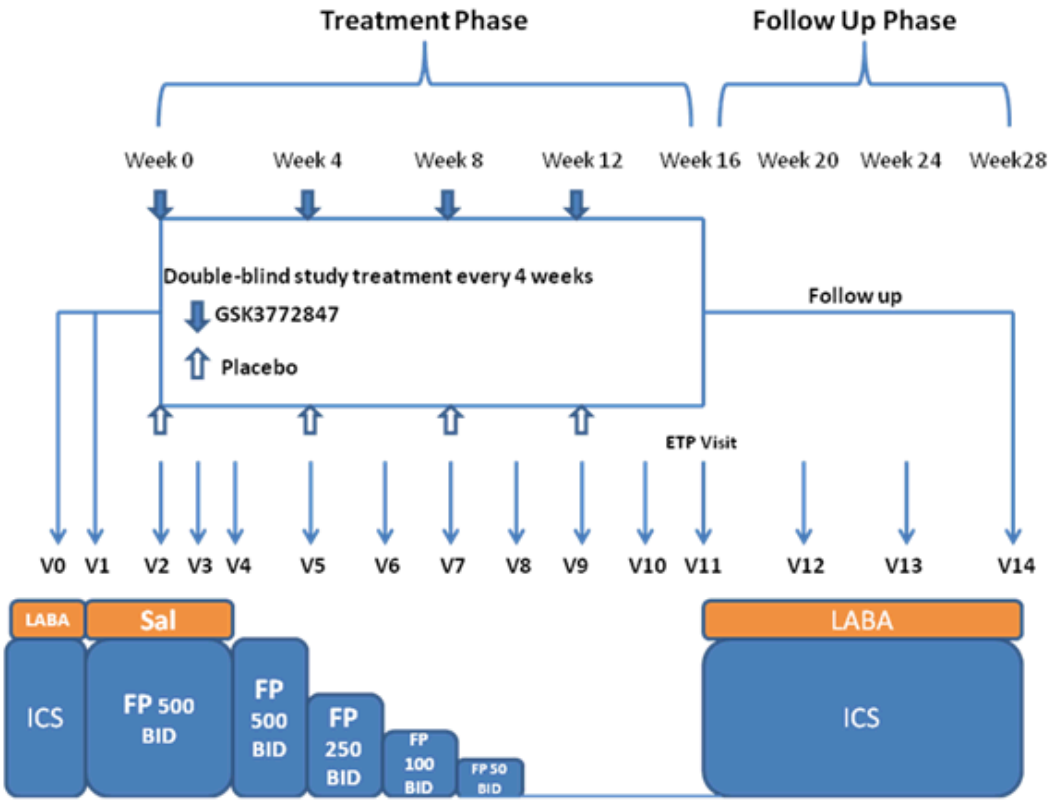
At Visit 4 (i.e. two weeks after Randomization) the open label background therapy will be switched from FP/Salmeterol 500/50 mcg BID to FP 500 mcg BID for 2 weeks. This will mark the beginning of the FP titration period. Every two weeks for the next six weeks the dose of FP will be reduced by approximately 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.

Participants will be monitored for loss of asthma control through daily use of an eDiary and twice-daily PEF measurements. The participants will use the eDiary to record asthma symptoms, rescue medication use, and nocturnal awakenings due to asthma symptoms requiring rescue medication use. This information will be transmitted daily to a centralized server and available to the investigators. Alerts for pre-defined changes in PEF or asthma symptoms, indicative of worsening asthma, will be programmed into the eDiary with prompts to the participants to contact the investigator if any of the alert criteria are met (Section 9.1.2.3). Additionally, email notifications will be sent to the investigator, if any of the alert criteria are met, as soon as the data is transmitted to the centralized server. The investigator will make every effort to contact the participants in order to discuss the participants' symptoms and evaluate whether they experienced loss of asthma control.

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.



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 9).

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 moderately severe 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**.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including, screening, run-in, the randomized treatment phase, and safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, parallel-group and placebo-controlled design. This is a well-established design to evaluate the efficacy, safety, PK and PD profiles of an investigational drug. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which changes in the level of asthma control were induced by medication withdrawal [Bel, 2014; Wenzel, 2013; Nair, 2009]. This design may not reflect real world fluctuations in asthma control, however studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on changes in asthma control in a relatively short period of time, before further investigations are conducted in longer term studies.

In this study, the target population would be participants with moderately severe asthma and with an ACQ5 score ≥1 and <4 whose symptoms must have been managed on a stable, high dose ICS/LABA for at least 4 months prior to Screening. The use of loss of asthma control as a composite study endpoint and a criterion for ICS titration allows for the overall clinical evaluation of the participant's asthma status taking into account both lung function and symptom control. Participants will also be monitored through the use of the eDiary. Pre-specified asthma symptom scores and participant-measured PEF that is inputted into the eDiary will be used as prompts for contacts between subjects and investigators (Section 9.1.2.3).

The FP titration period will occur during the Treatment Period of the study. The FP dose reduction will be assessed and managed at scheduled clinic visits. During the FP titration period the subjects' FP dose will be reduced as described in Section 5.1 and the SoA, unless the subject meets protocol defined criteria for loss of asthma control indicating that it is not acceptable for the participant to further reduce ICS. Prior to each FP dose reduction an assessment of the participants' asthma control should be completed and the decision to reduce the dose of FP will be based on: 1) the presence and severity of exacerbations, 2) changes in FEV1, 3) changes in the most recent ACQ-5 score, or 4) the ability to titrate ICS as per the pre-defined schedule, according to the investigator's clinical judgment. If loss of asthma control is confirmed during the FP titration period, the participant will discontinue IP immediately and should resume regular treatment for their asthma, as determined by the investigator. A similar methodology was recently reported [Wenzel, 2013] and successfully allowed titration of ICS.

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.

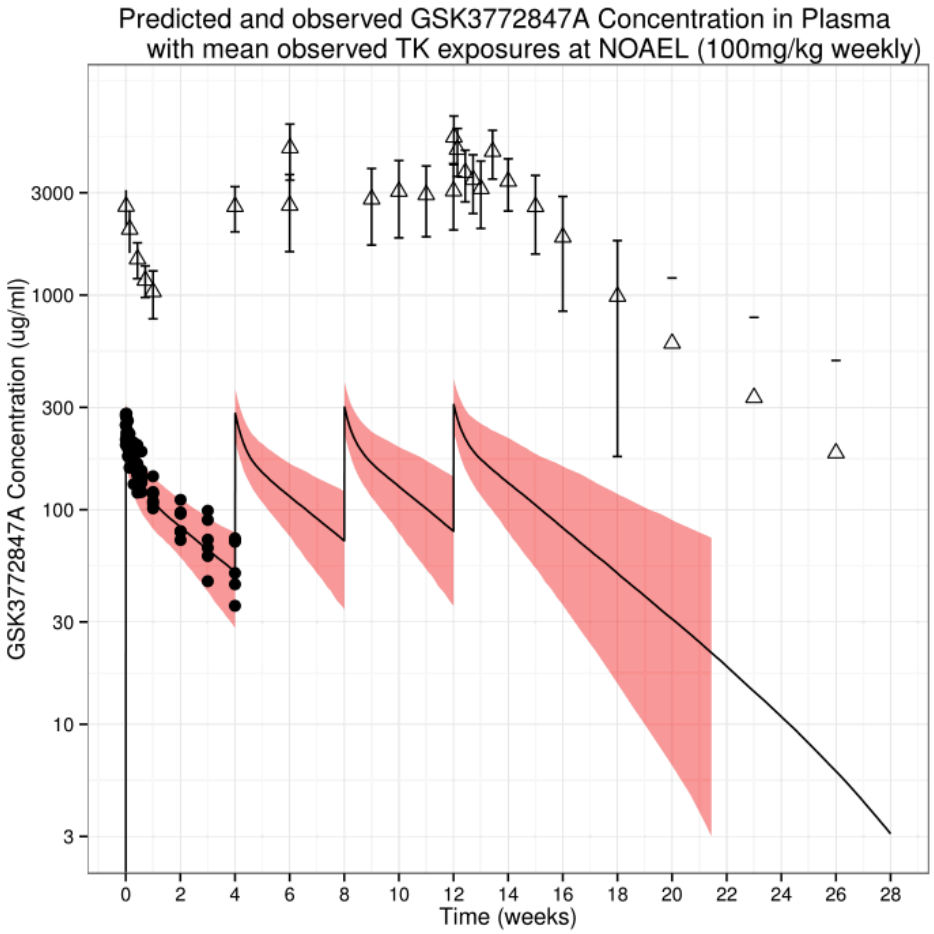
An inhaled short acting beta$_2$–receptor agonist, salbutamol/albuterol will be provided to all participants to use as needed to relieve asthma symptoms from Screening (Visit 1) to end of the Treatment Period. Both safety and efficacy parameters will be assessed regularly in the clinic to minimise any 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. Should a participant experience loss of asthma control, the same level of pre-study asthma control can be achieved following treatment/resolution of the acute event [Matz, 2001; McIvor, 1998]. Any event that defines loss of asthma control in this study should not result in an irreversible pathophysiological process that precludes the subject from achieving the level of asthma control that existed prior to study entry. The proposed study design allows the objectives of the trial to be addressed, but the same objectives will provide appropriate safety assessments to minimize the likelihood of participants experiencing an actual exacerbation.

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

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.

Table 1 Predicted clinical exposures and safety margins for study 207597 following dosing of 10 mg/kg at weeks 0, 4, 8 and 12.

Day 1 mean C_{max} (µg/mL)	Exposure margin[a]	Week 12 mean C_{max} (µg/mL)	Exposure margin[a]	0-28 weeks AUC (µg.day/mL)	Exposure margin[b]
245.3[c]	10.5	313.5[d]	17.4	16830.2[d]	18.2

a. Margins calculated against mean maximum serum concentration (C_{max}) on day 1 and day 84 (last dose) in study T-2013-007 (2592.55 and 5444.07 µg/mL respectively).
b. Margins calculated based on AUC (0-92 (13 weeks)) estimated using compartmental modelling of mean exposures in study T-2013-007.
c. Mean observed exposures in study CNTO7160ASH1001.
d. Predicted exposures using preliminary MM model

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. **Age:** At least 18 years of age at the time of signing the informed consent.
2. **Gender**: Males and females.

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

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

   i. OR

   - A WOCBP who agrees to follow one of the options listed in Appendix 5 from **4 weeks** prior to the first dose of study medication and until at least 16 weeks after the last dose of study medication and completion of the follow-up visit.
3. **Informed consent**: Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
4. **Asthma diagnosis and severity**: A participant with a documented diagnosis of moderate-severe asthma based on Global Initiative for Asthma (GINA), 2016 Guidelines, whose asthma has been managed with regular treatment of high dose ICS defined as fluticasone propionate 500 mcg twice daily (i.e. 1000 mcg total daily dose) or equivalent, and long-acting beta-2-agonist (LABA) for at least 4 months. Additional therapy with a leukotriene receptor antagonist (LTRA) is permissible.
5. **Reversibility:** Airway reversibility of at least 12 % and 200 mL in FEV1 at Screening (Visit 1), or documented reversibility prior to Screening (Visit 1), or documented history of bronchial hyperreactivity (e.g. fall in FEV1 from baseline of

≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge) from a bronchoprovocation study (e.g. methacholine challenge) prior to Screening (Visit 1).

Note: If the participant does not meet the above reversibility criteria at Screening (Visit 1) then the reversibility assessment may be repeated once within 7 days of Visit 1. Should the participant successfully demonstrate airway reversibility at the second attempt then, provided that all other eligibility criteria assessed at Screening (Visit 1) are met, the participant may enter the 2-week run-in period.

6. **Asthma Control Questionnaire (ACQ):** ACQ-5 score ≥1 and <4 at Screening (Visit 1).
7. **Exacerbation history**: Had at least one asthma exacerbation within 12 months prior to Screening that required treatment with systemic corticosteroid and/or hospitalization.
8. **Short-Acting Beta2-Agonists**: All subjects must be able to replace their current SABA treatment with albuterol/salbutamol aerosol inhaler at Visit 1 for use as needed, per product label, for the duration of the study.

6.2. Exclusion Criteria

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

1. **Smoking history**: Current smokers or former smokers with a smoking history ≥10 pack years.
2. **Concurrent respiratory diseases**: Presence of a known pre-existing, clinically important respiratory conditions (e.g. pneumonia, pneumothorax, atelectasis-segmental or larger, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other respiratory abnormalities) other than asthma.
3. **Severe airflow obstruction**: A pre-bronchodilator FEV1 <50 % predicted of normal value at Screening (Visit 1). Predicted values will be based upon Global Lung Function Initiative (GLI) [Quanjer, 2012] equations for spirometry reference values.

   Note: If the spirometry is deemed technically inadequate by the central reader, the spirometry assessment may be repeated once within 7 days of Screening (Visit 1).
4. **Malignancy:** Participants with a diagnosis of malignancy or in the process of investigation for a malignancy. Participants with carcinoma that have not been in complete remission for at least 5 years. Participants who have had carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the patient has been considered cured by treatment.
5. **Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result** at Screening (Visit 1) or within 3 months prior to first dose of study treatment.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C Ribonucleic acid (RNA) test is obtained.

6. **12-lead ECG assessment at Screening (Visit 1):** Site investigators will be provided with ECG over-read conducted by a centralized independent cardiologist, to assist in evaluation of subject eligibility. For this study, an abnormal and clinically significant ECG that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the findings in Table 2:

Table 2 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)

7. **Weight**: <50 kg and >150 kg
8. **Regular use of systemic corticosteroids** for conditions including asthma within 3 months prior to Screening (Visit 1).
9. **Participants with high parasympathetic tone** (e.g. trained athletes with baseline bradycardia) or chronic conditions associated with parasympathetic surges (e.g. migraines)
10. **Eosinophilic diseases**: Other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes. Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening (Visit 1).
11. **Cardiovascular disease**: Clinically significant organic heart disease (e.g. CAD, NYHA Class III/IV heart failure).
12. **Ongoing infections** (i.e. not resolved within 7 days prior to Screening [Visit 1]) or recurrent infections (i.e. requiring treatment for an identical diagnosis within 3 months) requiring systemic antibiotics. Known, pre-existing parasitic infestations within 6 months prior to Screening.
13. **Other Concurrent Diseases/Abnormalities:** A subject must not have any clinically significant, uncontrolled condition, or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study.

    The list of additional excluded conditions/diseases includes, but is not limited to, the following:

Addison's disease	hypertension[1] (uncontrolled)
aortic aneurysm (clinically significant)	peptic ulcer (recent or poorly controlled)
Cushing's disease	renal disease
diabetes mellitus (uncontrolled)	stroke within 3 months of Visit 1
hematological disease	thyroid disorder (uncontrolled)
hepatic disease	tuberculosis (current or untreated[2])

1. Two or more measurements with systolic pressure >160mmHg or diastolic pressure >100mmHg
2. Subjects with a history of tuberculosis infection who have completed an appropriate course of antituberculosis treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease.

14. **Immunodeficiency**: A known immunodeficiency such as human immunodeficiency virus infection.
15. **Hypersensitivity**: Participants with allergy or intolerance to a monoclonal antibody or biologic or to any components of the formulation used in this study.

16. **Alcohol and Substance abuse**: Participants with a history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Screening (Visit 1).
17. **Participants at risk of non-compliance, or unable to comply with the study procedures**. Participants who are unable to follow study instructions such as visit schedule, dosing directions, study eDiary completion, or use of a standard metered dose inhaler. Participants who have known evidence of lack of adherence to controller medication and/or ability to follow physician's recommendations. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
18. **Participants who have previously participated in a study of GSK3772847**.
19. **Excluded Medications**: Use of the medications listed in Table 3 is not permitted within the defined time intervals prior to Screening (Visit 1) and throughout the study. Potential participants should not be washed out of their medication solely for the purpose on enrolling in the trial.

Table 3 Prohibited Medications

Medication	Time interval prior to Visit 1
Investigational drug	One month or 5 half-lives whichever is longer
Live or attenuated vaccines[a]	2 weeks (i.e. 4 weeks prior to IP administration)
Biologics, for example Mepolizumab and Omalizumab	130 days or 5 half-lives whichever is longer
Experimental anti-inflammatory drugs (non-biologics)	3 months
Corticosteroids intramuscular, long acting depot Regular systemic corticosteroid - oral, parenteral, depot	3 months
Methotrexate, troleandomycin, oral gold, cyclosporin, azathioprine,	3 months
Theophylline	3 months
Chemotherapy and radiotherapy	12 months
Inhaled anti-cholinergics e.g. tiotropium	1 week

a. Vaccines containing killed bacteria or inactivated virus will be permitted

20. **Affiliation with Investigator Site**: A participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
21. **Inability to read**: In the opinion of the investigator, any participant who is unable to read and/or would not be able to complete a diary card/questionnaire.
22. **Questionable validity of consent**: Participants with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

6.3. Randomization Inclusion Criteria

At the end of the Run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

1. **Asthma Control Questionnaire (ACQ):** ACQ-5 score ≥1 and <4 at Visit 2.

2. **eDiary Compliance:** Compliance with completion of the eDiary reporting defined as completion of all questions/assessments on ≥4 of the last 7 days during the run-in period.

6.4. Randomization Exclusion Criteria

Participants meeting any of the following criteria **must not** be randomized to double-blind study medication at Visit 2:

1. **Clinically significant and abnormal laboratory finding at Screening (Visit 1):** Evidence of clinically significant abnormal laboratory tests during screening which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality.

2. **12-lead ECG over-read**: Evidence of clinically significant abnormal ECG findings (Table 2) at Screening (Visit 1).

3. **24-Hour Holter Monitoring**: An abnormal and significant finding from 24-hour Holter monitoring at Screening (Visit 1). Investigators will be provided with Holter reviews conducted by an independent cardiologist to assist in evaluation of subject eligibility. Specific findings that preclude subject eligibility are listed in Table 2. The study investigator will determine the medical significance of any Holter abnormalities not listed in Table 2.

4. **Liver function** at Screening (Visit 1)

    - ALT >2x upper limit of normal (ULN) and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35 %).
    - Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones.

5. **Asthma exacerbation:** Participants with ongoing asthma exacerbation at the time of Visit 2.

    Note: At the Investigator's discretion, participants with an ongoing asthma exacerbation at Visit 2 may be re-screened ≥2 weeks after Visit 2. In such cases, the full screening process (i.e. all Visit 0, 1 and Visit 2 assessments) must be repeated.

6. **Severe airflow obstruction:** a pre-bronchodilator FEV1 <50 % predicted of normal value at Visit 2. Predicted values will be based upon GLI [Quanjer, 2012] equations for spirometry reference values.

7. **Positive pregnancy test** at Visit 0, Screening (Visit 1) or Visit 2.

8. **Ongoing or recurrent infections** requiring systemic antibiotics.

6.5. Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.6. Pre-Screening/Screening/Run-in/Randomization Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the eCRF for participants who are pre-screen failures:

- Demographic information including race, age and gender
- Participant number
- Serious Adverse Event information only for any SAE considered as related to study participation

For the purposes of this study, pre-screening failures, screening failures, run-in failures and randomization failures will be defined as follows:

- **Pre-screening failures:** those participants that sign the informed consent document but do not have a Screening (Visit 1) procedure.
- **Screening failures:** those participants that complete at least one Screening (Visit 1) procedure but do not enter the run-in period.

  A participant who completes Visit 1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.
- **Run-in failures:** those participants that enter the run-in period but do not have any Visit 2 procedures.
- **Randomization failures:** those participants that complete at least one Visit 2 procedure but do not enter the double-blind study treatment period.

Any participant who completes the run-in period and then meets the randomization criteria and receives the double-blind study treatment at Visit 2 is considered to have entered the treatment period.

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).

Rescreening is only allowed in exceptional circumstances of technical errors and with prior approval from the GSK study team. Participants who are excluded due to an ongoing asthma exacerbation at Visit 2 (Randomization exclusion criterion 5) may be rescreened ≥2 weeks after Visit 2, at the investigators discretion. Rescreened participants will be assigned a new participant number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK3772847	Placebo	Fluticasone Propionate/Salmeterol	Fluticasone Propionate
Dosage formulation:	50mg/mL GSK377284, 15 mM Sodium Phosphate, 8.5% [w/v] Sucrose, and 0.04% [w/v] Polysorbate 20, pH 7.3.		DISKUS– 60 doses per device	DISKUS– 60 doses per device
Unit dose strength(s)/Dosage level(s):	10 mg/kg	Commercially sourced sterile normal saline	500/50 mcg per actuation	500, 250, 100 and 50 mcg per actuation
Route of Administration	IV infusion	IV infusion	Inhaled	Inhaled
Dosing instructions:	GSK3772847 for injection will require further reconstitution and dilution at the study site prior to administration: dilution between 10 and 30 mg/mL may be accomplished by using commercially sourced sterile normal saline		Twice daily; once in the morning and once in the evening	Twice daily; once in the morning and once in the evening

Study Treatment Name:	GSK3772847	Placebo	Fluticasone Propionate/Salmeterol	Fluticasone Propionate
Packaging and Labeling	Study Treatment will be provided as 100mg/vial, white to yellow, uniform lyophilized cake in a 5ml clear glass vial with 20mm closure sealed by red metal and yellow overseal. Each container will be labeled as required per country requirement.	Commercially sourced sterile normal saline will be sourced by the site	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip) Each container will be labeled as required per country requirement.	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip) Each container will be labeled as required per country requirement.

7.1.1. Description of Albuterol/Salbutamol

Albuterol/salbutamol via metered-dose inhaler (MDI) will be issued for reversibility testing at Screening (Visit 1). An albuterol/salbutamol MDI for as needed (prn) use throughout the study will be dispensed starting at Visit 1; at the Investigator's discretion, more than one MDI may be dispensed at any one time. Albuterol/salbutamol will be sourced from local commercial stock. The contents of the label will be in accordance with all applicable regulatory requirements.

7.1.2. DISKUS Return

DISKUS inhalers containing FP/Salmeterol and FP will be dispensed to a participant during their visit to the study clinic (as applicable). The participant must return all dispensed inhalers at the subsequent clinic visit. The schedule for dispensing and collecting FP/Sal and FP is provided in the SoA (Section 2).

All used and unused FP/Sal, FP will be returned to GSK at the end of the study to be available for disposal. In some instances, for sites outside the United States (US), study supplies will be disposed of locally either by the site, the country medical department or

third-party vendor. Detailed instructions for the return of the study drug can be found in the Study Reference Manual (SRM).

If any DISKUS inhaler fails to function properly, the participant should return to the clinic as soon as possible to obtain a new inhaler. The site will use the Interactive Web Response System (IWRS) (RAMOS NG) to obtain a new treatment pack number for the participant and dispense a new study treatment kit from the site's study treatment supply as instructed by the IWRS. Details of the failure will be documented in the eCRF. Additional information on how to handle medical device incidents can be found in the SRM.

7.2. Dose Modification

There are no dose modifications planned for this protocol.

7.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the randomization schedule. The randomization code will be generated by GSK using a validated computerized system. Participants will be randomized using an interactive web response system (IWRS) RAMOS NG. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 2-week Run-in period and subject to satisfying all eligibility criteria, participants will be randomized 1:1 to one of the following double-blind treatments for the duration of the Treatment Period:

- GSK3772847 (10 mg/kg) administered intravenously
- Placebo administered intravenously

The duration of the Treatment Period for each participant is 16 weeks. Each Investigator will be provided with sufficient supplies to conduct the trial. Additional treatment kits will be supplied as needed to the sites. Details of how to use the IWRS system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG manual and SRM.

7.4. Blinding

This will be a double-blind study and the following will 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.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

GSK3772847 a white to yellow, uniform lyophilized cake in a 5ml clear glass vial with 20mm closure sealed by red metal and yellow overseal. Each vial contains 100 mg of a lyophilised GSK3772847. When reconstituted with 2.0 mL of WFI, the final concentration of GSK3772847 is 50 mg/mL. Excipients include: sucrose, sodium phosphate buffer, and polysorbate 20 at a pH of 7.3. Vials contain no preservatives and thus are for single use. Vials must be stored 2º – 8°C, protected from light. Protection from light during preparation and administration is not required. Full details on specific 2º to 8°C storage temperature conditions, preparation and administration including requirements for filtration are provided separately.

Commercially available sterile normal saline will be used for dilution of study agent and will also serve as placebo for this study. Use of study agent sterile normal saline as placebo for injection provides an adequate comparator to broadly assess safety in early clinical development.

GSK3772847 must be prepared by an unblinded pharmacist or other appropriately licensed and authorized personnel and administered according to each participant's body weight at Screening (Visit 1). A different site staff member, who will be blinded to the treatment assignment, will administer the study agent. Aseptic procedures must be used during preparation and administration of the study agent. Diluted GSK3772847 at

volumes of 50 mL are to be administered by IV infusion over a period of at least 30 minutes using an in-line 0.22 micron filter. At least 30 mL of commercially available sterile normal saline will be used to flush diluted drug from the administration set to ensure full study agent administration.

Unblinded site staff will be responsible for receipt, storage, reconstitution, 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.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual or unblinded site staff reference manual.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.6. Treatment Compliance

- FP/Sal and FP during the run-in and treatment periods will be self-administered at home; compliance will be assessed via dose counter during the site visits and documented in the source documents and eCRF. A record of the number of doses on the DISKUS inhaler will be recorded in the eCRF. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.
- The double blind IP will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the eCRF.

7.7. Concomitant Therapy

All asthma medications used within approximately 12 weeks prior to screening and during the study (including the post-treatment period) should be recorded in the eCRF.

All non-asthma medications taken during the study (after randomization including post-treatment) and any changes to concomitant medications will be recorded in the eCRF. *Note: Study provided FP/Sal, FP, and albuterol/salbutamol should not be recorded in the ConMeds page of the eCRF.*

The minimum requirement is that the drug name, reason for use, dose (including unit e.g. mcg) and frequency, route and the dates of administration are to be recorded.

7.7.1. Permitted Non-asthma Medications

The following medications are permitted during the study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal] but they are disallowed 48 hours prior to ECG measurements, cromolyn, nedocromil, nasal decongestants)
- Antibiotics for short term treatment of acute infections. Long term treatment with topical or ophthalmic antibiotics are permitted.
- Decongestants: Participants may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.
- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and participants remain in the maintenance phase for the duration of the study.
- Topical and ophthalmic corticosteroids.

7.7.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed below is not permitted during the study:

- Inhaled anti-cholinergics (e.g.tiotropium).

- ICS/LABA other than the study-provided FP/Sal.
- Inhaled Corticosteroids other than the study-provided FP.
- LABA other than the salmeterol component in the study-provided FP/Sal.
- Biologics, e.g. Mepolizumab and Omalizumab.
- Potent CYP3A4 inhibitors, (e.g., ritonavir, ketoconazole, etc.)
- Anticonvulsants (barbiturates, hydantoins, and carbamazepine).
- Polycyclic antidepressants.
- Beta-adrenergic blocking agents.
- Phenothiazines.
- Monoamine oxidase (MAO) inhibitors.
- Live or attenuated vaccines (and up to 6 months after the last dose of blinded study treatment).
- Experimental anti-inflammatory drugs (non-biologics).
- Corticosteroids intramuscular, long acting depot, regular systemic (oral, parenteral, depot) corticosteroid.
- Methotrexate, troleandomycin, oral gold, cyclosporin, azathioprine.
- Theophylline.
- Chemotherapy and radiotherapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study or withdrawal of IP because other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

Participants who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up until the completion of the Safety Follow-up 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.

If this is not possible, the Investigator must encourage the participant to participate in as much of the study as they are willing (or able) to.

A participant may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy [including loss of asthma control], protocol deviation, Investigator discretion, consent withdrawn etc.) must be captured in the eCRF.

A participant must be withdrawn from study treatment if any of the following stopping criteria are met:

1. Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria.
2. QTc: Meets any of the protocol-defined stopping criteria.
3. Pregnancy: Positive pregnancy test.
4. Participant meets at least one of the following criteria for 'loss of asthma control':
   - ACQ-5 score increase from baseline (measured at Visit 2) ≥0.5 point.
   - Pre-bronchodilator FEV1 decrease from baseline (measured at Visit 2) >7.5 %.
   - Inability to continue inhaled corticosteroid titration which is assessed and determined by the investigator at any time point following randomization, including on scheduled clinic visits.
   - A clinically significant asthma exacerbation (requiring OCS and/or hospitalization).
5. Study treatment unblinded.

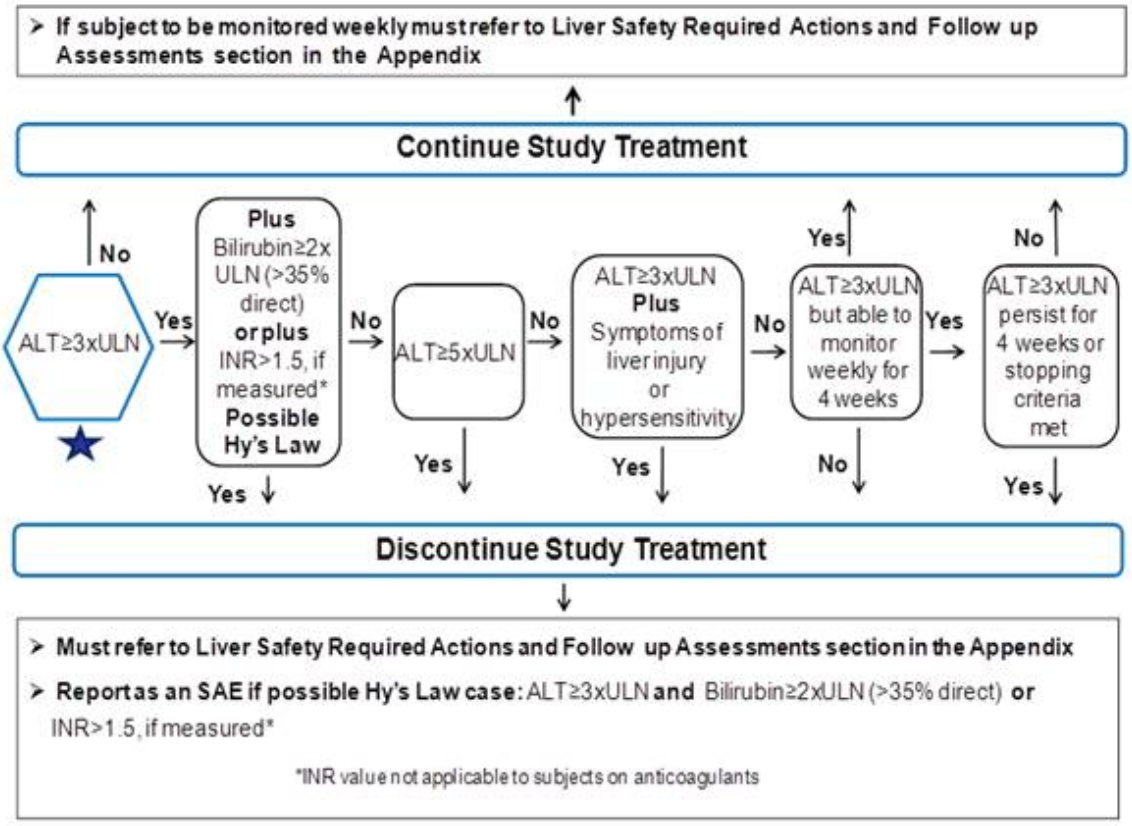
   Note: In the event of unblinding the Medical monitor/GSK team should be contacted to determine whether subject withdrawal is required.
6. Abnormal Holter of Mobitz II AVB, complete AVB, sustained or non-sustained ventricular tachycardia (VT), paroxysmal supraventricular tachycardia (PSVT), new onset atrial fibrillation/flutter will be a withdrawal/stopping criterion. These findings on ECG or findings of myocardial ischemia will also result in withdrawal/stopping.
7. Hypersensitivity or anaphylactic reaction

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



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

8.1.2. QTc Stopping Criteria

- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

- Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
- Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec.

See the SoA for data to be collected at the time of early withdrawal (EW visit) and follow-up and for any further evaluations that need to be completed.

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria or any of the individual discontinuation criteria listed in Section 8.1 of the protocol are met is not allowed. Additionally, if hypersensitivity or anaphylactic reaction occurs, infusion should be discontinued and study restart is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.

  Note: In order to achieve the stratification balance, as a result of participants' eosinophil count it may be necessary to withdraw participants from the study during the Run-in period.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of early withdrawal (EW visit) and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

No study related procedures may be performed until the informed consent form has been signed by the participant. Selection and modification of the participant's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each participant's needs. A participant's treatment must not be changed merely for the purpose of enabling the participant's participation in the study.

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in SoA.

9.1.1. Questionnaires

9.1.1.1. Asthma Control Questionnaire ACQ-5

The ACQ-5 measures attributes of asthma control [Juniper, 1999], measured with questions designed to be self-completed by the participant. Participants will complete the ACQ-5 with the use of an e-Diary device on a weekly basis. The ACQ-5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall 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 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 and transmit the data to the centralised server as soon as possible 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 daytime 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.

If any of the alert criteria are met, email notifications will be sent to the investigator as soon as the data is transmitted to the centralized server. The investigator will make every effort to contact the participants in order to discuss the participants' symptoms and evaluate whether they experienced loss of asthma control.

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 instructions on performing the spirometry manoeuvres are documented in the SRM and the third-party vendor manual.

9.1.3.1. Spirometry

Spirometry will be performed to assess FEV1 and FVC. At least 3 spirometry manoeuvres (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed. For spirometry data collected at Screening (Visits 1), the best spirometry effort will be selected from a measurement that meets American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines and has a minimum of 2 efforts which are considered valid and repeatable, in accordance with the ATS/ERS standards [Miller, 2005]. Measurements with 3 valid but non-repeatable efforts will not be accepted. For spirometry data collected during the Treatment Period (Visits 2 – 11, including EW visit), the best spirometry effort will be selected from a measurement that meets ATS/ERS guidelines and has a minimum of 2 efforts which are considered valid (not necessarily repeatable). As always, sites should continue to strive to collect at least 3 valid (with no more than 8) efforts, as per ATS/ERS guidelines. At each visit, spirometry assessments must be performed at the same time of day (± 2 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) prior to the clinic visit, if possible.

9.1.3.2. Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ ERS Task force: Standardization of Lung Function Testing [Miller, 2005]. A baseline spirometry assessment should be performed after a washout period of at least 6 hours for short-acting β_2- agonists and 1 dosing interval for long-acting β_2-agonists (or fixed dose combinations of LABA and ICS).

To perform the reversibility assessment, 4 puffs of the provided salbutamol/albuterol is administered following completion of the baseline assessment. A spacer device may be used for testing, if required. A second spirometry assessment is performed within 10 to 15 minutes after administration of the salbutamol/albuterol.

Reversibility assessment at Screening (Visit 1) is not required if there is documented reversibility prior to Screening (Visit 1), or documented history of bronchial hyperreactivity from a bronchoprovocation study (e.g. methacholine challenge) prior to Screening (Visit 1).

9.1.4. Fractional Exhaled Nitric Oxide (FeNO)

FeNO will be measured using a handheld electronic device. Measurements will be obtained in accordance with the ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide [Miller, 2005]. All sites will use standardized equipment provided by a central vendor. For each observation, at least 2 measurements will be obtained to establish reproducibility (up to 8 measurements can be performed). FeNO measurements will be interpreted in accordance with the Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications [Dweik, 2011]. FeNO observations must be completed before FEV1 assessments. Participants should not use their rescue medication for at least 6 hours before each FeNO assessment, unless essential for clinical need. Participants should also withhold LABAs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) before each FeNO assessment.

9.1.5. Review of Loss of Asthma Control

Loss of asthma control is defined as at least one of the following:

- ACQ-5 score increase from baseline (measured at the end of Run-in) ≥0.5 point) or
- Pre-bronchodilator 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
- A clinically significant asthma exacerbation (requiring OCS and/or hospitalisation.

At each clinic visit, the Investigator will utilize clinical discretion and available objective evidence (including but not limited to eDiary data, spirometry data, the most recent ACQ5 scores, history of exacerbations, conmeds, AEs) to determine if the patient is experiencing loss of asthma control. The paper Medical Problems/Medications Taken worksheet must also be reviewed by the Investigator (or appropriately trained designee) at each visit to the study site to assist the Investigator in the identification of loss of asthma control. It is expected that the Investigator will indicate which criterion (criteria) the subject met that constituted loss of asthma control.

9.2. Adverse Events

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

Asthma exacerbations or worsening of asthma should not be recorded as an AE, unless they meet the definition of an SAE. For the purposes of this study, asthma exacerbations

will be collected and recorded on the exacerbations log in the eCRF. The treatment details must also be recorded in the eCRF. The time period for collection of asthma exacerbations will begin from screening and will end after the follow-up period has been completed.

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

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

- All SAEs will be collected from the Visit 2 until the last follow-up visit at the time points specified in the SoA (Section 2). At Visits 0 and 1 SAE information will be collected only for any SAEs considered as related to study participation.
- All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting 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.
- 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.
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 and before other clinical tests such as blood draws and pulmonary function tests. 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. Participants should be reminded to avoid caffeine or caffeinated drinks for at least 8 hours before each 12-lead ECG assessment. Also, decongestants are disallowed for at least 24 hours and antihistamines for at least 48 hours before each 12-lead ECG assessment.

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.

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

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 eligible for randomisation at Visit 2 will be entered into the Sputum sub-study. In a subset of approximately 50% of eligible participants, sputum samples will be collected as specified in the SoA. The participants in the Sputum Sub-Study will be randomised equally in the two treatment groups.

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.

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 (mITT)	All randomized subjects who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually

Population	Description
	received.
PK	All randomized subjects who received at least one dose of study medication, and for whom at least one pharmacokinetic sample was obtained, analyzed and was measurable.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

All efficacy analyses will be performed on the mITT Population.

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint proportion of subjects with loss of asthma control will be analyzed using both Bayesian and Frequentist methods. A subject is deemed to have met the endpoint of loss of asthma control if they meet the criteria for any of the components of the definition of loss of asthma control. The posterior probabilities 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) will be calculated analytically assuming a non-informative prior. This will be supported by an estimate of the ratio with a 95% credible interval. Results will also be presented for the two eosinophils strata separately. In addition, the proportion of participants with loss of asthma control will be analyzed using logistic regression allowing for baseline eosinophils strata. The odds ratio, 95% CI and p-value for the comparison of GSK3772847 with placebo will be presented. Results will also be presented for the two eosinophils strata separately by fitting a separate model with an additional term for eosinophil strata by treatment interaction. The effect of eosinophils as a continuous covariate will also be examined in a separate-logistic regression model. Missing data will be handled using the following methods: 1) The loss of asthma control will be set to missing for participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control 2) A sensitivity analysis will be performed where participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control will have the endpoint set to loss of control
Secondary	The following secondary endpoints will be analyzed using the same statistical analysis as described for the primary endpoint: • Proportion of participants with a clinically significant asthma exacerbation

Endpoint	Statistical Analysis Methods
	(requiring OCS and/or hospitalisation) • Proportion of participants with Pre-bronchodilator FEV1 decrease from Baseline (measured at the end of Run-in) >7.5 % • Proportion of participants with Inability to titrate inhaled corticosteroid according to the pre-defined schedule (Section 5.1) • Proportion of participants with ACQ-5 score increase from Baseline (measured at the end of Run-in) ≥0.5 point. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule. In these analyses, the endpoint will be set to missing for participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control. Time to loss of asthma control will be analyzed using Kaplan-Meier analysis. Percentiles for time to loss of control will be presented for both treatment groups, along with graphical survival plots. Any early withdrawals from IP that did not experience loss of control will be censored. Results will be presented for both of the two eosinophil strata separately, and combined. The following endpoints will be analyzed using repeated logistic regression. This analysis will be repeated including an additional term for eosinophil strata by treatment by visit interaction to provide estimates for the two eosinophil strata separately: • Proportion of ACQ-5 responders (a ≥0.5 point improvement from baseline at Week 16) • Proportion of SGRQ responders (at least a 4 unit improvement from baseline at Week 16 These analyzes will be performed using two different methods for handling missing data: 1) If endpoint at a visit is missing then the responder status is set to missing 2) If endpoint at a visit is missing and the endpoint is also missing at all subsequent visits then the responder status is set to non-responder The odds ratio, 95% CI and p-value for the comparison of GSK3772847 with placebo will be presented for all models. Mixed model repeated measures will be used to analyze the following endpoints. The baseline value of each endpoint will be included along with baseline*visit and treatment*visit interactions. Treatment differences, 95% confidence intervals and p-values will be presented. • Change from baseline in ACQ-5 absolute score • Change from baseline in SGRQ total score • Change from baseline in Pre-bronchodilator FEV1 • Change from baseline in FeNO This analysis will be repeated including an additional term for eosinophil

Endpoint	Statistical Analysis Methods
	strata by treatment by visit interaction to provide estimates for each eosinophil strata separately. No adjustment will be made for missing data. Further information on how the following endpoints will be analyzed will be described in the report and analysis plan: • Hospitalisation or ER visit during the study treatment period • Morning and evening PEF • Daily asthma symptom score • Rescue medication use (albuterol/salbutamol): number of occasions per day • Night-time awakenings due to asthma symptoms requiring rescue medication Any changes to the planned analysis methods will be documented in the reporting and analysis plan. Details of subgroup analyses for the primary and secondary endpoints will be described in the reporting and analysis plan.
Exploratory	Will be described in the reporting and analysis plan

10.4.2. Safety Analyses

All safety analyses will be performed on the mITT Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary safety analysis.
Secondary	The following secondary safety endpoints will be analyzed descriptively by treatment group: • Incidence and frequency of AEs and SAEs • Vital signs • 12-lead ECG • 24 hours Holter • Clinical laboratory evaluation • Incidence of and titres of anti-GSK3772847 antibodies. Details will be described in the reporting and analysis plan

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.

10.4.3. Pharmacokinetic Analyses

All safety analyzes will be performed on the PK Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary pharmacokinetic analysis.
Secondary	The serum GSK3772847 levels from this study will be summarised by treatment and nominal time. Further details will be described in the report and analysis plan.

10.4.4. Pharmacodynamic Analyses

All pharmacodynamic analysis will be described in reporting and analysis plan.

10.4.5. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analysis will be described in the reporting and analysis plan. Any population PK analysis and pharmacodynamic analysis will be reported separately from the main clinical study report (CSR). Should a genetic/PGx analysis be performed, a separate reporting and analysis plan will be generated (See Appendix 6: Genetics).

10.4.6. Interim Analyses

Formal analyses will be performed at two timepoints.

End of Treatment Phase Analysis:

This will take place after all participants have completed the Week 16 visit. The data will be cleaned, the treatments unblinded and all clinic visits up to and including week 16 frozen. However, whilst no further efficacy data will be collected post week 16, due to an inability to lock log forms used for collection of exacerbation data, the end of treatment phase analysis will be considered an interim analysis for both efficacy and safety. Any safety data collected for participants who have completed clinic visits after Week 16 will also be cleaned and included in the analysis.

There will be no modifications to dosing regimens, sample size or any other aspects of the trial based on this data, as all study assessments, apart from follow-up, will have already been completed. As such an Independent Data Monitoring Committee (IDMC)

will not be used, as no further investigational product will be prescribed after this analysis has taken place.

Final Analysis:

This will take place after all subjects have completed the study. Data for visits after Week 16 as well as data collected on log pages will be cleaned and the database frozen. This will be the final analysis for the study.

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

Instream review:

An 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 Charter.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BID	Twice a day
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
CI	Confidence Interval
CV	Cardiovascular
Cmax	maximum serum concentration
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Serum creatine phosphokinase
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
ER	Emergency Room
eDiary	Electronic Diary
ETP	End of Treatment Phase
ERS	European Respiratory Society
EW	Early Withdrawal
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced expiratory volume in 1 second
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyltransferase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GLP	Good laboratory practice
GSK	GlaxoSmithKline

HBsAg	hepatitis B surface antigen
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
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
mITT	Modified Intent-to-treat
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
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

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory.
- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual and the SoA. Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference for all safety parameters will be provided to the site by the laboratory responsible for the assessments.
- All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.
- Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit White Cell Count RDW	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils These will be blinded from Visit 3 onwards.	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin

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		
Cardiac Markers	• Cardiac troponin I (cTn I) • N-terminal pro-brain natriuretic peptide (NT-proBNP)			
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.			

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

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

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

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 eCRF 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.

Study and Site Closure

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

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

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

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

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

Definition of AE

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

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

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

Definition of SAE

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the 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. • 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 eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

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

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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 or to the assigned SAE contact by telephone. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page

SAE Reporting to GSK via Paper eCRF
• Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the assigned SAE contact by telephone. • 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 eCRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 6.

Table 6 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed during the treatment period as specified in the Table of Events
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

- Pregnancy testing, with a sensitivity of 5, 10, 25 mIU/mL will be performed and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female Participants who become pregnant

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

Any female participant who becomes pregnant while participating will discontinue study treatment

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for Deoxyribonucleic acid (DNA) analysis
- DNA samples will be used for research related to GSK3772847 or asthma and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3772847 or other treatments which may regulate neutrophils and eosinophils or other study treatments including, but not limited to, steroids, long-acting beta-agonists, and other drugs used in the treatment of asthma, or for asthma and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
- DNA samples may be analyzed 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 analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3772847 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3772847 (or study treatments of this class) or asthma and related diseases continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • Obtain blood sample for pharmacokinetic (PK) analysis within 1 week after the liver event[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications

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	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
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

12.8. Appendix 8: 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 02-JUN-2017

Overall Rationale for the Amendment: To address clarifications regarding the aim of the study, the eligibility criteria, the schedule of activities, the clinical assessments, and the recording of lab data and adverse events. The benefit:risk section was also updated based on the Part 2 results from study CNTO7160ASH1001. Also, a few typographical errors were corrected.

Section # and Name	Description of Change	Brief Rationale
Protocol title; Section 1 Synopsis; Section 3.1 Study Rationale; Section 5.2 Number of participants; Section 5.4 Scientific Rationale for study design Section 6.1 Inclusion Criteria	Clarified that the study will recruit participants with moderately severe asthma.	Participants with severe asthma for whom it is felt oral corticosteroids (OCS) or biologics are warranted (Step 5 Global Initiative for Asthma GINA), are not eligible for this study.
Section 1 Synopsis; Section 3.1 Study Rationale	Clarified that the steroid titration design in this study will include inhaled corticosteroids.	To clarify that inhaled steroids will be titrated. Oral steroids are not allowed in this study.
Section 1 Synopsis; Section 3.1 Study Rationale Section 5.4 Scientific Rationale	Clarified that the aim of the steroid titration design is not to induce instability and exacerbations but changes in the level of asthma control.	The aim of the study is to assess the effects on changes in the level of asthma control and not on exacerbations.
Section 1 Synopsis; Section 4	Clarified that the objective of this study is to evaluate the efficacy, safety, pharmacokinetic, pharmacodynamics of	The study will recruit participants with moderately severe asthma. Participants with severe asthma for whom it is felt OCS or biologics are warranted (Step 5

Section # and Name	Description of Change	Brief Rationale
Objectives and Endpoints	GSK3772847 in participants with moderately severe asthma and not in patients with severe asthma.	GINA), are not eligible for this study.
Section 1 Synopsis; Section 4 Objectives and Endpoints	Included information on when the change from baseline will be measured for the safety and tolerability, pharmacokinetic and pharmacodynamics endpoints	To clarify how these endpoints will be analysed and reported.
Section 2 Schedule of Activities	The assessments and procedures have been grouped together under efficacy, safety, laboratory, and study treatment	To make the SoA easier to read and follow.
Section 2 Schedule of Activities	Reduced the visit window for Visits (V) 3 and 4 to ± 2 days.	With the previously allowed visit window of ± 3 days for weekly visits 3 and 4, these visits, in theory, could occur on consecutive days. To avoid this, the time window for these visits was reduced to ± 2 days.
Section 2 Schedule of Activities	Removed “Review of Loss of asthma control criteria” line item “X” at Visit 2.	Sites will not be able to review any of the criteria for loss of asthma control at V2 so this assessment is not required at Visit 2
Section 2 Schedule of Activities	Corrected “Medical history (includes substance usage)” line item to “Medical history (includes substance abuse)”.	Information on substance abuse is required as part of the medical history.
Section 2 Schedule of Activities	Removed “caffeine” from the examples of substances for which information on abuse is required as part of medical history.	Information on caffeine usage or abuse is not required. This had been included in the previous protocol version in error.
Section 2 Schedule of Activities	Corrected Week 8 as Day 57, rather than Day 49.	Typographical error
Section 2 Schedule of	Included in line item “Laboratory Assessments” that clinical chemistry tests will be performed	Added information on the frequency of clinical chemistry tests.

Section # and Name	Description of Change	Brief Rationale
Activities	at study visits indicated with a superscript 1.	
Section 2 Schedule of Activities	Included in line item “Laboratory Assessments” that cardiac lab tests will be performed at every clinic visit.	Added information on the frequency of cardiac lab markers.
Section 2 Schedule of Activities	Included in line item “Laboratory Assessments” that routine urinalysis will be performed at Screening	Added information on the frequency of urinalysis test.
Section 2 Schedule of Activities	Included in line item “Double blind Study Treatment (IP)” in the Notes column that patients will be monitored for 2 hours after the end of infusion	Added information on the duration of post-dose monitoring.
Section 3.3.1 Risk Assessment	Included more information on the identified risks based on the final data analysis from study CNTO7160ASH1001.	To update the risk assessment with information that became available after the final analysis of Part 2 of study CNTO7160ASH1001
Section 3.3.2 Benefit Assessment	Included that there are no existing efficacy data from molecules with the same mode of action and that the aim of the study is to provide evidence of efficacy in eosinophilic but also in non-eosinophilic asthma.	To provide further information on risk:benefit.
Section 3.3.2 Benefit Assessment	Included that the IL-33 pathway may be implicated in type 2 and non-type 2 driven disease.	To add more information on the anticipated benefits from this study.
Section 3.3.2 Benefit Assessment	Clarified that the electronic Diary (eDiary), the peak expiratory flow (PEF) measurement and the programmed safety alerts will be used in order to monitor the participants’ asthma status.	To clarify the safety measures that are in place in order to monitor the participants during the study.
Section 5.1 Overall Design Section 8.2	Clarified that participants may need to be withdrawn during the run-in period depending on their	For this study, the aim is to randomize at least 30% of participants with low eosinophil count. Therefore, participants

Section # and Name	Description of Change	Brief Rationale
Withdrawal from the study	blood eosinophil count in order to achieve the stratification balance.	may have to be withdrawn based on their eosinophil count measured at screening.
Section 5.1 Overall Design	Clarified that the data from the eDiary and the safety alerts will be available to the sites and provided information on how these data should be used by the participants and the sites in order to ensure adequate monitoring of the participant's asthma status.	To clarify the safety measures that are in place in order to monitor the participants during the study.
Section 6.1 Inclusion Criteria	Inclusion criterion 5: Added information on the eligibility criteria for participants with a history of bronchial hyperreactivity from bronchial challenge studies.	To clarify that for participants with a documented history of bronchial challenge tests, GINA guidelines and values will be used in order to determine eligibility.
Section 6.1 Inclusion Criteria	Inclusion criterion 8: Added the requirement to use the study-provided rescue medication as an inclusion criterion.	All participants must use the same rescue medication during the study.
Section 6.1 Inclusion criteria; Section 6.3 Randomisation inclusion criteria	Inclusion criterion 6: Reduced the lower limit of ACQ5 to ≥1 and added an upper limit of <4.	To clarify that participants with well-controlled symptoms or participants with very severe and uncontrolled symptoms are not eligible.
Section 6.2 Exclusion Criteria	Exclusion criterion 3: Added that the predicted values used for the spirometry eligibility will be based on the Global Lung Function Initiative (GLI) equations.	To clarify that the predicted values for spirometry will be based on the GLI equations.
Section 6.2 Exclusion Criteria	Exclusion Criterion 4: Added the years in remission required for eligibility and provided clarification on eligibility of participants with certain types of carcinomas.	To provide clarification on the eligibility of participants.
Section 6.2 Exclusion Criteria	Exclusion criterion 12: Added that participants with known or	To provide further clarification on this exclusion criterion.

Section # and Name	Description of Change	Brief Rationale
	parasitic infestation 6 months prior to visit 1 are not eligible. Also, provided a definition for ongoing and recurrent infections.	
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Added that participants should not be withdrawn or washed out of their medication for the sole purpose of participating in the study.	To clarify that participants' treatment should not be changed only for study eligibility purposes.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Clarified that systemic corticosteroids are oral and parenteral, depot.	To provide clarification on systemic corticosteroids.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Highlighted that potential participants should not be washed out of their regular medication for the sole purpose on enrolling in the trial.	The participants' medication should not be altered for the sole purpose on participating in the trial.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Added the wash-out period for inhaled anticholinergics.	To clarify that inhaled anticholinergics are not allowed 1 week prior to screening visit.
Section 6.4 Randomisation Exclusion Criteria	Exclusion criterion 6: Added that the predicted values used for the spirometry eligibility will be based on the Global Lung Function Initiative (GLI) equations.	To clarify that the predicted values for spirometry will be based on the GLI equations.
Section 7.1 Treatments Administered; Section 7.5 Preparation, Handling, Storage, Accountability	Clarified that normal saline will be used as a diluent for dilution of the study treatment and as placebo.	To provide information on the acceptable diluent.
Section 7.5 Preparation, Handling, Storage, Accountability	Removed the pre-dilution filtration step from the description of the treatment preparation	This step is not required.
Section 7.7.1	Clarified that antihistamines	To clarify the wash-out period for

Section # and Name	Description of Change	Brief Rationale
Permitted non-asthma medications	should be avoided 48 hours prior to electrocardiogram (ECG) measurements	antihistamines prior to an ECG.
Section 7.7.2 Prohibited Medications and Drug Therapies	Included that live or attenuated vaccines are prohibited 6 months after the last dose of blinded study treatment. Also clarified that systemic corticosteroids are oral and parenteral, depot.	To provide further clarifications on the prohibited medications.
Section 9.1.2.3 Alerts	Added that in case of an alert the participant will receive notification to send the data to the centralised server as soon as possible and that the investigator will receive notification as soon as the data is transferred to the centralised server.	To provide further information on the alert notification process.
Section 9.1.3.1 Spirometry	Clarified that a minimum of 2 valid and 2 repeatable efforts are required at V1 and a minimum of 2 valid (not necessarily repeatable) efforts are required at V2-11.	Different quality criteria apply for spirometry at various visits.
Section 9.1.3.2 Reversibility	Included that a spacer may be used for reversibility.	To clarify the use of a spacer for reversibility.
Section 9.2 Adverse Events	Clarified that asthma exacerbations will not be captured as adverse events (AEs)	To clarify the way that asthma exacerbations will be captured in the electronic Case Report Form (eCRF).
Section 9.4.3 Electrocardiograms	Clarified that ECGs should be performed before any blood draws and lung function tests.	To clarify the order of assessments.
Section 9.4.3 Electrocardiograms	Added that the participants should refrain from caffeine-containing products, antihistamines and decongestants for a certain period of time prior to an ECG.	To clarify the wash-out period of caffeine, antihistamines and decongestants prior to an ECG.

Section # and Name	Description of Change	Brief Rationale
Section 9.8.1.1 Sputum Sub-Study	Clarified that the participants in the sputum sub-study will be randomised equally in the two treatment groups.	To provide clarification on the randomization strategy for the Sputum Sub-Study.
Section 10.4.1 Efficacy Analysis	Added that the posterior probabilities will be calculated assuming a non-informative prior.	To clarify the analysis method that will be used.
Section 11 Reference	Included the reference on the paper by Quanjer et al.	To provide the reference paper on the predicted values for spirometry that will be used in this study.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Added that the white blood cell (WBC) count differential will be blinded form V3 onwards	To clarify that these lab data will be blinded after randomisation.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Added that cardiac markers measured are Troponin I and N-terminal prohormone of brain natriuretic peptide (NT-proBNP).	To clarify the cardiac markers that will be measured.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Removed the sentence "The results of each test should be entered into the eCRF" from the table.	Lab results will be electronically transferred from the central lab vendor to GSK. Sites are not required to transcribe lab data in the eCRF.
Section 12.7 Appendix 7: Liver Safety: Required Actions and Follow-up Assessments	Added that a PK sample should be obtained within 1 week after the liver event.	Typographical error. This edit removes the wording “insert time interval recommended by clinical pharmacokinetics representative after last dose” that was inadvertently copied from the protocol template to the final version of the protocol.

TITLE PAGE

Protocol Title: A randomized, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma

Protocol Number: 207597/01

Short Title: A study to evaluate the effect of GSK3772847 in patients with moderately severe asthma.

Compound Number: GSK3772847

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
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Medical Monitor Name and Contact Information

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Regulatory Agency Identifying Number(s): IND number 134366, EudraCT number: 2017-001072-34

Approval Date: 02-JUN-2017

SPONSOR SIGNATORY:

PPD

2 June 2017

Courtney PPD MD

Date

Director, Clinical Development

Respiratory Medicines Discovery and Development

GlaxoSmithKline

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	*02-JUN-2017*
Original Protocol-2017N311825_00	*06-MAR-2017*

Amendment 1 02-JUN-2017

Overall Rationale for the Amendment: To address clarifications regarding the aim of the study, the eligibility criteria, the schedule of activities, the clinical assessments, and the recording of lab data and adverse events. The benefit:risk section was also updated based on the Part 2 results from study CNTO7160ASH1001. Also, a few typographical errors were corrected.

Section # and Name	Description of Change	Brief Rationale
Protocol title; Section 1 Synopsis; Section 3.1 Study Rationale; Section 5.2 Number of participants; Section 5.4 Scientific Rationale for study design Section 6.1 Inclusion Criteria	Clarified that the study will recruit participants with moderately severe asthma.	Participants with severe asthma for whom it is felt oral corticosteroids (OCS) or biologics are warranted (Step 5 Global Initiative for Asthma GINA), are not eligible for this study.
Section 1 Synopsis; Section 3.1 Study Rationale	Clarified that the steroid titration design in this study will include inhaled corticosteroids.	To clarify that inhaled steroids will be titrated. Oral steroids are not allowed in this study.
Section 1 Synopsis; Section 3.1 Study Rationale Section 5.4 Scientific Rationale	Clarified that the aim of the steroid titration design is not to induce instability and exacerbations but changes in the level of asthma control.	The aim of the study is to assess the effects on changes in the level of asthma control and not on exacerbations.

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis; Section 4 Objectives and Endpoints	Clarified that the objective of this study is to evaluate the efficacy, safety, pharmacokinetic, pharmacodynamics of GSK3772847 in participants with moderately severe asthma and not in patients with severe asthma.	The study will recruit participants with moderately severe asthma. Participants with severe asthma for whom it is felt OCS or biologics are warranted (Step 5 GINA), are not eligible for this study.
Section 1 Synopsis; Section 4 Objectives and Endpoints	Included information on when the change from baseline will be measured for the safety and tolerability, pharmacokinetic and pharmacodynamics endpoints	To clarify how these endpoints will be analysed and reported.
Section 2 Schedule of Activities	The assessments and procedures have been grouped together under efficacy, safety, laboratory, and study treatment	To make the SoA easier to read and follow.
Section 2 Schedule of Activities	Reduced the visit window for Visits (V) 3 and 4 to $\pm$ 2 days.	With the previously allowed visit window of $\pm$ 3 days for weekly visits 3 and 4, these visits, in theory, could occur on consecutive days. To avoid this, the time window for these visits was reduced to $\pm$ 2 days.
Section 2 Schedule of Activities	Removed “Review of Loss of asthma control criteria” line item “X” at Visit 2.	Sites will not be able to review any of the criteria for loss of asthma control at V2 so this assessment is not required at Visit 2
Section 2 Schedule of Activities	Corrected “Medical history (includes substance usage)” line item to “Medical history (includes substance abuse)”.	Information on substance abuse is required as part of the medical history.
Section 2 Schedule of Activities	Removed “caffeine” from the examples of substances for which information on abuse is required as part of medical history.	Information on caffeine usage or abuse is not required. This had been included in the previous protocol version in error.
Section 2 Schedule of	Corrected Week 8 as Day 57, rather than Day 49.	Typographical error

Section # and Name	Description of Change	Brief Rationale
Activities		
Section 2 Schedule of Activities	Included in line item “Laboratory Assessments” that clinical chemistry tests will be performed at study visits indicated with a superscript 1.	Added information on the frequency of clinical chemistry tests.
Section 2 Schedule of Activities	Included in line item “Laboratory Assessments” that cardiac lab tests will be performed at every clinic visit.	Added information on the frequency of cardiac lab markers.
Section 2 Schedule of Activities	Included in line item “Laboratory Assessments” that routine urinalysis will be performed at Screening	Added information on the frequency of urinalysis test.
Section 2 Schedule of Activities	Included in line item “Double blind Study Treatment (IP)” in the Notes column that patients will be monitored for 2 hours after the end of infusion	Added information on the duration of post-dose monitoring.
Section 3.3.1 Risk Assessment	Included more information on the identified risks based on the final data analysis from study CNTO7160ASH1001.	To update the risk assessment with information that became available after the final analysis of Part 2 of study CNTO7160ASH1001
Section 3.3.2 Benefit Assessment	Included that there are no existing efficacy data from molecules with the same mode of action and that the aim of the study is to provide evidence of efficacy in eosinophilic but also in non-eosinophilic asthma.	To provide further information on risk:benefit.
Section 3.3.2 Benefit Assessment	Included that the IL-33 pathway may be implicated in type 2 and non-type 2 driven disease.	To add more information on the anticipated benefits from this study.
Section 3.3.2 Benefit Assessment	Clarified that the electronic Diary (eDiary), the peak expiratory flow (PEF) measurement and the programmed safety alerts will be used in order to monitor the	To clarify the safety measures that are in place in order to monitor the participants during the study.

Section # and Name	Description of Change	Brief Rationale
	participants' asthma status.	
Section 5.1 Overall Design Section 8.2 Withdrawal from the study	Clarified that participants may need to be withdrawn during the run-in period depending on their blood eosinophil count in order to achieve the stratification balance.	For this study, the aim is to randomize at least 30% of participants with low eosinophil count. Therefore, participants may have to be withdrawn based on their eosinophil count measured at screening.
Section 5.1 Overall Design	Clarified that the data from the eDiary and the safety alerts will be available to the sites and provided information on how these data should be used by the participants and the sites in order to ensure adequate monitoring of the participant's asthma status.	To clarify the safety measures that are in place in order to monitor the participants during the study.
Section 6.1 Inclusion Criteria	Inclusion criterion 5: Added information on the eligibility criteria for participants with a history of bronchial hyperreactivity from bronchial challenge studies.	To clarify that for participants with a documented history of bronchial challenge tests, GINA guidelines and values will be used in order to determine eligibility.
Section 6.1 Inclusion Criteria	Inclusion criterion 8: Added the requirement to use the study-provided rescue medication as an inclusion criterion.	All participants must use the same rescue medication during the study.
Section 6.1 Inclusion criteria; Section 6.3 Randomisation inclusion criteria	Inclusion criterion 6: Reduced the lower limit of ACQ5 to ≥1 and added an upper limit of <4.	To clarify that participants with well-controlled symptoms or participants with very severe and uncontrolled symptoms are not eligible.
Section 6.2 Exclusion Criteria	Exclusion criterion 3: Added that the predicted values used for the spirometry eligibility will be based on the Global Lung Function Initiative (GLI) equations.	To clarify that the predicted values for spirometry will be based on the GLI equations.
Section 6.2 Exclusion Criteria	Exclusion Criterion 4: Added the years in remission required for eligibility and provided clarification on eligibility of	To provide clarification on the eligibility of participants.

Section # and Name	Description of Change	Brief Rationale
	participants with certain types of carcinomas.	
Section 6.2 Exclusion Criteria	Exclusion criterion 12: Added that participants with known or parasitic infestation 6 months prior to visit 1 are not eligible. Also, provided a definition for ongoing and recurrent infections.	To provide further clarification on this exclusion criterion.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Added that participants should not be withdrawn or washed out of their medication for the sole purpose of participating in the study.	To clarify that participants' treatment should not be changed only for study eligibility purposes.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Clarified that systemic corticosteroids are oral and parenteral, depot.	To provide clarification on systemic corticosteroids.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Highlighted that potential participants should not be washed out of their regular medication for the sole purpose on enrolling in the trial.	The participants' medication should not be altered for the sole purpose on participating in the trial.
Section 6.2 Exclusion Criteria	Exclusion criterion 19: Added the wash-out period for inhaled anticholinergics.	To clarify that inhaled anticholinergics are not allowed 1 week prior to screening visit.
Section 6.4 Randomisation Exclusion Criteria	Exclusion criterion 6: Added that the predicted values used for the spirometry eligibility will be based on the Global Lung Function Initiative (GLI) equations.	To clarify that the predicted values for spirometry will be based on the GLI equations.
Section 7.1 Treatments Administered; Section 7.5 Preparation, Handling, Storage, Accountability	Clarified that normal saline will be used as a diluent for dilution of the study treatment and as placebo.	To provide information on the acceptable diluent.
Section 7.5	Removed the pre-dilution	This step is not required.

Section # and Name	Description of Change	Brief Rationale
Preparation, Handling, Storage, Accountability	filtration step from the description of the treatment preparation	
Section 7.7.1 Permitted non-asthma medications	Clarified that antihistamines should be avoided 48 hours prior to electrocardiogram (ECG) measurements	To clarify the wash-out period for antihistamines prior to an ECG.
Section 7.7.2 Prohibited Medications and Drug Therapies	Included that live or attenuated vaccines are prohibited 6 months after the last dose of blinded study treatment. Also clarified that systemic corticosteroids are oral and parenteral, depot.	To provide further clarifications on the prohibited medications.
Section 9.1.2.3 Alerts	Added that in case of an alert the participant will receive notification to send the data to the centralised server as soon as possible and that the investigator will receive notification as soon as the data is transferred to the centralised server.	To provide further information on the alert notification process.
Section 9.1.3.1 Spirometry	Clarified that a minimum of 2 valid and 2 repeatable efforts are required at V1 and a minimum of 2 valid (not necessarily repeatable) efforts are required at V2-11.	Different quality criteria apply for spirometry at various visits.
Section 9.1.3.2 Reversibility	Included that a spacer may be used for reversibility.	To clarify the use of a spacer for reversibility.
Section 9.2 Adverse Events	Clarified that asthma exacerbations will not be captured as adverse events (AEs)	To clarify the way that asthma exacerbations will be captured in the electronic Case Report Form (eCRF).
Section 9.4.3 Electrocardiograms	Clarified that ECGs should be performed before any blood draws and lung function tests.	To clarify the order of assessments.
Section 9.4.3 Electrocardiograms	Added that the participants should refrain from caffeine-	To clarify the wash-out period of caffeine, antihistamines and

Section # and Name	Description of Change	Brief Rationale
	containing products, antihistamines and decongestants for a certain period of time prior to an ECG.	decongestants prior to an ECG.
Section 9.8.1.1 Sputum Sub-Study	Clarified that the participants in the sputum sub-study will be randomised equally in the two treatment groups.	To provide clarification on the randomization strategy for the Sputum Sub-Study.
Section 10.4.1 Efficacy Analysis	Added that the posterior probabilities will be calculated assuming a non-informative prior.	To clarify the analysis method that will be used.
Section 11 Reference	Included the reference on the paper by Quanjer et al.	To provide the reference paper on the predicted values for spirometry that will be used in this study.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Added that the white blood cell (WBC) count differential will be blinded form V3 onwards	To clarify that these lab data will be blinded after randomisation.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Added that cardiac markers measured are Troponin I and N-terminal prohormone of brain natriuretic peptide (NT-proBNP).	To clarify the cardiac markers that will be measured.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Removed the sentence "The results of each test should be entered into the eCRF" from the table.	Lab results will be electronically transferred from the central lab vendor to GSK. Sites are not required to transcribe lab data in the eCRF.
Section 12.7 Appendix 7: Liver Safety: Required Actions and Follow-up Assessments	Added that a PK sample should be obtained within 1 week after the liver event.	Typographical error. This edit removes the wording “insert time interval recommended by clinical pharmacokinetics representative after last dose” that was inadvertently copied from the protocol template to the final version of the protocol.

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma.

Short Title: A study to evaluate the effect of GSK3772847 in patients with moderately severe asthma.

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.

At the time of writing this protocol, a two-part, single and multiple ascending dose first time in human (FTIH) study has completed dosing (final clinical study report is pending). The safety information from this study is included in the investigator brochure (GlaxoSmithKline Document Number 2017N316832_00). There are no efficacy data available to date.

The present study is the first GSK sponsored study with GSK3772847. It is a Phase IIa / proof of concept study to investigate efficacy, safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of GSK3772847 in participants with moderately severe asthma. The study will use an inhaled steroid titration design in order to evaluate whether GSK3772847 maintains protection of asthma control. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which changes in the level of asthma control were induced by medication withdrawal. This design may not reflect real world fluctuations in asthma control; however, studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on changes in asthma control in a relatively short period of time, before further investigations are conducted in longer term studies.

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 moderately 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: • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥0.5 point 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 • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation).
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with moderately severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • 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 who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • 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

Objectives	Endpoints
	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 moderately severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28. • Change between post-dose and pre-dose in vital signs at weeks 0, 4, 8 and 12. • Change from baseline in 12-lead electrocardiogram (ECG) measurements at weeks 4, 8, 12 and 16. • Change between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12. • Change from baseline in 24 hours Holter measurements at weeks 4 and 12. • Change from baseline in clinical chemistry at weeks 2, 4, 8, 12, 16 and 28. • Change from baseline in hematology and cardiac markers at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28. • Incidence of and titres of anti- GSK3772847 antibodies at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with moderately severe asthma.	• Serum concentrations of GSK3772847 at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with moderately severe asthma.	• Free and total soluble ST2 levels in serum at weeks 2, 4, 8, 12, 16, 20, 24 and 28.

Overall Design:

This is a Phase IIa, multicenter, randomized, placebo-controlled, double-blind, stratified, parallel group study in participants with moderately severe asthma.

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.

Number of Participants:

Approximately 300 participants with moderately severe 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. High-dose ICS is defined as fluticasone propionate 500 mcg twice daily (i.e. 1000 mcg /day) or equivalent. For the purpose of this study an evaluable participant is defined as a participant who completes the Week 16 clinic visit whilst remaining on investigational product (IP) or who withdraws from IP having met the primary endpoint.

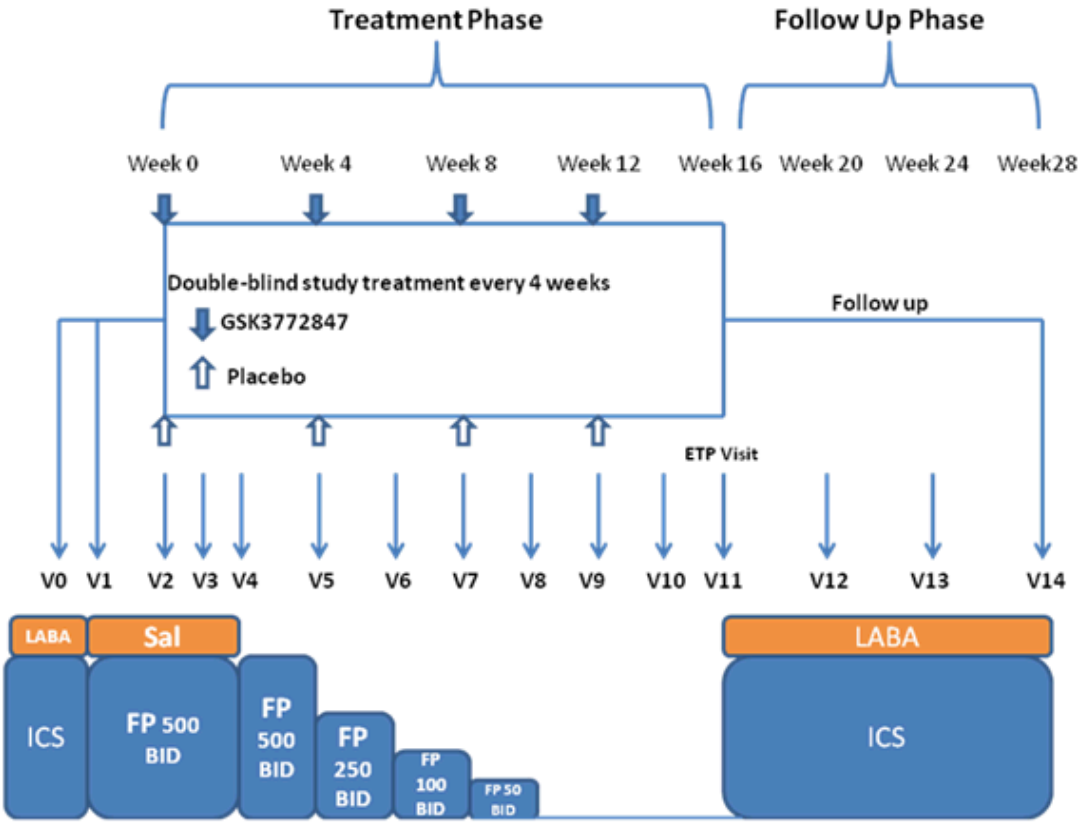
Treatment Groups and Duration:

When required, a pre-screening visit (Visit 0) can be scheduled for signing the informed consent, up to 2 weeks prior to Screening (Visit 1). The pre-screening visit can also occur on the same day as the Screening visit. Participants who meet the eligibility criteria at Screening (Visit 1) will withdraw their regular ICS/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 twice daily (BID). At the end of the Run-in period at Visit 2 (Week 0), participants who meet pre-defined randomization criteria will be randomized in a 1:1 ratio to enter a double-blind 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, two weeks after Randomization, the open label background therapy will be switched from FP/Sal 500/50 mcg BID to FP 500 mcg BID for 2 weeks. Visit 4 will be the beginning of a six week 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 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.

An End of Treatment Phase (ETP) Visit will be performed 4 weeks after the final dose of the blinded study treatment is administered at Week 12. 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. 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/EW Visit for safety assessments.



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 9). 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.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period**										**Follow-up Period[2] (± 3 days)**			**Notes**
			± 2 days			**± 3 days**										
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**	**57**	**71**	**85**	**99**	**113**				
Informed consent (ICF)	X															
Genetic ICF	X															
ICF for sputum	X															
Inclusion and exclusion criteria		X														
Randomisation Criteria			X													
Demography	X															
Full physical exam including height and weight		X														
Medical history (includes substance abuse)		X														Substances [Drugs, Alcohol, tobacco] and family history of premature CV disease]): [including cardiovascular medical history]
Laboratory																

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period**										**Follow-up Period[2] (± 3 days)**			**Notes**
			± 2 days			**± 3 days**										
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**	**57**	**71**	**85**	**99**	**113**				
Laboratory assessments		X[1, 2]	X[1]	X	X[1]	X[1]	X	X[1]	X	X[1]	X	X[1]			X[1]	Haematology (including eosinophil count) and cardiac markers measured at all clinic visits. 1. Clinical chemistry (including liver chemistry). 2. Routine urinalysis at screening (Visit 1)
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.

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
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**	**57**	**71**	**85**	**99**	**113**				
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
Sputum sample collection			X					X				X				Pre-dose collection and in a sub-set of participants (~50 %) at selected sites; also collected for EW participants
PK, target engagement and immunogenicity assessments			X	X	X	X		X		X		X	X	X	X	See SoA Table 2 for details
Exploratory Biomarkers			X					X				X				Pre dose collection
Efficacy																
Spirometry		X	X		X	X	X	X	X	X	X	X				Test to be performed pre-dose during the Treatment period
Reversibility		X														
FeNO			X	X	X	X	X	X	X	X	X	X				Test to be performed pre-dose
Review loss of asthma control criteria				X	X	X	X	X	X	X	X	X				It will include review of data to determine loss of asthma control. See Section 9.1.5.
Dispense eDiary		X														

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
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**	**57**	**71**	**85**	**99**	**113**				
Collect eDiary												X				
Review eDiary			X	X	X	X	X	X	X	X	X	X				
Safety																
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.
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.
Dispense paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X		
Review paper Medical Problems/Medications Taken worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Pre-Screening[1]**	**Screen Run-in**	**Treatment Period**										**Follow-up Period[2] (± 3 days)**			**Notes**
			± 2 days			**± 3 days**										
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**	**57**	**71**	**85**	**99**	**113**				
AE/SAE review	X[1]	X[1]	←==========									→	X	X	X	1. At V0 and V1 collect only SAEs considered as related to study participation.
Concomitant medication review	X	X	←==========									→	X	X	X	
Questionnaires																
ACQ-5		X	X													After randomization, ACQ5 will be completed by the participants every 7 days.
SGRQ			X			X		X		X		X				
Study Treatment																
Double blind Study Treatment (IP)			X			X		X		X						Patients will remain in the clinic for monitoring for at least 2 hours after the end of infusion.
FP/Sal (500/50) dispensing		X	X													
FP (mcg) dispensing					500	250	100	50								
Dispense albuterol (as needed)		X	X	X	X	X	X	X	X	X	X	X				

SoA Table 2: Timings of PK, target engagement and immunogenicity samples

Procedure	**Treatment Period**										**Follow-up[2] (± 3 days)**			**Notes**
	± 2 days			**± 3 days**										
Visit	**2[1]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (ETP or EW)**	**12**	**13**	**14**	1. Visit 2 = Day 1 (first dose of IP). 2. FU period to start 4 weeks after ETP or EW visit.
Week	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	
Study Day	**1**	**8**	**15**	**29**	**43**	**49**	**71**	**85**	**99**	**113**				
Double blind Study Treatment (IP)	**X**			**X**		**X**		**X**						
PK sample	X[2]	X	X	X[3]		X[3]		X[1]		X	X	X	X	1. Pre dose and post dose. 2. Post dose only. 3. Pre dose only. <u>Pre-dose samples</u> within 2 hours from the planned dosing time. <u>Post-dose samples</u> as soon as possible after end of infusion but must be taken within 4 hours.
Free and total sST2	X[1]	X	X	X[3]		X[3]		X[1]		X	X	X	X	
Immunogenicity sample	X[3]		X	X[3]		X[3]		X[3]		X	X	X	X	

3. INTRODUCTION

3.1. Study Rationale

GSK3772847 is a human immunoglobulin G2 sigma isotype (IgG2σ) antibody that binds Domain 1 of the cell-surface receptor 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.

At the time of writing this protocol, a two-part, single and multiple ascending dose first time in human (FTIH) study has completed dosing (final report is pending). The safety information from this study is included in the investigator brochure (IB [GlaxoSmithKline Document Number 2017N316832_00]). There are no efficacy data available to date.

The present study is the first GSK sponsored study with GSK3772847. It is a Phase IIa / proof of concept study to investigate efficacy, safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of GSK3772847 in participants with moderately severe asthma. The study will use an inhaled steroid titration design in order to evaluate whether GSK3772847 maintains protection of asthma control. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which changes in the level of asthma control were induced by medication withdrawal [Bel, 2014; Wenzel, 2013; Nair, 2009]. This design may not reflect real world fluctuations in asthma control; however, studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on changes in asthma control in a relatively short period of time, before further investigations are conducted in longer term studies.

3.2. 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 [Chung, 2014; Aburuz, 2007; 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 signaling. 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].

In a 3-month good laboratory practice (GLP) toxicology study, GSK3772847 was administered to cynomolgus monkeys as a weekly 15-minute IV infusion (20 or 100 mg/kg) and was found to be well-tolerated at both doses.

Janssen (Study CNTO7160ASH1001) have conducted a Phase I randomized, double-blind, placebo-controlled, intravenous (IV) single ascending dose study in healthy participants and multiple ascending dose study in participants with asthma and participants with atopic dermatitis. The study has completed dosing. The final clinical study report is still pending. There are no efficacy data available to date.

More information about the non-clinical and clinical studies is available in the GSK3772847 IB (GlaxoSmithKline Document Number 2017N316832_00).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks and reasonably expected adverse events of GSK3772847 may be found in the IB (GlaxoSmithKline Document Number 2017N316832_00).

3.3.1. 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 GLP 3 month IV repeat dose toxicity study at doses ≤100 mg/kg/week) or subcutaneous (SC) administration. 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). 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	Exclude participants with existing clinically significant organic heart disease (e.g. Coronary artery disease [CAD], New York Heart Association (NYHA) Class III/IV heart failure) and abnormal, clinically significant findings from 12-lead ECG and 24-hour holter monitoring (Section 6.2 and Section 6.3). CV events will be monitored (including ECG and Holter monitoring) as specified in Section 2. All cardiac-related AEs will be reviewed by an independent safety review committee (iSRC). Protocol-defined stopping criteria are specified in Section 8.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. The abnormalities were considered clinically significant and recorded as treatment emergent 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 a pattern thought not to be indicative of increased risk for sudden ventricular tachycardia and sudden death. Heart rate (HR) analysis did not	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
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 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+ inate 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.	**Preclinical**: 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 or IV 3 month toxicity 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).	Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening are excluded from participation in the study (Section 6.2) Participants who develop an infection will be requested to seek medical advice, and subject to close monitoring. 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 and routinely as

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 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	part of the post marketing pharmacovigilance process. Exclude patients with ongoing or recurrent infections. Close monitoring of infection AEs (including 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**: Not observed in studies to date. **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	If a hypersensitivity or anaphylactic reaction occurs, infusion should be discontinued immediately and appropriate therapy instituted. Agents to treat reactions should be available immediately. Stopping & continuation criteria will be included in protocols. Painkillers can be prescribed for pain at site of injection. Patients developing hypersensitivity, anaphylactic reactions or anaphylactic shock will be withdrawn from the study. All doses in this trial will be administered in the clinic.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CNTO7160ASH1001 the risk of CRS is considered negligible.	
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. Steroid withdrawal is expected to augment a pro-inflammatory response in the lung of the patients that drives the asthma phenotype. 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.	**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. This data is indicative that healthy 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).	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.
Gastrointestinal disorders • Nausea • Vomiting	**Clinical:** In Part 2 of Janssen study CNTO7160ASH1001, the incidence of gastrointestinal disorders was greater in participants in the GSK3772847	The incidence and severity of nausea and vomiting will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
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.	The incidence and severity of contact dermatitis will be monitored.

3.3.2. Benefit Assessment

Efficacy of GSK3772847 has not yet been demonstrated and there are no existent data from molecules with the same or similar mode of action. Taking part in this study may or may not improve a participant's health, and may or may not directly benefit a participant. This study will provide additional safety and efficacy information on GSK3772847.

Whilst the *in vivo* models of T2 asthma support a role for IL-33 pathway in eosinophilic asthma disease, it is clear that IL-33 plays a significant role in other types of immune responses and cell types including amplification of Th1 and Th17 responses in combination with other cytokines [Arshad, 2016; Smithgall, 2008]. Agents targeting this mechanism could be expected to have effects on both type 2 (T2)-driven and non-T2-driven disease.

All study participants will receive open label salbutamol/albuterol to use as needed for asthma symptom relief from Screening to the end of the Treatment Period. Medical assessments are planned during the study to evaluate participants' health status. The assessments include physical examination, vital signs, electrocardiogram (ECG), Holter monitoring, and clinical laboratory evaluation including liver chemistry and blood chemistry panel at a number of clinic visits. Participants will be monitored for changes in asthma control through daily use of an electronic Diary (eDiary) and twice-daily PEF measurements. Safety alerts will be provided to the participants and the sites in case of worsening of asthma. Participants' health status will also be evaluated by ACQ-5 and SGRQ during the study. Participants' safety will be assured by having criteria for withdrawal from study medication/reinstatement of usual care in case of loss of asthma control. The aim will be to retain participants in the study post withdrawal of study medication to follow-up for safety.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize the risk to the participants participating in the study, the balance of anticipated benefits and apparent risks associated with GSK3772847 continues to be acceptable. There is an opportunity to determine if there is a new drug that can be developed for patients with severe asthma who may benefit from the broad spectrum effects hypothesized for GSK3772847.

4. 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 moderately 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: • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥0.5 point 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 • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation).
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with moderately severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • 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 who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • 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

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 moderately severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28. • Change between post-dose and pre-dose in vital signs at weeks 0, 4, 8 and 12. • Change from baseline in 12-lead electrocardiogram (ECG) measurements at weeks 4, 8, 12 and 16. • Change between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12. • Change from baseline in 24 hours Holter measurements at weeks 4 and 12. • Change from baseline in clinical chemistry at weeks 2, 4, 8, 12, 16 and 28. • Change from baseline in hematology and cardiac markers at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28. • Incidence of and titres of anti- GSK3772847 antibodies at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with moderately severe asthma.	• Serum concentrations of GSK3772847 at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with moderately	• Free and total soluble ST2 levels in serum at weeks 2, 4, 8, 12, 16, 20, 24 and 28.

Objectives	Endpoints
severe asthma.	
Exploratory	
• To compare the effect of GSK3772847 with placebo on biomarkers in serum and sputum.	• Changes from baseline in induced sputum biomarkers (subset) at weeks 8 and 16. • Changes from baseline in exploratory serum markers at weeks 8 and 16.

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. In order to achieve the stratification balance, as a result of participants' eosinophil count it may be necessary to withdraw participants from the study during the Run-in period.**

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 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

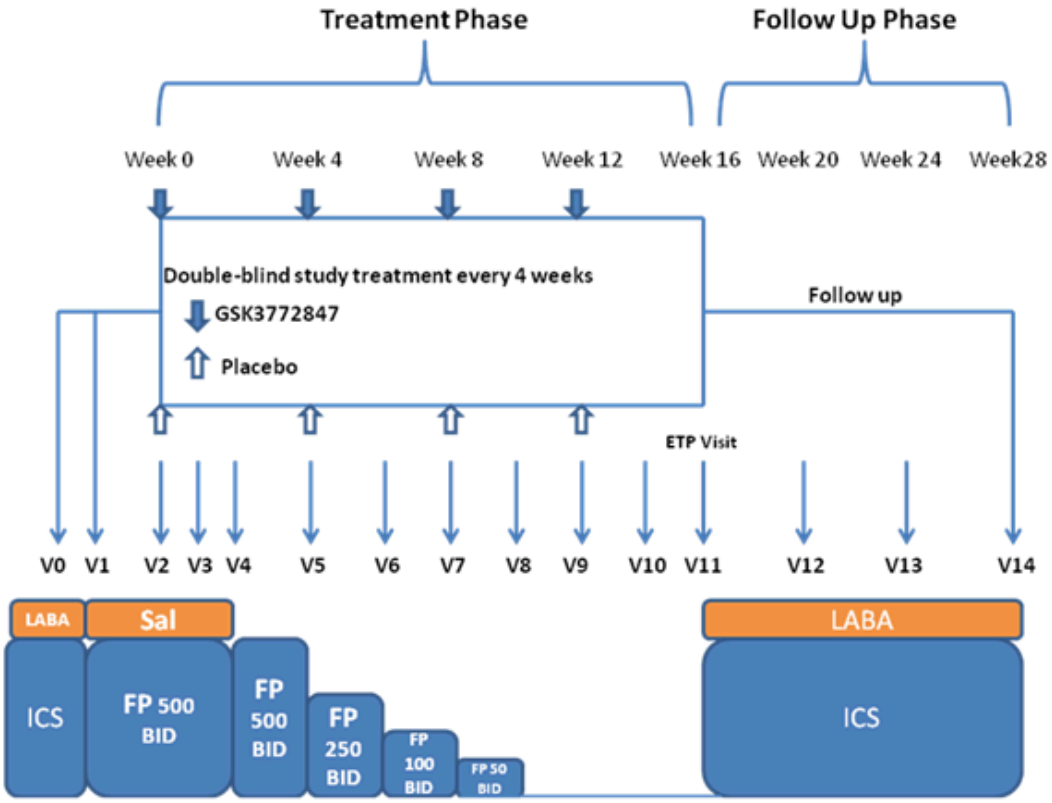
for loss of asthma control are met during the Treatment Period, participants will be withdrawn from the investigational product (IP) and should resume regular treatment for their asthma, as determined by the investigator.

Participants will be monitored for loss of asthma control through daily use of an eDiary and twice-daily PEF measurements. The participants will use the eDiary to record asthma symptoms, rescue medication use, and nocturnal awakenings due to asthma symptoms requiring rescue medication use. This information will be transmitted daily to a centralized server and available to the investigators. Alerts for pre-defined changes in PEF or asthma symptoms, indicative of worsening asthma, will be programmed into the eDiary with prompts to the participants to contact the investigator if any of the alert criteria are met (Section 9.1.2.3). Additionally, email notifications will be sent to the investigator, if any of the alert criteria are met, as soon as the data is transmitted to the centralized server. The investigator will make every effort to contact the participants in order to discuss the participants' symptoms and evaluate whether they experienced loss of asthma control.

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.



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 moderately severe 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**.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including, screening, run-in, the randomized treatment phase, and safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, parallel-group and placebo-controlled design. This is a well-established design to evaluate the efficacy, safety, PK and PD profiles of an investigational drug. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which changes in the level of asthma control were induced by medication withdrawal [Bel, 2014; Wenzel, 2013; Nair, 2009]. This design may not reflect real world fluctuations in asthma control, however studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on changes in asthma control in a relatively short period of time, before further investigations are conducted in longer term studies.

In this study, the target population would be participants with moderately severe asthma and with an ACQ5 score ≥1 and <4 whose symptoms must have been managed on a stable, high dose ICS/LABA for at least 4 months prior to Screening. The use of loss of asthma control as a composite study endpoint and a criterion for ICS titration allows for the overall clinical evaluation of the participant's asthma status taking into account both lung function and symptom control. Participants will also be monitored through the use of the eDiary. Pre-specified asthma symptom scores and participant-measured PEF that is inputted into the eDiary will be used as prompts for contacts between subjects and investigators (Section 9.1.2.3).

The FP titration period will occur during the Treatment Period of the study. The FP dose reduction will be assessed and managed at scheduled clinic visits. During the FP titration period the subjects' FP dose will be reduced as described in Section 5.1 and the SoA, unless the subject meets protocol defined criteria for loss of asthma control indicating that it is not acceptable for the participant to further reduce ICS. Prior to each FP dose reduction an assessment of the participants' asthma control should be completed and the decision to reduce the dose of FP will be based on: 1) the presence and severity of exacerbations, 2) changes in FEV1, 3) changes in the most recent ACQ-5 score, or 4) the ability to titrate ICS as per the pre-defined schedule, according to the investigator's clinical judgment. If loss of asthma control is confirmed during the FP titration period, the participant will discontinue IP immediately and should resume regular treatment for their asthma, as determined by the investigator. A similar methodology was recently reported [Wenzel, 2013] and successfully allowed titration of ICS.

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.

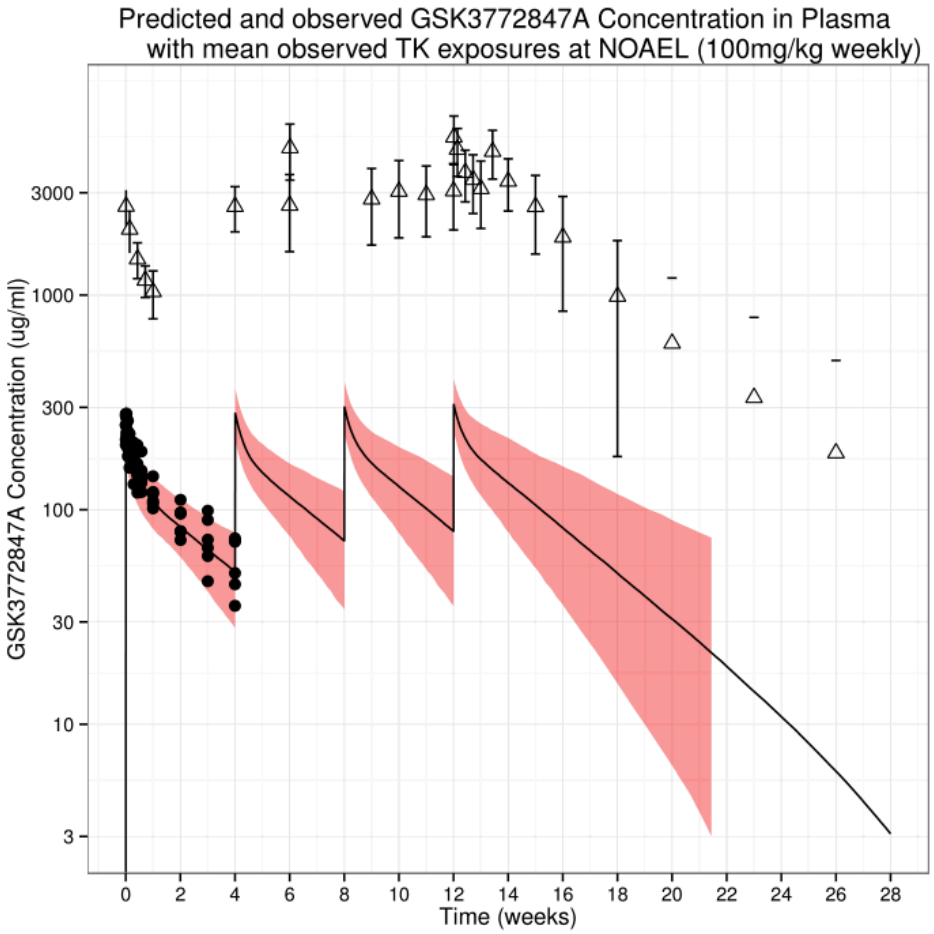
An inhaled short acting $beta_2$–receptor agonist, salbutamol/albuterol will be provided to all participants to use as needed to relieve asthma symptoms from Screening (Visit 1) to end of the Treatment Period. Both safety and efficacy parameters will be assessed regularly in the clinic to minimise any 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

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.

Table 1 Predicted clinical exposures and safety margins for study 207597 following dosing of 10 mg/kg at weeks 0, 4, 8 and 12.

Day 1 mean C_{max} (µg/mL)	Exposure margin[a]	Week 12 mean C_{max} (µg/mL)	Exposure margin[a]	0-28 weeks AUC (µg.day/mL)	Exposure margin[b]
245.3[c]	10.5	313.5[d]	17.4	16830.2[d]	18.2

a. Margins calculated against mean maximum serum concentration (C_{max}) on day 1 and day 84 (last dose) in study T-2013-007 (2592.55 and 5444.07 µg/mL respectively).
b. Margins calculated based on AUC (0-92 (13 weeks)) estimated using compartmental modelling of mean exposures in study T-2013-007.
c. Mean observed exposures in study CNTO7160ASH1001.
d. Predicted exposures using preliminary MM model

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. **Age:** At least 18 years of age at the time of signing the informed consent.
2. **Gender**: Males and females.
   A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   - Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

   i. OR
   - A WOCBP who agrees to follow one of the options listed in Appendix 5 from **4 weeks** prior to the first dose of study medication and until at least 16 weeks after the last dose of study medication and completion of the follow-up visit.
3. **Informed consent**: Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
4. **Asthma diagnosis and severity**: A participant with a documented diagnosis of moderate-severe asthma based on Global Initiative for Asthma (GINA) 2016 Guidelines, whose asthma has been managed with regular treatment of high dose ICS defined as fluticasone propionate 500 mcg twice daily (i.e. 1000 mcg total daily dose) or equivalent, and long-acting beta-2-agonist (LABA) for at least 4 months. Additional therapy with a leukotriene receptor antagonist (LTRA) is permissible.
5. **Reversibility:** Airway reversibility of at least 12 % and 200 mL in FEV1 at Screening (Visit 1), or documented reversibility prior to Screening (Visit 1), or

documented history of bronchial hyperreactivity (e.g. fall in FEV1 from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge) from a bronchoprovocation study (e.g. methacholine challenge) prior to Screening (Visit 1).

Note: If the participant does not meet the above reversibility criteria at Screening (Visit 1) then the reversibility assessment may be repeated once within 7 days of Visit 1. Should the participant successfully demonstrate airway reversibility at the second attempt then, provided that all other eligibility criteria assessed at Screening (Visit 1) are met, the participant may enter the 2-week run-in period.

6. **Asthma Control Questionnaire (ACQ):** ACQ-5 score ≥1 and <4 at Screening (Visit 1).
7. **Exacerbation history**: Had at least one asthma exacerbation within 12 months prior to Screening that required treatment with systemic corticosteroid and/or hospitalization.
8. **Short-Acting Beta2-Agonists**: All subjects must be able to replace their current SABA treatment with albuterol/salbutamol aerosol inhaler at Visit 1 for use as needed, per product label, for the duration of the study.

6.2. Exclusion Criteria

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

1. **Smoking history**: Current smokers or former smokers with a smoking history ≥10 pack years.
2. **Concurrent respiratory diseases**: Presence of a known pre-existing, clinically important respiratory conditions (e.g. pneumonia, pneumothorax, atelectasis-segmental or larger, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other respiratory abnormalities) other than asthma.
3. **Severe airflow obstruction**: A pre-bronchodilator FEV1 <50 % predicted of normal value at Screening (Visit 1). Predicted values will be based upon Global Lung Function Initiative (GLI) [Quanjer, 2012] equations for spirometry reference values.

   Note: If the spirometry is deemed technically inadequate by the central reader, the spirometry assessment may be repeated once within 7 days of Screening (Visit 1).
4. **Malignancy:** Participants with a diagnosis of malignancy or in the process of investigation for a malignancy. Participants with carcinoma that have not been in complete remission for at least 5 years. Participants who have had carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the patient has been considered cured by treatment.
5. **Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result** at Screening (Visit 1) or within 3 months prior to first dose of study treatment.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C Ribonucleic acid (RNA) test is obtained.

6. **12-lead ECG assessment at Screening (Visit 1):** Site investigators will be provided with ECG over-read conducted by a centralized independent cardiologist, to assist in evaluation of subject eligibility. For this study, an abnormal and clinically significant ECG that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the findings in Table 2:

Table 2 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)

7. **Weight**: <50 kg and >150 kg

8. **Regular use of systemic corticosteroids** for conditions including asthma within 3 months prior to Screening (Visit 1).
9. **Participants with high parasympathetic tone** (e.g. trained athletes with baseline bradycardia) or chronic conditions associated with parasympathetic surges (e.g. migraines)
10. **Eosinophilic diseases**: Other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes. Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening (Visit 1).
11. **Cardiovascular disease**: Clinically significant organic heart disease (e.g. CAD, NYHA Class III/IV heart failure).
12. **Ongoing infections** (i.e. not resolved within 7 days prior to Screening [Visit 1]) or recurrent infections (i.e. requiring treatment for an identical diagnosis within 3 months) requiring systemic antibiotics. Known, pre-existing parasitic infestations within 6 months prior to Screening.
13. **Other Concurrent Diseases/Abnormalities:** A subject must not have any clinically significant, uncontrolled condition, or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study.

    The list of additional excluded conditions/diseases includes, but is not limited to, the following:

Addison's disease	hypertension[1] (uncontrolled)
aortic aneurysm (clinically significant)	peptic ulcer (recent or poorly controlled)
Cushing's disease	renal disease
diabetes mellitus (uncontrolled)	stroke within 3 months of Visit 1
hematological disease	thyroid disorder (uncontrolled)
hepatic disease	tuberculosis (current or untreated[2])

1. Two or more measurements with systolic pressure >160mmHg or diastolic pressure >100mmHg
2. Subjects with a history of tuberculosis infection who have completed an appropriate course of antituberculosis treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease.

14. **Immunodeficiency**: A known immunodeficiency such as human immunodeficiency virus infection.
15. **Hypersensitivity**: Participants with allergy or intolerance to a monoclonal antibody or biologic or to any components of the formulation used in this study.
16. **Alcohol and Substance abuse**: Participants with a history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Screening (Visit 1).
17. **Participants at risk of non-compliance, or unable to comply with the study procedures**. Participants who are unable to follow study instructions such as visit schedule, dosing directions, study eDiary completion, or use of a standard metered dose inhaler. Participants who have known evidence of lack of adherence to controller medication and/or ability to follow physician's recommendations. Any

infirmity, disability, or geographic location that would limit compliance for scheduled visits.

18. **Participants who have previously participated in a study of GSK3772847**.

19. **Excluded Medications**: Use of the medications listed in Table 3 is not permitted within the defined time intervals prior to Screening (Visit 1) and throughout the study. Potential participants should not be washed out of their medication solely for the purpose on enrolling in the trial.

Table 3 Prohibited Medications

Medication	Time interval prior to Visit 1
Investigational drug	One month or 5 half-lives whichever is longer
Live or attenuated vaccines[a]	2 weeks (i.e. 4 weeks prior to IP administration)
Biologics, for example Mepolizumab and Omalizumab	130 days or 5 half-lives whichever is longer
Experimental anti-inflammatory drugs (non-biologics)	3 months
Corticosteroids intramuscular, long acting depot Regular systemic corticosteroid - oral, parenteral, depot	3 months
Methotrexate, troleandomycin, oral gold, cyclosporin, azathioprine,	3 months
Theophylline	3 months
Chemotherapy and radiotherapy	12 months
Inhaled anti-cholinergics e.g. tiotropium	1 week

a. Vaccines containing killed bacteria or inactivated virus will be permitted

20. **Affiliation with Investigator Site**: A participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.

21. **Inability to read**: In the opinion of the investigator, any participant who is unable to read and/or would not be able to complete a diary card/questionnaire.

22. **Questionable validity of consent**: Participants with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

6.3. Randomization Inclusion Criteria

At the end of the Run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

1. **Asthma Control Questionnaire (ACQ):** ACQ-5 score ≥1 and <4 at Visit 2.

2. **eDiary Compliance:** Compliance with completion of the eDiary reporting defined as completion of all questions/assessments on ≥4 of the last 7 days during the run-in period.

6.4. Randomization Exclusion Criteria

Participants meeting any of the following criteria **must not** be randomized to double-blind study medication at Visit 2:

1. **Clinically significant and abnormal laboratory finding at Screening (Visit 1):** Evidence of clinically significant abnormal laboratory tests during screening which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality.

2. **12-lead ECG over-read**: Evidence of clinically significant abnormal ECG findings (Table 2) at Screening (Visit 1).

3. **24-Hour Holter Monitoring**: An abnormal and significant finding from 24-hour Holter monitoring at Screening (Visit 1). Investigators will be provided with Holter reviews conducted by an independent cardiologist to assist in evaluation of subject eligibility. Specific findings that preclude subject eligibility are listed in Table 2. The study investigator will determine the medical significance of any Holter abnormalities not listed in Table 2.

4. **Liver function** at Screening (Visit 1)

   - ALT >2x upper limit of normal (ULN) and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35 %).
   - Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones.

5. **Asthma exacerbation:** Participants with ongoing asthma exacerbation at the time of Visit 2.

   Note: At the Investigator's discretion, participants with an ongoing asthma exacerbation at Visit 2 may be re-screened ≥2 weeks after Visit 2. In such cases, the full screening process (i.e. all Visit 0, 1 and Visit 2 assessments) must be repeated.

6. **Severe airflow obstruction:** a pre-bronchodilator FEV1 <50 % predicted of normal value at Visit 2. Predicted values will be based upon GLI [Quanjer, 2012] equations for spirometry reference values.

7. **Positive pregnancy test** at Visit 0, Screening (Visit 1) or Visit 2.

8. **Ongoing or recurrent infections** requiring systemic antibiotics.

6.5. Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.6. Pre-Screening/Screening/Run-in/Randomization Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the eCRF for participants who are pre-screen failures:

- Demographic information including race, age and gender
- Participant number
- Serious Adverse Event information only for any SAE considered as related to study participation

For the purposes of this study, pre-screening failures, screening failures, run-in failures and randomization failures will be defined as follows:

- **Pre-screening failures:** those participants that sign the informed consent document but do not have a Screening (Visit 1) procedure.
- **Screening failures:** those participants that complete at least one Screening (Visit 1) procedure but do not enter the run-in period.

  A participant who completes Visit 1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.
- **Run-in failures:** those participants that enter the run-in period but do not have any Visit 2 procedures.
- **Randomization failures:** those participants that complete at least one Visit 2 procedure but do not enter the double-blind study treatment period.

Any participant who completes the run-in period and then meets the randomization criteria and receives the double-blind study treatment at Visit 2 is considered to have entered the treatment period.

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).

Rescreening is only allowed in exceptional circumstances of technical errors and with prior approval from the GSK study team. Participants who are excluded due to an ongoing asthma exacerbation at Visit 2 (Randomization exclusion criterion 5) may be rescreened ≥2 weeks after Visit 2, at the investigators discretion. Rescreened participants will be assigned a new participant number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK3772847	Placebo	Fluticasone Propionate/Salmeterol	Fluticasone Propionate
Dosage formulation:	50mg/mL GSK377284, 15 mM Sodium Phosphate, 8.5% [w/v] Sucrose, and 0.04% [w/v] Polysorbate 20, pH 7.3.		DISKUS– 60 doses per device	DISKUS– 60 doses per device
Unit dose strength(s)/Dosage level(s):	10 mg/kg	Commercially sourced sterile normal saline	500/50 mcg per actuation	500, 250, 100 and 50 mcg per actuation
Route of Administration	IV infusion	IV infusion	Inhaled	Inhaled
Dosing instructions:	GSK3772847 for injection will require further reconstitution and dilution at the study site prior to administration: dilution between 10 and 30 mg/mL may be accomplished by using commercially sourced sterile normal saline		Twice daily; once in the morning and once in the evening	Twice daily; once in the morning and once in the evening

Study Treatment Name:	GSK3772847	Placebo	Fluticasone Propionate/Salmeterol	Fluticasone Propionate
Packaging and Labeling	Study Treatment will be provided as 100mg/vial, white to yellow, uniform lyophilized cake in a 5ml clear glass vial with 20mm closure sealed by red metal and yellow overseal. Each container will be labeled as required per country requirement.	Commercially sourced sterile normal saline will be sourced by the site	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip) Each container will be labeled as required per country requirement.	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip) Each container will be labeled as required per country requirement.

7.1.1. Description of Albuterol/Salbutamol

Albuterol/salbutamol via metered-dose inhaler (MDI) will be issued for reversibility testing at Screening (Visit 1). An albuterol/salbutamol MDI for as needed (prn) use throughout the study will be dispensed starting at Visit 1; at the Investigator's discretion, more than one MDI may be dispensed at any one time. Albuterol/salbutamol will be sourced from local commercial stock. The contents of the label will be in accordance with all applicable regulatory requirements.

7.1.2. DISKUS Return

DISKUS inhalers containing FP/Salmeterol and FP will be dispensed to a participant during their visit to the study clinic (as applicable). The participant must return all dispensed inhalers at the subsequent clinic visit. The schedule for dispensing and collecting FP/Sal and FP is provided in the SoA (Section 2).

All used and unused FP/Sal, FP will be returned to GSK at the end of the study to be available for disposal. In some instances, for sites outside the United States (US), study supplies will be disposed of locally either by the site, the country medical department or third-party vendor. Detailed instructions for the return of the study drug can be found in the Study Reference Manual (SRM).

If any DISKUS inhaler fails to function properly, the participant should return to the clinic as soon as possible to obtain a new inhaler. The site will use the Interactive Web Response System (IWRS) (RAMOS NG) to obtain a new treatment pack number for the participant and dispense a new study treatment kit from the site's study treatment supply as instructed by the IWRS. Details of the failure will be documented in the eCRF. Additional information on how to handle medical device incidents can be found in the SRM.

7.2. Dose Modification

There are no dose modifications planned for this protocol.

7.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the randomization schedule. The randomization code will be generated by GSK using a validated computerized system. Participants will be randomized using an interactive web response system (IWRS) RAMOS NG. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 2-week Run-in period and subject to satisfying all eligibility criteria, participants will be randomized 1:1 to one of the following double-blind treatments for the duration of the Treatment Period:

- GSK3772847 (10 mg/kg) administered intravenously
- Placebo administered intravenously

The duration of the Treatment Period for each participant is 16 weeks. Each Investigator will be provided with sufficient supplies to conduct the trial. Additional treatment kits will be supplied as needed to the sites. Details of how to use the IWRS system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG manual and SRM.

7.4. Blinding

This will be a double-blind study and the following will 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.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.

- 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.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

GSK3772847 a white to yellow, uniform lyophilized cake in a 5ml clear glass vial with 20mm closure sealed by red metal and yellow overseal. Each vial contains 100 mg of a lyophilised GSK3772847. When reconstituted with 2.0 mL of WFI, the final concentration of GSK3772847 is 50 mg/mL. Excipients include: sucrose, sodium phosphate buffer, and polysorbate 20 at a pH of 7.3. Vials contain no preservatives and thus are for single use. Vials must be stored 2º – 8°C, protected from light. Protection from light during preparation and administration is not required. Full details on specific 2º to 8°C storage temperature conditions, preparation and administration including requirements for filtration are provided separately.

Commercially available sterile normal saline will be used for dilution of study agent and will also serve as placebo for this study. Use of study agent sterile normal saline as placebo for injection provides an adequate comparator to broadly assess safety in early clinical development.

GSK3772847 must be prepared by an unblinded pharmacist or other appropriately licensed and authorized personnel and administered according to each participant's body weight at Screening (Visit 1). A different site staff member, who will be blinded to the treatment assignment, will administer the study agent. Aseptic procedures must be used during preparation and administration of the study agent. Diluted GSK3772847 at volumes of 50 mL are to be administered by IV infusion over a period of at least 30 minutes using an in-line 0.22 micron filter. At least 30 mL of commercially available sterile normal saline will be used to flush diluted drug from the administration set to ensure full study agent administration.

Unblinded site staff will be responsible for receipt, storage, reconstitution, 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.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual or unblinded site staff reference manual.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.6. Treatment Compliance

- FP/Sal and FP during the run-in and treatment periods will be self-administered at home; compliance will be assessed via dose counter during the site visits and documented in the source documents and eCRF. A record of the number of doses on the DISKUS inhaler will be recorded in the eCRF. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

- The double blind IP will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the eCRF.

7.7. Concomitant Therapy

All asthma medications used within approximately 12 weeks prior to screening and during the study (including the post-treatment period) should be recorded in the eCRF.

All non-asthma medications taken during the study (after randomization including post-treatment) and any changes to concomitant medications will be recorded in the eCRF. *Note: Study provided FP/Sal, FP, and albuterol/salbutamol should not be recorded in the ConMeds page of the eCRF.*

The minimum requirement is that the drug name, reason for use, dose (including unit e.g. mcg) and frequency, route and the dates of administration are to be recorded.

7.7.1. Permitted Non-asthma Medications

The following medications are permitted during the study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal] but they are disallowed 48 hours prior to ECG measurements, cromolyn, nedocromil, nasal decongestants)
- Antibiotics for short term treatment of acute infections. Long term treatment with topical or ophthalmic antibiotics are permitted.
- Decongestants: Participants may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.
- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and participants remain in the maintenance phase for the duration of the study.
- Topical and ophthalmic corticosteroids.

7.7.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed below is not permitted during the study:

- Inhaled anti-cholinergics (e.g.tiotropium).
- ICS/LABA other than the study-provided FP/Sal.
- Inhaled Corticosteroids other than the study-provided FP.
- LABA other than the salmeterol component in the study-provided FP/Sal.
- Biologics, e.g. Mepolizumab and Omalizumab.
- Potent CYP3A4 inhibitors, (e.g., ritonavir, ketoconazole, etc.)
- Anticonvulsants (barbiturates, hydantoins, and carbamazepine).
- Polycyclic antidepressants.
- Beta-adrenergic blocking agents.
- Phenothiazines.

- Monoamine oxidase (MAO) inhibitors.
- Live or attenuated vaccines (and up to 6 months after the last dose of blinded study treatment).
- Experimental anti-inflammatory drugs (non-biologics).
- Corticosteroids intramuscular, long acting depot, regular systemic (oral, parenteral, depot) corticosteroid.
- Methotrexate, troleandomycin, oral gold, cyclosporin, azathioprine.
- Theophylline.
- Chemotherapy and radiotherapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study or withdrawal of IP because other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

Participants who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up until the completion of the Safety Follow-up 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.

If this is not possible, the Investigator must encourage the participant to participate in as much of the study as they are willing (or able) to.

A participant may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy [including loss of asthma control], protocol deviation, Investigator discretion, consent withdrawn etc.) must be captured in the eCRF.

A participant must be withdrawn from study treatment if any of the following stopping criteria are met:

1. Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria.
2. QTc: Meets any of the protocol-defined stopping criteria.
3. Pregnancy: Positive pregnancy test.
4. Participant meets at least one of the following criteria for 'loss of asthma control':
   - ACQ-5 score increase from baseline (measured at Visit 2) ≥0.5 point.
   - Pre-bronchodilator FEV1 decrease from baseline (measured at Visit 2) >7.5 %.
   - Inability to continue inhaled corticosteroid titration which is assessed and determined by the investigator at any time point following randomization, including on scheduled clinic visits.
   - A clinically significant asthma exacerbation (requiring OCS and/or hospitalization).
5. Study treatment unblinded.

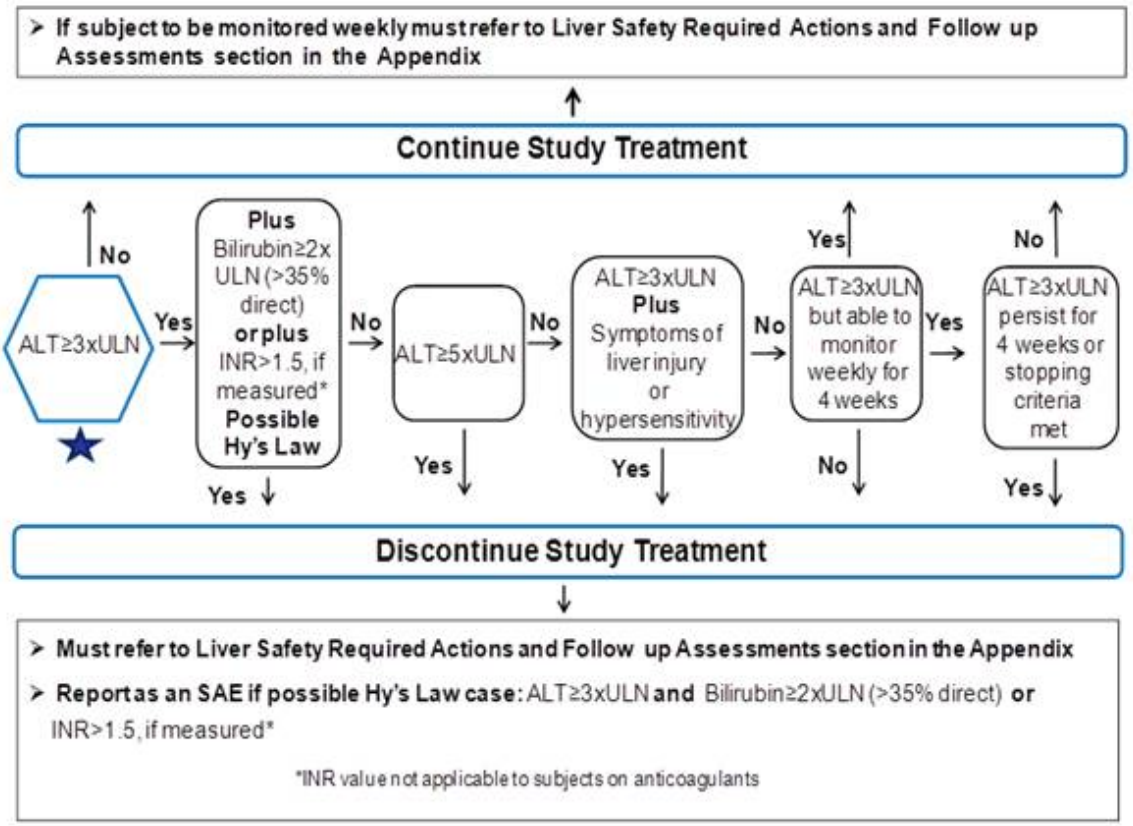
   Note: In the event of unblinding the Medical monitor/GSK team should be contacted to determine whether subject withdrawal is required.
6. Abnormal Holter of Mobitz II AVB, complete AVB, sustained or non-sustained ventricular tachycardia (VT), paroxysmal supraventricular tachycardia (PSVT), new onset atrial fibrillation/flutter will be a withdrawal/stopping criterion. These findings on ECG (baseline, V4, V6) or findings of myocardial ischemia will also result in withdrawal/stopping.
7. Hypersensitivity or anaphylactic reaction

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



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

8.1.2. QTc Stopping Criteria

- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

- Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
- Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec.

See the SoA for data to be collected at the time of early withdrawal (EW visit) and follow-up and for any further evaluations that need to be completed.

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed. Additionally, if hypersensitivity or anaphylactic reaction occurs, infusion should be discontinued and study restart is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.

  Note: In order to achieve the stratification balance, as a result of participants' eosinophil count it may be necessary to withdraw participants from the study during the Run-in period.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of early withdrawal (EW visit) and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

No study related procedures may be performed until the informed consent form has been signed by the participant. Selection and modification of the participant's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each participant's needs. A participant's treatment must not be changed merely for the purpose of enabling the participant's participation in the study.

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in SoA.

9.1.1. Questionnaires

9.1.1.1. Asthma Control Questionnaire ACQ-5

The ACQ-5 measures attributes of asthma control [Juniper, 1999], measured with questions designed to be self-completed by the participant. Participants will complete the ACQ-5 with the use of an e-Diary device on a weekly basis. The ACQ-5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of

symptoms over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall 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 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 and transmit the data to the centralised server as soon as possible 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 daytime 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.

If any of the alert criteria are met, email notifications will be sent to the investigator as soon as the data is transmitted to the centralized server. The investigator will make every effort to contact the participants in order to discuss the participants' symptoms and evaluate whether they experienced loss of asthma control.

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 instructions on performing the spirometry manoeuvres are documented in the SRM and the third-party vendor manual.

9.1.3.1. Spirometry

Spirometry will be performed to assess FEV1 and FVC. At least 3 spirometry manoeuvres (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed. For spirometry data collected at Screening (Visits 1), the best spirometry effort will be selected from a measurement that meets American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines and has a minimum of 2 efforts which are considered valid and repeatable, in accordance with the ATS/ERS standards [Miller, 2005]. Measurements with 3 valid but non-repeatable efforts will not be accepted. For spirometry data collected during the Treatment Period (Visits 2 – 11, including EW visit), the best spirometry effort will be selected from a measurement that meets ATS/ERS guidelines and has a minimum of 2 efforts which are considered valid (not necessarily repeatable). As always, sites should continue to strive to collect at least 3 valid (with no more than 8) efforts, as per ATS/ERS guidelines. At each visit, spirometry assessments must be performed at the same time of day (± 2 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) prior to the clinic visit, if possible.

9.1.3.2. Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ ERS Task force: Standardization of Lung Function Testing [Miller, 2005]. A baseline spirometry assessment should be performed after a washout period of at least 6 hours for short-acting β_2- agonists and 1 dosing interval for long-acting β_2-agonists (or fixed dose combinations of LABA and ICS).

To perform the reversibility assessment, 4 puffs of the provided salbutamol/albuterol is administered following completion of the baseline assessment. A spacer device may be used for testing, if required. A second spirometry assessment is performed within 10 to 15 minutes after administration of the salbutamol/albuterol.

Reversibility assessment at Screening (Visit 1) is not required if there is documented reversibility prior to Screening (Visit 1), or documented history of bronchial hyperreactivity from a bronchoprovocation study (e.g. methacholine challenge) prior to Screening (Visit 1).

9.1.4. Fractional Exhaled Nitric Oxide (FeNO)

FeNO will be measured using a handheld electronic device. Measurements will be obtained in accordance with the ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide [Miller, 2005]. All sites will use standardized equipment provided by a central vendor. For each observation, at least 2 measurements will be obtained to establish reproducibility (up to 8 measurements can be performed). FeNO measurements will be interpreted in accordance with the Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications [Dweik, 2011]. FeNO observations must be completed before FEV1 assessments. Participants should not use their rescue medication for at least 6 hours before each FeNO assessment, unless essential for clinical need. Participants should also withhold LABAs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) before each FeNO assessment.

9.1.5. Review of Loss of Asthma Control

Loss of asthma control is defined as at least one of the following:

- ACQ-5 score increase from baseline (measured at the end of Run-in) ≥0.5 point) or
- Pre-bronchodilator 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
- A clinically significant asthma exacerbation (requiring OCS and/or hospitalisation.

At each clinic visit, the Investigator will utilize clinical discretion and available objective evidence (including but not limited to eDiary data, spirometry data, the most recent ACQ5 scores, history of exacerbations, conmeds, AEs) to determine if the patient is experiencing loss of asthma control. The paper Medical Problems/Medications Taken worksheet must also be reviewed by the Investigator (or appropriately trained designee) at each visit to the study site to assist the Investigator in the identification of loss of asthma control. It is expected that the Investigator will indicate which criterion (criteria) the subject met that constituted loss of asthma control.

9.2. Adverse Events

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

Asthma exacerbations or worsening of asthma should not be recorded as an AE, unless they meet the definition of an SAE. For the purposes of this study, asthma exacerbations will be collected and recorded on the exacerbations log in the eCRF. The treatment details must also be recorded in the eCRF. The time period for collection of asthma exacerbations will begin from screening and will end after the follow-up period has been completed.

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

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

- All SAEs will be collected from the Visit 2 until the last follow-up visit at the time points specified in the SoA (Section 2). At Visits 0 and 1 SAE information will be collected only for any SAEs considered as related to study participation.
- All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting 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.
- 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.
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 and before other clinical tests such as blood draws and pulmonary function tests. 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. Participants should be reminded to avoid caffeine or caffeinated drinks for at least 8 hours before each 12-lead ECG assessment. Also, decongestants are disallowed for at least 24 hours and antihistamines for at least 48 hours before each 12-lead ECG assessment.

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.

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

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 eligible for randomisation at Visit 2 will be entered into the Sputum sub-study. In a subset of approximately 50% of eligible participants, sputum samples will be collected as specified in the SoA. The participants in the Sputum Sub-Study will be randomised equally in the two treatment groups.

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.

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

Population	Description
(ITT)	received.
Safety	This population will be the same as the Modified Intent-to-treat population.
PK	All randomized subjects who received at least one dose of study medication, and for whom at least one pharmacokinetic sample was obtained, analyzed and was measurable.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint proportion of subjects with loss of asthma control will be analyzed using both Bayesian and Frequentist methods. A subject is deemed to have met the endpoint of loss of asthma control if they meet the criteria for any of the components of the definition of loss of asthma control. The posterior probabilities 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) will be calculated analytically assuming a non-informative prior. This will be supported by an estimate of the ratio with a 95% credible interval. Results will also be presented for the two eosinophils strata separately. In addition, the proportion of participants with loss of asthma control will be analyzed using logistic regression allowing for baseline eosinophils strata. The odds ratio, 95% CI and p-value for the comparison of GSK3772847 with placebo will be presented. Results will also be presented for the two eosinophils strata separately by fitting a separate model with an additional term for eosinophil strata by treatment interaction. The effect of eosinophils as a continuous covariate will also be examined in a separate-logistic regression model. Missing data will be handled using the following methods: 1) The loss of asthma control will be set to missing for participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control 2) A sensitivity analysis will be performed where participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control will have the endpoint set to loss of control

Endpoint	Statistical Analysis Methods
Secondary	The following secondary endpoints will be analyzed using the same statistical analysis as described for the primary endpoint: • Proportion of participants with a clinically significant asthma exacerbation (requiring OCS and/or hospitalisation) • Proportion of participants with Pre-bronchodilator FEV1 decrease from Baseline (measured at the end of Run-in) >7.5 % • Proportion of participants with Inability to titrate inhaled corticosteroid according to the pre-defined schedule (Section 5.1) • Proportion of participants with ACQ-5 score increase from Baseline (measured at the end of Run-in) ≥0.5 point. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule. In these analyses, the endpoint will be set to missing for participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control. Time to loss of asthma control will be analyzed using Kaplan-Meier analysis. Percentiles for time to loss of control will be presented for both treatment groups, along with graphical survival plots. Any early withdrawals from IP that did not experience loss of control will be censored. Results will be presented for both of the two eosinophil strata separately, and combined. The following endpoints will be analyzed using repeated logistic regression. This analysis will be repeated including an additional term for eosinophil strata by treatment by visit interaction to provide estimates for the two eosinophil strata separately: • Proportion of ACQ-5 responders (a ≥0.5 point improvement from baseline at Week 16) • Proportion of SGRQ responders (at least a 4 unit improvement from baseline at Week 16 These analyzes will be performed using two different methods for handling missing data: 1) If endpoint at a visit is missing then the responder status is set to missing 2) If endpoint at a visit is missing and the endpoint is also missing at all subsequent visits then the responder status is set to non-responder The odds ratio, 95% CI and p-value for the comparison of GSK3772847 with placebo will be presented for all models. Mixed model repeated measures will be used to analyze the following endpoints. The baseline value of each endpoint will be included along with baseline*visit and treatment*visit interactions. Treatment differences, 95% confidence intervals and p-values will be presented. • Change from baseline in ACQ-5 absolute score • Change from baseline in SGRQ total score

Endpoint	Statistical Analysis Methods
	• Change from baseline in Pre-bronchodilator FEV1 • Change from baseline in FeNO This analysis will be repeated including an additional term for eosinophil strata by treatment by visit interaction to provide estimates for each eosinophil strata separately. No adjustment will be made for missing data. Further information on how the following endpoints will be analyzed will be described in the report and analysis plan: • Hospitalisation or ER visit during the study treatment period • Morning and evening PEF • Daily asthma symptom score • Rescue medication use (albuterol/salbutamol): number of occasions per day • Night-time awakenings due to asthma symptoms requiring rescue medication Any changes to the planned analysis methods will be documented in the reporting and analysis plan. Details of subgroup analyses for the primary and secondary endpoints will be described in the reporting and analysis plan.
Exploratory	Will be described in the reporting and analysis plan

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary safety analysis.
Secondary	The following secondary safety endpoints will be analyzed descriptively by treatment group: • Incidence and frequency of AEs and SAEs • Vital signs • 12-lead ECG • 24 hours Holter • Clinical laboratory evaluation • Incidence of and titres of anti-GSK3772847 antibodies. Details will be described in the reporting and analysis plan

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.

10.4.3. Pharmacokinetic Analyses

All safety analyzes will be performed on the PK Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary pharmacokinetic analysis.
Secondary	The serum GSK3772847 levels from this study will be summarised by treatment and nominal time. Further details will be described in the report and analysis plan.

10.4.4. Pharmacodynamic Analyses

All pharmacodynamic analysis will be described in reporting and analysis plan.

10.4.5. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analysis will be described in the reporting and analysis plan. Any population PK analysis and pharmacodynamic analysis will be reported separately from the main clinical study report (CSR). Should a genetic/PGx analysis be performed, a separate reporting and analysis plan will be generated (See Appendix 6: Genetics).

10.4.6. Interim Analyses

Formal analyses will be performed at two timepoints.

End of Treatment Phase Analysis:

This will take place after all participants have completed the Week 16 visit. The data will be cleaned, the treatments unblinded and all clinic visits up to and including week 16 frozen. However, whilst no further efficacy data will be collected post week 16, due to an inability to lock log forms used for collection of exacerbation data, the end of treatment phase analysis will be considered an interim analysis for both efficacy and safety. Any safety data collected for participants who have completed clinic visits after Week 16 will also be cleaned and included in the analysis.

There will be no modifications to dosing regimens, sample size or any other aspects of the trial based on this data, as all study assessments, apart from follow-up, will have

already been completed. As such an Independent Data Monitoring Committee (IDMC) will not be used, as no further investigational product will be prescribed after this analysis has taken place.

Final Analysis:

This will take place after all subjects have completed the study. Data for visits after Week 16 as well as data collected on log pages will be cleaned and the database frozen. This will be the final analysis for the study.

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

Instream review:

An 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 Charter.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BID	Twice a day
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
CI	Confidence Interval
CV	Cardiovascular
Cmax	maximum serum concentration
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Serum creatine phosphokinase
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
ER	Emergency Room
eDiary	Electronic Diary
ETP	End of Treatment Phase
ERS	European Respiratory Society
EW	Early Withdrawal
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced expiratory volume in 1 second
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyltransferase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GLP	Good laboratory practice
GSK	GlaxoSmithKline

HBsAg	hepatitis B surface antigen
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
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
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None

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory.
- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual and the SoA. Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference for all safety parameters will be provided to the site by the laboratory responsible for the assessments.
- All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.
- Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit White Cell Count RDW	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils These will be blinded from Visit 3 onwards.	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin

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		
Cardiac Markers	• Cardiac troponin I (cTn I) • N-terminal pro-brain natriuretic peptide (NT-proBNP)			
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.			

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

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

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

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 eCRF 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.

Study and Site Closure

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

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

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

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

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

Definition of AE

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

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

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

Definition of SAE

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the 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. • 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 eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

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

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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 or to the assigned SAE contact by telephone. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page

SAE Reporting to GSK via Paper eCRF
• Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the assigned SAE contact by telephone. • 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 eCRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 6.

Table 6 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed during the treatment period as specified in the Table of Events
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

- Pregnancy testing, with a sensitivity of 5, 10, 25 mIU/mL will be performed and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female Participants who become pregnant

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

Any female participant who becomes pregnant while participating will discontinue study treatment

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for Deoxyribonucleic acid (DNA) analysis
- DNA samples will be used for research related to GSK3772847 or asthma and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3772847 or other treatments which may regulate neutrophils and eosinophils or other study treatments including, but not limited to, steroids, long-acting beta-agonists, and other drugs used in the treatment of asthma, or for asthma and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
- DNA samples may be analyzed 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 analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3772847 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3772847 (or study treatments of this class) or asthma and related diseases continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • Obtain blood sample for pharmacokinetic (PK) analysis within 1 week after the liver event[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications

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	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
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

TITLE PAGE

Protocol Title: A randomized, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with severe asthma.

Protocol Number: 207597

Short Title: A study to evaluate the effect of GSK3772847 in patients with severe asthma.

Compound Number: GSK3772847

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with severe asthma.

Short Title: A study to evaluate the effect of GSK3772847 in patients with severe asthma.

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.

At the time of writing this protocol, a two-part, single and multiple ascending dose first time in human (FTIH) study has completed dosing (final clinical study report is pending).The safety information from this study is included in the investigator brochure. There are no efficacy data available to date.

The present study is the first GSK sponsored study with GSK3772847. It is a Phase IIa study to investigate efficacy, safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of GSK3772847 in participants with severe asthma. The study will use a steroid titration design in order to induce instability and evaluate whether GSK3772847 maintains protection of asthma control. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which exacerbations were induced by medication withdrawal. This design may not reflect real world exacerbations; however studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on exacerbations in a relatively short period of time, before further investigations are conducted in longer term studies.

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

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.

Overall Design:

This is a Phase IIa, multicenter, randomized, placebo-controlled, double-blind, stratified, parallel group study in participants with severe asthma.

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.

Number of Participants:

Approximately 300 participants with severe 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 investigational product (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 /day) or equivalent.

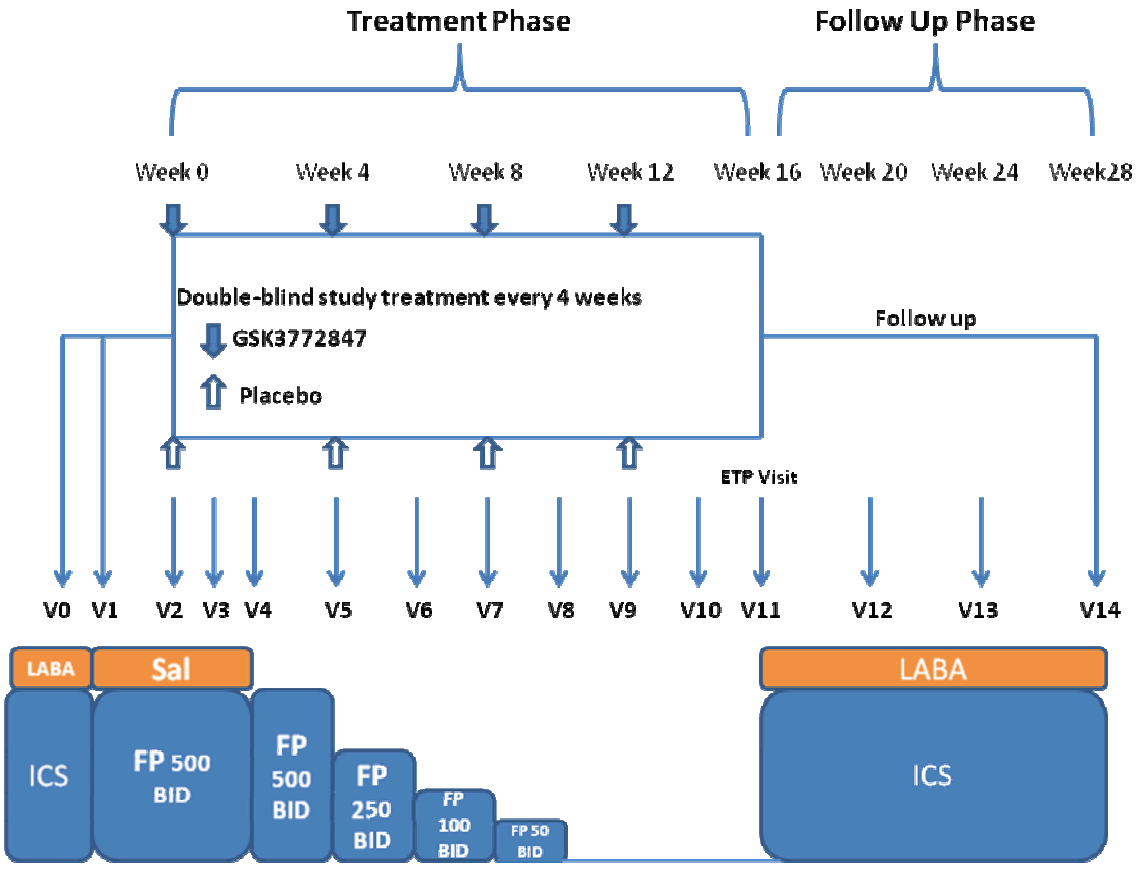
Treatment Groups and Duration:

When required, a pre-screening visit (Visit 0) can be scheduled for signing the informed consent, up to 2 weeks prior to Screening (Visit 1). The pre-screening visit can also occur on the same day as the Screening visit. Participants who meet the eligibility criteria at Screening (Visit 1) will withdraw their regular ICS/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 twice daily (BID). At the end of the Run-in period at Visit 2 (Week 0), participants who meet pre-defined randomization criteria will be randomized in a 1:1 ratio to enter a double-blind 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, two weeks after Randomization, the open label background therapy will be switched from FP/Sal 500/50 mcg BID to FP 500 mcg BID for 2 weeks. Visit 4 will be the beginning of a six week 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 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.

An End of Treatment Phase (ETP) Visit will be performed 4 weeks after the final dose of the blinded study treatment is administered at Week 12. 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. 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/EW Visit for safety assessments.



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 9). 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.

2. SCHEDULE OF ACTIVITIES (SOA)

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**				
Informed consent (ICF)	X															
Genetic ICF	X															
ICF for sputum			X													
Inclusion and exclusion criteria		X														
Demography	X															
Full physical exam including height and weight		X														
Medical history (includes substance usage)		X														Substances [Drugs, Alcohol, tobacco and caffeine] and family history of premature CV disease]): [including cardiovascular medical history]
Laboratory assessments		X[1]	X[1]	X	X[1]	X[1]	X	X[1]	X	X[1]	X	X[1]			X[1]	Haematology (including eosinophil count) measured at all clinic visits. 1. Include liver chemistries.

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.

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				

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**				
Review loss of asthma control criteria			X	X	X	X	X	X	X	X	X	X				It will include review of data to determine loss of asthma control. See Section 9.1.5.
Sputum sample collection			X					X				X				Pre-dose collection and in a sub-set of participants (~50 %) at selected sites; also collected for EW participants
PK, target engagement and immunogenicity assessments			X	X	X	X		X		X		X	X	X	X	See SoA Table 2 for details
FeNO			X	X	X	X	X	X	X	X	X	X				Test to be performed pre-dose
Exploratory Biomarkers			X					X				X				Pre dose collection
Dispense eDiary		X														
Collect eDiary												X				
Review eDiary			X	X	X	X	X	X	X	X	X	X				
Dispense paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X		
Review paper Medical Problems/Medications Taken worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	

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**				
Dispense albuterol (as needed)		X	X	X	X	X	X	X	X	X	X	X				
AE/SAE review	X[1]	X[1]	←==========									→	X	X	X	1. At V0 and V1 collect only SAEs considered as related to study participation.
Concomitant medication review	X	X	←==========									→	X	X	X	

SoA Table 2: Timings of PK, target engagement and immunogenicity samples

Procedure	Treatment Period (Visit window ± 3 days)										Follow-up[2] (± 3 days)			Notes
Visit	**2[1]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (ETP or EW)**	**12**	**13**	**14**	1. Visit 2 = Day 1 (first dose of IP). 2. FU period to start 4 weeks after ETP or EW visit.
Week	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	
Study Day	**1**	**8**	**15**	**29**	**43**	**49**	**71**	**85**	**99**	**113**				
Double blind Study Treatment (IP)	**X**			**X**		**X**		**X**						
PK sample	X[2]	X	X	X[3]		X[3]		X[1]		X	X	X	X	1. Pre dose and post dose. 2. Post dose only. 3. Pre dose only. Pre-dose samples within 2 hours from the planned dosing time. Post-dose samples as soon as possible after end of infusion but must be taken within 4 hours.
Free and total sST2	X[1]	X	X	X[3]		X[3]		X[1]		X	X	X	X	
Immunogenicity sample	X[3]		X	X[3]		X[3]		X[3]		X	X	X	X	

3. INTRODUCTION

3.1. Study Rationale

GSK3772847 is a human immunoglobulin G2 sigma isotype (IgG2σ) antibody that binds Domain 1 of the cell-surface receptor 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.

At the time of writing this protocol, a two-part, single and multiple ascending dose first time in human (FTIH) study has completed dosing (final report is pending). The safety information from this study is included in the investigator brochure. There are no efficacy data available to date.

The present study is the first GSK sponsored study with GSK3772847. It is a Phase IIa study to investigate efficacy, safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of GSK3772847 in participants with severe asthma. The study will use a steroid titration design in order to induce instability and evaluate whether GSK3772847 maintains protection of asthma control. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which exacerbations were induced by medication withdrawal [Bel, 2014; Wenzel, 2013; Nair, 2009]. This design may not reflect real world exacerbations; however studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on exacerbations in a relatively short period of time, before further investigations are conducted in longer term studies.

3.2. 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 [Chung, 2014; Aburuz, 2007; 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 signaling. 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].

In a 3-month good laboratory practice (GLP) toxicology study, GSK3772847 was administered to cynomolgus monkeys as a weekly 15-minute IV infusion (20 or 100 mg/kg) and was found to be well-tolerated at both doses.

Janssen (Study CNTO7160ASH1001) have conducted a Phase I randomized, double-blind, placebo-controlled, intravenous (IV) single ascending dose study in healthy participants and multiple ascending dose study in participants with asthma and participants with atopic dermatitis. The study has completed dosing. The final clinical study report is still pending. There are no efficacy data available to date.

More information about the non-clinical and clinical studies is available in the GSK3772847 Investigator's Brochure (IB).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks and reasonably expected adverse events of GSK3772847 may be found in the Investigator's Brochure.

3.3.1. 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 GLP 3 month IV repeat dose toxicity study at doses ≤100 mg/kg/week) or subcutaneous (SC) administration. 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 CNTO 7160ASH1001, several episodes of sinus tachycardia on telemetry was 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). 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	Exclude participants with existing clinically significant organic heart disease (e.g. Coronary artery disease [CAD], New York Heart Association (NYHA) Class III/IV heart failure) and abnormal, clinically significant findings from 12-lead ECG and 24-hour holter monitoring (Section 6.2 and Section 6.3). CV events will be monitored (including ECG and Holter monitoring) as specified in Section 2. All cardiac-related AEs will be reviewed by an independent safety review committee (iSRC). Protocol-defined stopping criteria are specified in Section 8.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	temperature. The event was considered by the investigator to be likely related to IP. 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. In Part 2 of the Janssen study CNTO 7160ASH1001, there were three reports of non-sustained ventricular tachycardia. Of these reports, one participant received placebo and two received GSK3772847 at 3 mg/kg. The events were non-symptomatic, and a monomorphic pattern (i.e., not Torsades de pointes), which is 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). Dosing was continued as planned, and the dose escalated to 10 mg/kg.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In Part 2, abnormal Holter findings of 2nd degree AV block were observed in two participants at 10 mg/kg. Following review, an independent electrophysiologist stated that these Holter findings were not evidence of "malignant conduction disease". The Janssen Safety Management team advised that one subject should not receive the final scheduled dose; the 2nd subject had received the final dose by the time of review by the Safety Management team. Following unblinding it was noted that one participant received GSK3772847 whilst the other participant had received placebo.	
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 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	**Preclinical**: 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 or IV 3 month toxicity at doses ≤100 mg/kg/week. **Clinical**: Safety data from Janssen study CNTO7160ASH1001 Single Ascending Dose (SAD) has shown the most frequent adverse	Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening are excluded from participation in the study (Section 6.2) Participants who develop an infection will be requested to seek medical advice, and subject to close monitoring. EU Regulatory guidance on development of asthma drugs request that agents that interact with the immune system should be investigated

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
number of clusters of differentiated CD90+ and cluster of differentiated CD25+ inate 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.	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).	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 and routinely as part of the post marketing pharmacovigilance process. Exclude patients with ongoing or recurrent infections. Close monitoring of infection AEs (including 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**: Not observed in studies to date. **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, q2W over four weeks).	If a hypersensitivity or anaphylactic reaction occurs, infusion should be discontinued immediately and appropriate therapy instituted. Agents to treat reactions should be available immediately. Stopping & continuation criteria will be included in protocols. Painkillers can be prescribed for pain at site of injection. Patients developing hypersensitivity, anaphylactic reactions or anaphylactic shock will be withdrawn from the study. All doses in this trial will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Based on in vitro cytokine release data and safety experience in Janssen study CNTO7160ASH1001 the risk of CRS is considered negligible.	administered in the clinic.
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 vaccine response 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. This data is indicative that healthy 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, q2W over four weeks).	In the study, subjects should not be vaccinated with live or attenuated vaccines within 4 weeks prior to receiving IP or during the study. However vaccines containing killed bacteria or inactivated virus will be permitted.

3.3.2. Benefit Assessment

Efficacy of GSK3772847 has not yet been demonstrated. Taking part in this study may or may not improve a participant's health, and may or may not directly benefit a participant. This study will provide additional safety and efficacy information on GSK3772847.

All study participants will receive open label salbutamol/albuterol to use as needed for asthma symptom relief from Screening to the end of the Treatment Period. Medical assessments are planned during the study to evaluate participants' health status. The assessments include physical examination, vital signs, electrocardiogram (ECG), Holter monitoring, and clinical laboratory evaluation including liver chemistry and blood chemistry panel at a number of clinic visits. Participants' health status will also be evaluated by ACQ-5 and SGRQ during the study. Participants' safety will also be assured by having criteria for withdrawal from study medication/reinstatement of usual care in case of loss of asthma control. The aim will be to retain participants in the study post withdrawal of study medication to follow-up for safety.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize the risk to the participants participating in the study, the overall benefit:risk is considered to be positive. There is an opportunity to determine if there is a new drug that can be developed for patients with severe asthma who may benefit from the broad spectrum effects hypothesized for GSK3772847.

4. 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	Other efficacy endpoints (at or by Week 16): • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or

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).

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

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:

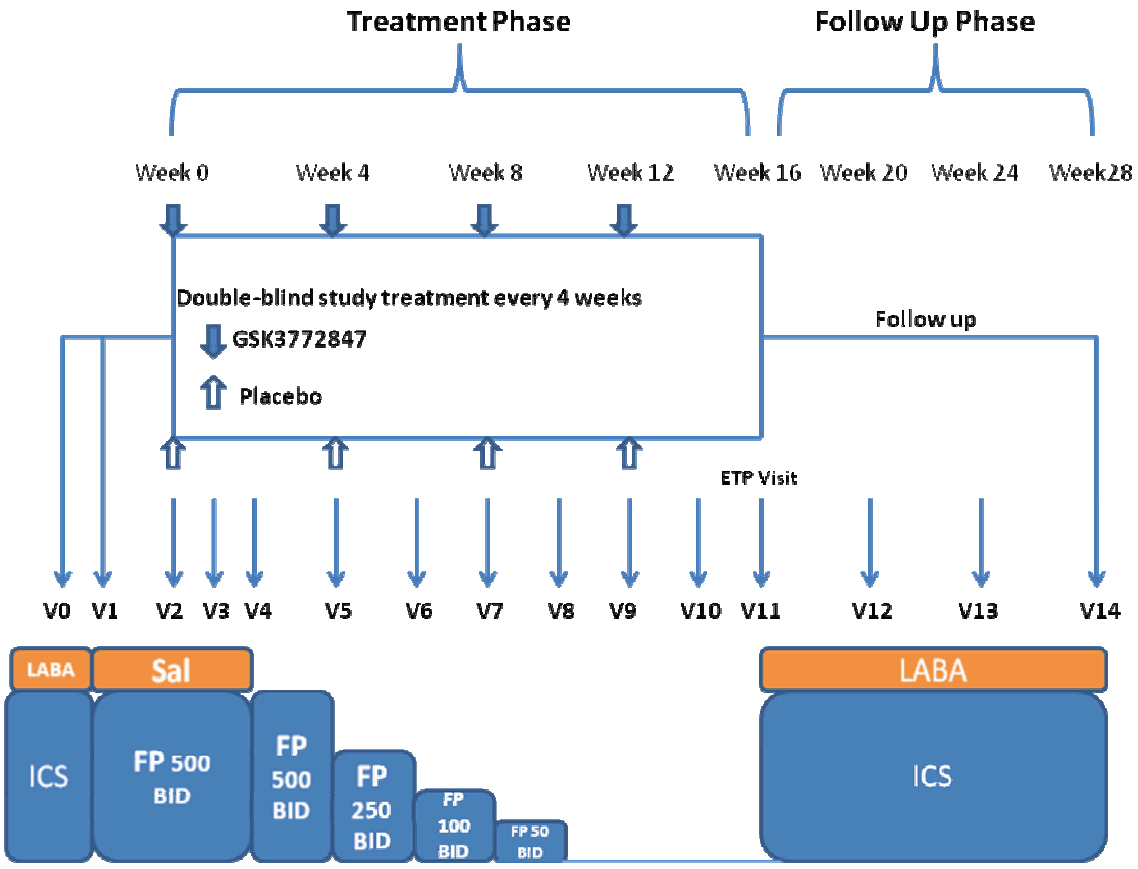
- GSK3772847 administered intravenously or
- Placebo administered intravenously

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.



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**.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including, screening, run-in, the randomized treatment phase, and safety follow-up.

Distinguish between the end of the study (EU definition) and study completion (US CT Registry definition: Final date on which data was or is expected to be collected) if they are not the same.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, parallel-group and placebo-controlled design. This is a well-established design to evaluate the efficacy, safety, PK and PD profiles of an investigational drug. The design of steroid titration (oral or inhaled) in participants with asthma has been used in various studies with different investigational products, in which exacerbations were induced by medication withdrawal [Bel, 2014; Wenzel, 2013; Nair, 2009]. This design may not reflect real world exacerbations, however studies with the design of steroid titration have shown the ability to assess effects of a potential treatment on exacerbations in a relatively short period of time, before further investigations are conducted in longer term studies.

In this study, the target population would be participants with severe asthma and with an ACQ5 ≥1.5 whose symptoms must have been managed on a stable, high dose ICS/LABA for at least 4 months prior to Screening. The use of loss of asthma control as a composite study endpoint and a criterion for ICS titration allows for the overall clinical evaluation of the participant's asthma status taking into account both lung function and symptom control. Participants will also be monitored through the use of the eDiary. Pre-specified asthma symptom scores and participant-measured PEF that is inputted into the eDiary will be used as prompts for contacts between subjects and investigators (Section 9.1.2.3).

The FP titration period will occur during the Treatment Period of the study. The FP dose reduction will be assessed and managed at scheduled clinic visits. During the FP titration period the subjects' FP dose will be reduced as described in Section 5.1 and the SoA, unless the subject meets protocol defined criteria for loss of asthma control indicating that it is not acceptable for the participant to further reduce ICS. Prior to each FP dose reduction an assessment of the participants' asthma control should be completed and the decision to reduce the dose of FP will be based on: 1) the presence and severity of exacerbations, 2) changes in FEV1, 3) changes in the most recent ACQ-5 score, or 4) the ability to titrate ICS as per the pre-defined schedule, according to the investigator's clinical judgment. If loss of control is confirmed during the FP titration period, the participant will discontinue IP immediately and should resume regular treatment for their asthma, as determined by the investigator. A similar methodology was recently reported [Wenzel, 2013] and successfully allowed titration of ICS.

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.

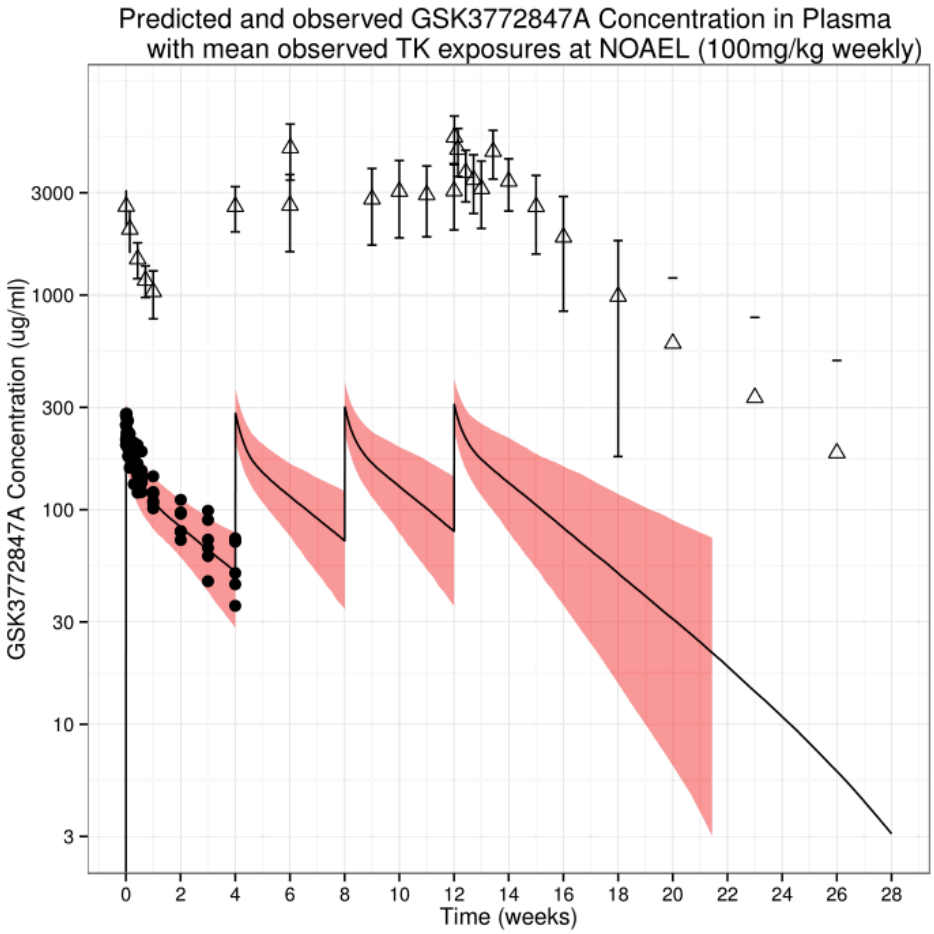
An inhaled short acting beta$_2$–receptor agonist, salbutamol/albuterol will be provided to all participants to use as needed to relieve asthma symptoms from Screening (Visit 1) to end of the Treatment Period. Both safety and efficacy parameters will be assessed regularly in the clinic to minimise any 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

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.

Table 1 Predicted clinical exposures and safety margins for study 207597 following dosing of 10 mg/kg at weeks 0, 4, 8 and 12.

Day 1 mean C_{max} (µg/mL)	Exposure margin[a]	Week 12 mean C_{max} (µg/mL)	Exposure margin[a]	0-28 weeks AUC (µg.day/mL)	Exposure margin[b]
245.3[c]	10.5	313.5[d]	17.4	16830.2[d]	18.2

a. Margins calculated against mean maximum serum concentration (C_{max}) on day 1 and day 84 (last dose) in study T-2013-007 (2592.55 and 5444.07 µg/mL respectively).
b. Margins calculated based on AUC (0-92 (13 weeks)) estimated using compartmental modelling of mean exposures in study T-2013-007.
c. Mean observed exposures in study CNTO7160ASH1001.
d. Predicted exposures using preliminary MM model

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. **Age:** At least 18 years of age at the time of signing the informed consent.
2. **Gender**: Males and females.
   A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   - Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

     OR
   - A WOCBP who agrees to follow one of the options listed in Appendix 5 from **4 weeks** prior to the first dose of study medication and until at least 16 weeks after the last dose of study medication and completion of the follow-up visit.
3. **Informed consent**: Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
4. **Asthma diagnosis and severity**: A participant with a documented diagnosis of severe asthma based on Global Initiative for Asthma (GINA) 2016 Guidelines, whose asthma has been managed with regular treatment of high dose ICS defined as fluticasone propionate 500 mcg twice daily (i.e. 1000 mcg total daily dose) or equivalent, and long-acting beta-2-agonist (LABA) for at least 4 months. Additional therapy with a leukotriene receptor antagonist (LTRA) is permissible.
5. **Reversibility:** Airway reversibility of at least 12 % and 200 mL in FEV1 at Screening (Visit 1), or documented reversibility prior to Screening (Visit 1), or

documented history of bronchial hyperreactivity from a bronchoprovocation study (e.g. methacholine challenge) prior to Screening (Visit 1).

Note: If the participant does not meet the above reversibility criteria at Screening (Visit 1) then the reversibility assessment may be repeated once within 7 days of Visit 1. Should the participant successfully demonstrate airway reversibility at the second attempt then, provided that all other eligibility criteria assessed at Screening (Visit 1) are met, the participant may enter the 2 week run-in period.

6. **Asthma Control Questionnaire (ACQ):** ACQ-5 score ≥1.5 at Screening (Visit 1).
7. **Exacerbation history**: Had at least one asthma exacerbation within 12 months prior to Screening that required treatment with systemic corticosteroid and/or hospitalization.

6.2. Exclusion Criteria

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

1. **Smoking history**: Current smokers or former smokers with a smoking history ≥10 pack years.
2. **Concurrent respiratory diseases**: Presence of a known pre-existing, clinically important respiratory conditions (e.g. pneumonia, pneumothorax, atelectasis-segmental or larger, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other respiratory abnormalities) other than asthma.
3. **Severe airflow obstruction**: A pre-bronchodilator FEV1 <50 % predicted of normal value at Screening (Visit 1).

   Note: If the spirometry is deemed technically inadequate by the central reader, the spirometry assessment may be repeated once within 7 days of Screening (Visit 1).
4. **Malignancy:** Participants with a diagnosis of malignancy or in the process of investigation for a malignancy.
5. **Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result** at Screening (Visit 1) or within 3 months prior to first dose of study treatment.

   NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C Ribonucleic acid (RNA) test is obtained.
6. **12-lead ECG assessment at Screening (Visit 1):** Site investigators will be provided with ECG over-read conducted by a centralized independent cardiologist, to assist in evaluation of subject eligibility. For this study, an abnormal and clinically significant ECG that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the findings in Table 2:

Table 2 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)

7. **Weight**: <50 kg and >150 kg

8. **Regular use of systemic corticosteroids** for conditions including asthma within 3 months prior to Screening (Visit 1).
9. **Participants with high parasympathetic tone** (e.g. trained athletes with baseline bradycardia) or chronic conditions associated with parasympathetic surges (e.g. migraines)
10. **Eosinophilic diseases**: Other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes. Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening (Visit 1).
11. **Cardiovascular disease**: Clinically significant organic heart disease (e.g. CAD, NYHA Class III/IV heart failure).
12. **Ongoing or recurrent infections** requiring systemic antibiotics.
13. **Other Concurrent Diseases/Abnormalities:** A subject must not have any clinically significant, uncontrolled condition, or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study.

    The list of additional excluded conditions/diseases includes, but is not limited to, the following:

Addison's disease	hypertension[1] (uncontrolled)
aortic aneurysm (clinically significant)	peptic ulcer (recent or poorly controlled)
Cushing's disease	renal disease
diabetes mellitus (uncontrolled)	stroke within 3 months of Visit 1
hematological disease	thyroid disorder (uncontrolled)
hepatic disease	tuberculosis (current or untreated[2])

1. Two or more measurements with systolic pressure >160mmHg or diastolic pressure >100mmHg
2. Subjects with a history of tuberculosis infection who have completed an appropriate course of antituberculosis treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease.

14. **Immunodeficiency**: A known immunodeficiency such as human immunodeficiency virus infection.
15. **Hypersensitivity**: Participants with allergy or intolerance to a monoclonal antibody or biologic or to any components of the formulation used in this study.
16. **Alcohol and Substance abuse**: Participants with a history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Screening (Visit 1).
17. **Participants at risk of non-compliance, or unable to comply with the study procedures**. Participants who are unable to follow study instructions such as visit schedule, dosing directions, study electronic diary (eDiary) completion, or use of a standard metered dose inhaler. Participants who have known evidence of lack of adherence to controller medication and/or ability to follow physician's recommendations. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
18. **Participants who have previously participated in a study of GSK3772847**.

19. **Excluded Medications**: Use of the medications listed in Table 3 is not permitted within the defined time intervals prior to Screening (Visit 1) and throughout the study.

Table 3 Prohibited Medications

Medication	Time interval prior to Visit 1
Investigational drug	One month or 5 half-lives whichever is longer
Live or attenuated vaccines[a]	2 weeks (i.e. 4 weeks prior to IP administration)
Biologics, for example Mepolizumab and Omalizumab	130 days or 5 half-lives whichever is longer
Experimental anti-inflammatory drugs (non-biologics)	3 months
Corticosteroids intramuscular, long acting depot Regular systemic corticosteroid	3 months
Methotrexate, troleandomycin, oral gold, cyclosporin, azathioprine,	3 months
Theophylline	3 months
Chemotherapy and radiotherapy	12 months

a. Vaccines containing killed bacteria or inactivated virus will be permitted

20. **Affiliation with Investigator Site**: A participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
21. **Inability to read**: In the opinion of the investigator, any participant who is unable to read and/or would not be able to complete a diary card/questionnaire.
22. **Questionable validity of consent**: Participants with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

6.3. Randomization Inclusion Criteria

At the end of the Run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

1. **Asthma Control Questionnaire (ACQ):** ACQ-5 score ≥1.5 at Visit 2.

2. **eDiary Compliance:** Compliance with completion of the Daily eDiary reporting defined as completion of all questions/assessments on ≥4 of the last 7 days during the run-in period.

6.4. Randomization Exclusion Criteria

Participants meeting any of the following criteria **must not** be randomized to double-blind study medication at Visit 2:

1. **Clinically significant and abnormal laboratory finding at Screening (Visit 1):** Evidence of clinically significant abnormal laboratory tests during screening which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality.

2. **12-lead ECG over-read**: Evidence of clinically significant abnormal ECG findings (Table 2) at Screening (Visit 1).

3. **24-Hour Holter Monitoring**: An abnormal and significant finding from 24-hour Holter monitoring at Screening (Visit 1). Investigators will be provided with Holter reviews conducted by an independent cardiologist to assist in evaluation of subject eligibility. Specific findings that preclude subject eligibility are listed in Table 2. The study investigator will determine the medical significance of any Holter abnormalities not listed in Table 2.

4. **Liver function** at Screening (Visit 1)

    - ALT >2x upper limit of normal (ULN) and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35 %).
    - Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones.

5. **Asthma exacerbation:** Participants with ongoing asthma exacerbation at the time of Visit 2.

    Note: At the Investigator's discretion, participants with an ongoing asthma exacerbation at Visit 2 may be re-screened ≥2 weeks after Visit 2. In such cases, the full screening process (i.e. all Visit 0, 1 and Visit 2 assessments) must be repeated.

6. **Severe airflow obstruction:** a pre-bronchodilator FEV1 <50 % predicted of normal value at Visit 2.

7. **Positive pregnancy test** at Visit 0, Screening (Visit 1) or Visit 2.

8. **Ongoing or recurrent infections** requiring systemic antibiotics.

6.5. Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.6. Pre-Screening/Screening/Run-in/Randomization Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the eCRF for participants who are pre-screen failures:

- Demographic information including race, age and gender
- Participant number
- Serious Adverse Event information only for any SAE considered as related to study participation

For the purposes of this study, pre-screening failures, screening failures, run-in failures and randomization failures will be defined as follows:

- **Pre-screening failures:** those participants that sign the informed consent document but do not have a Screening (Visit 1) procedure.
- **Screening failures:** those participants that complete at least one Screening (Visit 1) procedure but do not enter the run-in period.

  A participant who completes Visit 1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.
- **Run-in failures:** those participants that enter the run-in period but do not have any Visit 2 procedures.
- **Randomization failures:** those participants that complete at least one Visit 2 procedure but do not enter the double-blind study treatment period.

Any participant who completes the run-in period and then meets the randomization criteria and receives the double-blind study treatment at Visit 2 is considered to have entered the treatment period.

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).

Rescreening is only allowed in exceptional circumstances of technical errors and with prior approval from the GSK study team.. Participants who are excluded due to an ongoing asthma exacerbation at Visit 2 (Randomization exclusion criterion 5) may be rescreened ≥2 weeks after Visit 2, at the investigators discretion. Rescreened participants will be assigned a new participant number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK3772847	Placebo	Fluticasone Propionate/Salmeterol	Fluticasone Propionate
Dosage formulation:	50mg/mL GSK377284, 15 mM Sodium Phosphate, 8.5% [w/v] Sucrose, and 0.04% [w/v] Polysorbate 20, pH 7.3.		DISKUS– 60 doses per device	DISKUS– 60 doses per device
Unit dose strength(s)/Dosage level(s):	10 mg/kg	Commercially sourced sterile diluent	500/50 mcg per actuation	500, 250, 100 and 50 mcg per actuation
Route of Administration	IV infusion	IV infusion	Inhaled	Inhaled
Dosing instructions:	GSK3772847 for injection will require further reconstitution and dilution at the study site prior to administration: dilution between 10 and 30 mg/mL may be accomplished by using commercially sourced sterile diluent		Twice daily; once in the morning and once in the evening	Twice daily; once in the morning and once in the evening

Study Treatment Name:	GSK3772847	Placebo	Fluticasone Propionate/Salmeterol	Fluticasone Propionate
Packaging and Labeling	Study Treatment will be provided as 100mg/vial, white to yellow, uniform lyophilized cake in a 5ml clear glass vial with 20mm closure sealed by red metal and yellow overseal. Each container will be labeled as required per country requirement.	Commercially sourced sterile diluent will be sourced by the site	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip) Each container will be labeled as required per country requirement.	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip) Each container will be labeled as required per country requirement.

7.1.1. Description of Albuterol/Salbutamol

Albuterol/salbutamol via metered-dose inhaler (MDI) will be issued for reversibility testing at Screening (Visit 1). An albuterol/salbutamol MDI for as needed (prn) use throughout the study will be dispensed starting at Visit 1; at the Investigator's discretion, more than one MDI may be dispensed at any one time. Albuterol/salbutamol will be sourced from local commercial stock. The contents of the label will be in accordance with all applicable regulatory requirements.

7.1.2. DISKUS Return

DISKUS inhalers containing FP/Salmeterol and FP will be dispensed to a participant during their visit to the study clinic (as applicable). The participant must return all dispensed inhalers at the subsequent clinic visit. The schedule for dispensing and collecting FP/Sal and FP is provided in the SoA (Section 2).

All used and unused FP/Sal, FP will be returned to GSK at the end of the study to be available for disposal. In some instances for sites outside the United States (US), study supplies will be disposed of locally either by the site, the country medical department or third-party vendor. Detailed instructions for the return of the study drug can be found in the Study Reference Manual (SRM).

If any DISKUS inhaler fails to function properly, the participant should return to the clinic as soon as possible to obtain a new inhaler. The site will use the Interactive Web Response System (IWRS) (RAMOS NG) to obtain a new treatment pack number for the participant and dispense a new study treatment kit from the site's study treatment supply as instructed by the IWRS. Details of the failure will be documented in the eCRF. Additional information on how to handle medical device incidents can be found in the SRM.

7.2. Dose Modification

There are no dose modifications planned for this protocol.

7.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the randomization schedule. The randomization code will be generated by GSK using a validated computerized system. Participants will be randomized using an interactive web response system (IWRS) RAMOS NG. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 2-week Run-in period and subject to satisfying all eligibility criteria, participants will be randomized 1:1 to one of the following double-blind treatments for the duration of the Treatment Period:

- GSK3772847 (10 mg/kg) administered intravenously
- Placebo administered intravenously

The duration of the Treatment Period for each participant is 16 weeks. Each Investigator will be provided with sufficient supplies to conduct the trial. Additional treatment kits will be supplied as needed to the sites. Details of how to use the IWRS system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG manual and SRM.

7.4. Blinding

This will be a double-blind study and the following will 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.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.

- 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.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

GSK3772847 a white to yellow, uniform lyophilized cake in a 5ml clear glass vial with 20mm closure sealed by red metal and yellow overseal. Each vial contains 100 mg of a lyophilised GSK3772847. When reconstituted with 2.0 mL of WFI, the final concentration of GSK3772847 is 50 mg/mL. Excipients include: sucrose, sodium phosphate buffer, and polysorbate 20 at a pH of 7.3. Vials contain no preservatives and thus are for single use. Vials must be stored 2º – 8°C, protected from light. Protection from light during preparation and administration is not required. Full details on specific 2º to 8°C storage temperature conditions, preparation and administration including requirements for filtration are provided separately.

Commercially available diluent will be used for dilution of study agent and will also serve as placebo for this study. Use of study agent diluent as placebo for injection provides an adequate comparator to broadly assess safety in early clinical development.

GSK3772847 must be prepared by an unblinded pharmacist or other appropriately licensed and authorized personnel and administered according to each participant's body weight at Screening (Visit 2). A different site staff member, who will be blinded to the treatment assignment, will administer the study agent. Aseptic procedures must be used during preparation and administration of the study agent. GSK3772847 must be filtered with a 0.22 micron filter before being diluted in sterile commercially available diluent. Diluted GSK3772847 at volumes of 50 mL are to be administered by IV infusion over a period of at least 30 minutes using an in-line 0.22 micron filter. At least 30 mL of commercially available diluent will be used to flush diluted drug from the administration set to ensure full study agent administration.

Unblinded site staff will be responsible for receipt, storage, reconstitution, 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.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual or unblinded site staff reference manual.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.6. Treatment Compliance

- FP/Sal and FP during the run-in and treatment periods will be self-administered at home; compliance will be assessed via dose counter during the site visits and documented in the source documents and eCRF. A record of the number of doses on the DISKUS inhaler will be recorded in the eCRF. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

- The double blind IP will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the eCRF.

7.7. Concomitant Therapy

All asthma medications used within approximately 12 weeks prior to screening and during the study (including the post-treatment period) should be recorded in the eCRF.

All non-asthma medications taken during the study (after randomization including post-treatment) and any changes to concomitant medications will be recorded in the eCRF. *Note: Study provided FP/Sal, FP, and albuterol/salbutamol should not be recorded in the ConMeds page of the eCRF.*

The minimum requirement is that the drug name, reason for use, dose (including unit e.g. mcg) and frequency, route and the dates of administration are to be recorded.

7.7.1. Permitted Non-asthma Medications

The following medications are permitted during the study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal], cromolyn, nedocromil, nasal decongestants)
- Antibiotics for short term treatment of acute infections. Long term treatment with topical or ophthalmic antibiotics are permitted.
- Decongestants: Participants may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.
- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and participants remain in the maintenance phase for the duration of the study.
- Topical and ophthalmic corticosteroids.

7.7.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed below is not permitted during the study:

- Inhaled anti-cholinergics (e.g.tiotropium).
- ICS/LABA other than the study-provided FP/Sal .
- Inhaled Corticosteroids other than the study-provided FP.
- LABA other than the salmeterol component in the study-provided FP/Sal.
- Biologics, e.g. Mepolizumab and Omalizumab.
- Potent CYP3A4 inhibitors, (e.g., ritonavir, ketoconazole, etc.)
- Anticonvulsants (barbiturates, hydantoins, and carbamazepine).
- Polycyclic antidepressants.
- Beta-adrenergic blocking agents.
- Phenothiazines.
- Monoamine oxidase (MAO) inhibitors.

- Live or attenuated vaccines.
- Experimental anti-inflammatory drugs (non-biologics).
- Corticosteroids intramuscular, long acting depot regular systemic corticosteroid.
- Methotrexate, troleandomycin, oral gold, cyclosporin, azathioprine.
- Theophylline.
- Chemotherapy and radiotherapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study or withdrawal of IP because other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

Participants who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up until the completion of the Safety Follow-up 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.

If this is not possible, the Investigator must encourage the participant to participate in as much of the study as they are willing (or able) to.

A participant may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy [including loss of asthma control], protocol deviation, Investigator discretion, consent withdrawn etc.) must be captured in the eCRF.

A participant must be withdrawn from study treatment if any of the following stopping criteria are met:

1. Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria.
2. QTc: Meets any of the protocol-defined stopping criteria.
3. Pregnancy: Positive pregnancy test.
4. Participant meets at least one of the following criteria for 'loss of asthma control':
   - A clinically significant asthma exacerbation (requiring OCS and/or hospitalization).
   - Pre-bronchodilator FEV1 decrease from baseline (measured at Visit 2) >7.5 %.
   - Inability to continue inhaled corticosteroid titration which is assessed and determined by the investigator at any time point following randomization, including on scheduled clinic visits.
   - ACQ-5 score increase from baseline (measured at Visit 2) ≥0.5 point
5. Study treatment unblinded.

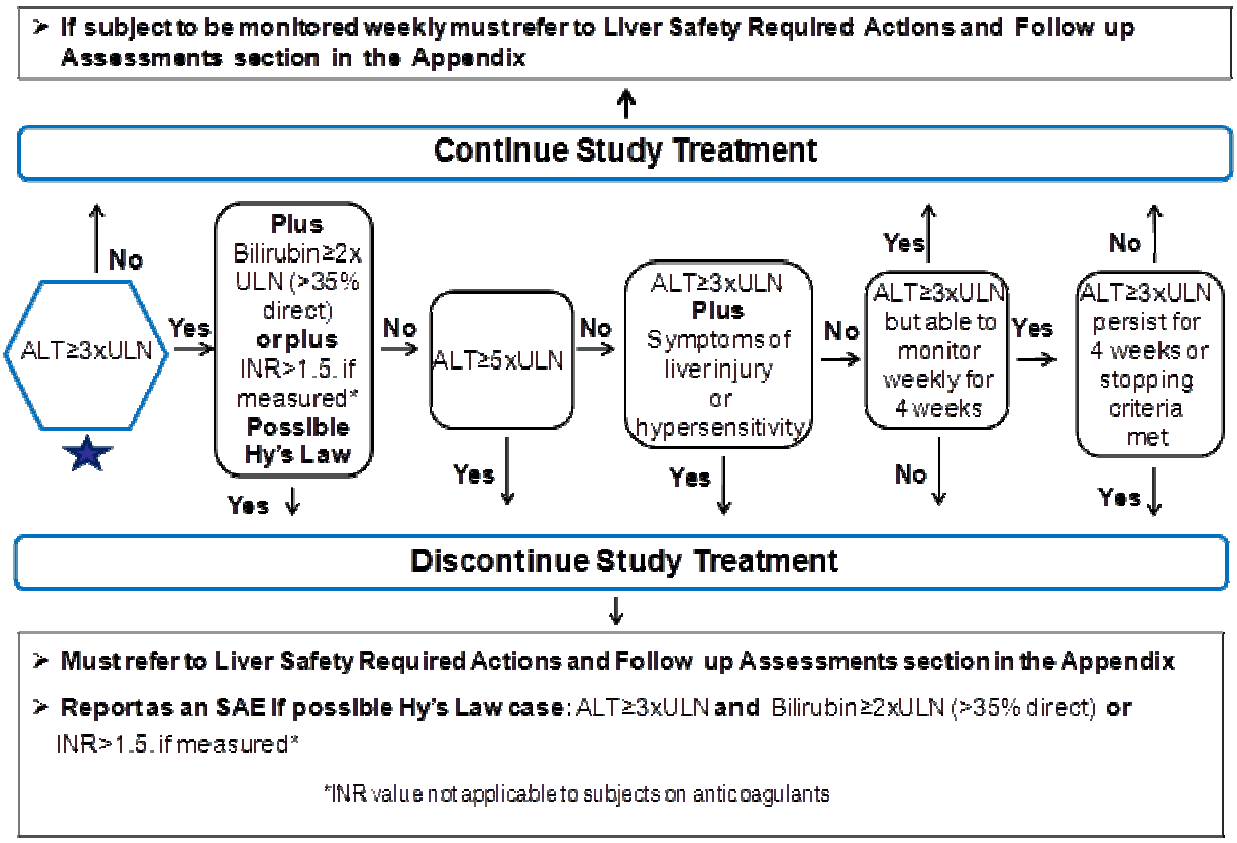
   Note: In the event of unblinding the Medical monitor/GSK team should be contacted to determine whether subject withdrawal is required.
6. Abnormal Holter of Mobitz II AVB, complete AVB, sustained or non-sustained ventricular tachycardia (VT), paroxysmal supraventricular tachycardia (PSVT), new onset atrial fibrillation/flutter will be a withdrawal/stopping criterion. These findings on ECG (baseline, V4, V6) or findings of myocardial ischemia will also result in withdrawal/stopping.
7. Hypersensitivity or anaphylactic reaction

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



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

8.1.2. QTc Stopping Criteria

- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

- Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
- Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec.

See the SoA for data to be collected at the time of early withdrawal (EW visit) and follow-up and for any further evaluations that need to be completed.

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed. Additionally, if hypersensitivity or anaphylactic reaction occurs, infusion should be discontinued and study restart is not allowed.

8.2. Withdrawal from the Study

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

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

No study related procedures may be performed until the informed consent form has been signed by the participant. Selection and modification of the participant's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each participant's needs. A participant's treatment must not be changed merely for the purpose of enabling the participant's participation in the study.

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in SoA.

9.1.1. Questionnaires

9.1.1.1. Asthma Control Questionnaire ACQ-5

The ACQ-5 measures attributes of asthma control [Juniper, 1999], measured with questions designed to be self-completed by the participant. Participants will complete the ACQ-5 with the use of an e-Diary device on a weekly basis. The ACQ-5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall

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

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

instructions on performing the spirometry manoeuvres are documented in the SRM and the third-party vendor manual.

9.1.3.1. Spirometry

Spirometry will be performed to assess FEV1 and FVC. At least 3 spirometry manoeuvres (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed. The best spirometry effort will be selected from a measurement that meets American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines and has a minimum of 2 efforts which are considered valid and repeatable, in accordance with the ATS/ERS standards [Miller, 2005]. At each visit, spirometry assessments must be performed at the same time of day (± 2 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) prior to the clinic visit, if possible.

9.1.3.2. Reversibility

All reversibility evaluations should follow the recommendations of the ATS/European Respiratory Society (ERS) Task force: Standardization of Lung Function Testing [Miller, 2005]. A baseline spirometry assessment should be performed after a washout period of at least 6 hours for short-acting β_2- agonists and 1 dosing interval for long-acting β_2-agonists (or fixed dose combinations of LABA and ICS).

To perform the reversibility assessment, 4 puffs of the provided salbutamol/albuterol is administered following completion of the baseline assessment. A second spirometry assessment is performed within 10 to 15 minutes after administration of the salbutamol/albuterol.

Reversibility assessment at Screening (Visit 1) is not required if there is documented reversibility prior to Screening (Visit 1), or documented history of bronchial hyperreactivity from a bronchoprovocation study (e.g. methacholine challenge) prior to Screening (Visit 1).

9.1.4. Fractional Exhaled Nitric Oxide (FeNO)

FeNO will be measured using a handheld electronic device. Measurements will be obtained in accordance with the ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide [Miller, 2005]. All sites will use standardized equipment provided by a central vendor. For each observation, at least 2 measurements will be obtained to establish reproducibility (up to 8 measurements can be performed). FeNO measurements will be interpreted in accordance with the Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications [Dweik, 2011]. FeNO observations must be completed before FEV1 assessments. Participants should not use their rescue medication for at least 6 hours before each FeNO assessment, unless essential for clinical need. Participants should also

withhold LABAs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) before each FeNO assessment.

9.1.5. Review of Loss of Asthma Control

Loss of asthma control is defined as at least one of the following:

- A clinically significant asthma exacerbation (requiring OCS and/or hospitalisation) or
- Pre-bronchodilator 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
- ACQ-5 score increase from baseline (measured at the end of Run-in) ≥0.5 point.

At each clinic visit, the Investigator will utilize clinical discretion and available objective evidence (including but not limited to eDiary data, spirometry data, the most recent ACQ5 scores, history of exacerbations, conmeds, AEs) to determine if the patient is experiencing loss of asthma control. The paper Medical Problems/Medications Taken worksheet must also be reviewed by the Investigator (or appropriately trained designee) at each visit to the study site to assist the Investigator in the identification of loss of asthma control. It is expected that the Investigator will indicate which criterion (criteria) the subject met that constituted loss of asthma control.

9.2. Adverse Events

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

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

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

- All SAEs will be collected from the Visit 2 until the last follow-up visit at the time points specified in the SoA (Section 2). At Visits 0 and 1 SAE information will be collected only for any SAEs considered as related to study participation.
- All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting 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.

- 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.

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.

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

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.

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

Population	Description
(ITT)	received.
Safety	This population will be the same as the Modified Intent-to-treat population.
PK	All randomized subjects who received at least one dose of study medication, and for whom at least one pharmacokinetic sample was obtained, analyzed and was measurable.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint proportion of subjects with loss of asthma control will be analyzed using both Bayesian and Frequentist methods. A subject is deemed to have met the endpoint of loss of asthma control if they meet the criteria for any of the components of the definition of loss of asthma control. The posterior probabilities 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) will be calculated analytically using a normal approximation for the logarithm of the ratio of proportions. This will be supported by an estimate of the ratio with a 95% credible interval. Results will also be presented for the two eosinophils strata separately. In addition, the proportion of participants with loss of asthma control will be analyzed using logistic regression allowing for baseline eosinophils strata. The odds ratio, 95% CI and p-value for the comparison of GSK3772847 with placebo will be presented. Results will also be presented for the two eosinophils strata separately by fitting a separate model with an additional term for eosinophil strata by treatment interaction. The effect of eosinophils as a continuous covariate will also be examined in a separate-logistic regression model. Missing data will be handled using the following methods: 1) The loss of asthma control will be set to missing for participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control 2) A sensitivity analysis will be performed where participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control will have the endpoint set to loss of control

Endpoint	Statistical Analysis Methods
Secondary	The following secondary endpoints will be analyzed using the same statistical analysis as described for the primary endpoint: • Proportion of participants with a clinically significant asthma exacerbation (requiring OCS and/or hospitalisation) • Proportion of participants with Pre-bronchodilator FEV1 decrease from Baseline (measured at the end of Run-in) >7.5 % • Proportion of participants with Inability to titrate inhaled corticosteroid according to the pre-defined schedule (Section 5.1) • Proportion of participants with ACQ-5 score increase from Baseline (measured at the end of Run-in) ≥0.5 point. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule. In these analyses, the endpoint will be set to missing for participants who withdraw from IP prior to Week 16 for reasons other than loss of asthma control. Time to loss of asthma control will be analyzed using Kaplan-Meier analysis. Percentiles for time to loss of control will be presented for both treatment groups, along with graphical survival plots. Any early withdrawals from IP that did not experience loss of control will be censored. Results will be presented for both of the two eosinophil strata separately, and combined. The following endpoints will be analyzed using repeated logistic regression. This analysis will be repeated including an additional term for eosinophil strata by treatment by visit interaction to provide estimates for the two eosinophil strata separately: • Proportion of ACQ-5 responders (a ≥0.5 point improvement from baseline at Week 16) • Proportion of SGRQ responders (at least a 4 unit improvement from baseline at Week 16 These analyzes will be performed using two different methods for handling missing data: 1) If endpoint at a visit is missing then the responder status is set to missing 2) If endpoint at a visit is missing and the endpoint is also missing at all subsequent visits then the responder status is set to non-responder The odds ratio, 95% CI and p-value for the comparison of GSK3772847 with placebo will be presented for all models. Mixed model repeated measures will be used to analyze the following endpoints. The baseline value of each endpoint will be included along with baseline*visit and treatment*visit interactions. Treatment differences, 95% confidence intervals and p-values will be presented. • Change from baseline in ACQ-5 absolute score • Change from baseline in SGRQ total score

Endpoint	Statistical Analysis Methods
	• Change from baseline in Pre-bronchodilator FEV1 • Change from baseline in FeNO This analysis will be repeated including an additional term for eosinophil strata by treatment by visit interaction to provide estimates for each eosinophil strata separately. No adjustment will be made for missing data. Further information on how the following endpoints will be analyzed will be described in the report and analysis plan: • Hospitalisation or ER visit during the study treatment period • Morning and evening PEF • Daily asthma symptom score • Rescue medication use (albuterol/salbutamol): number of occasions per day • Night-time awakenings due to asthma symptoms requiring rescue medication Any changes to the planned analysis methods will be documented in the reporting and analysis plan. Details of subgroup analyses for the primary and secondary endpoints will be described in the reporting and analysis plan.
Exploratory	Will be described in the reporting and analysis plan

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary safety analysis.
Secondary	The following secondary safety endpoints will be analyzed descriptively by treatment group: • Incidence and frequency of AEs and SAEs • Vital signs • 12-lead ECG • 24 hours Holter • Clinical laboratory evaluation • Incidence of and titres of anti-GSK3772847 antibodies. Details will be described in the reporting and analysis plan

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.

10.4.3. Pharmacokinetic Analyses

All safety analyzes will be performed on the PK Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary pharmacokinetic analysis.
Secondary	The serum GSK3772847 levels from this study will be summarised by treatment and nominal time. Further details will be described in the report and analysis plan.

10.4.4. Pharmacodynamic Analyses

All pharmacodynamic analysis will be described in reporting and analysis plan.

10.4.5. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analysis will be described in the reporting and analysis plan. Any population PK analysis and pharmacodynamic analysis will be reported separately from the main clinical study report (CSR). Should a genetic/PGx analysis be performed, a separate reporting and analysis plan will be generated (See Appendix 6: Genetics).

10.4.6. Interim Analyses

Formal analyses will be performed at two timepoints.

End of Treatment Phase Analysis:

This will take place after all participants have completed the Week 16 visit. The data will be cleaned, the treatments unblinded and all clinic visits up to and including week 16 frozen.However, whilst no further efficacy data will be collected post week 16, due to an inability to lock log forms used for collection of exacerbation data, the end of treatment phase analysis will be considered an interim analysis for both efficacy and safety. Any safety data collected for participants who have completed clinic visits after Week 16 will also be cleaned and included in the analysis.

There will be no modifications to dosing regimens, sample size or any other aspects of the trial based on this data, as all study assessments, apart from follow-up, will have

already been completed. As such an Independent Data Monitoring Committee (IDMC) will not be used, as no further investigational product will be prescribed after this analysis has taken place.

Final Analysis:

This will take place after all subjects have completed the study. Data for visits after Week 16 as well as data collected on log pages will be cleaned and the database frozen. This will be the final analysis for the study.

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

Instream review:

An 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 Charter.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BID	Twice a day
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
CI	Confidence Interval
CV	Cardiovascular
Cmax	maximum serum concentration
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Serum creatine phosphokinase
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
ER	Emergency Room
eDiary	Electronic Diary
ETP	End of Treatment Phase
ERS	European Respiratory Society
EW	Early Withdrawal
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced expiratory volume in 1 second
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyltransferase
GINA	Global Initiative for Asthma
GLP	Good laboratory practice
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen

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

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

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory.
- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual and the SoA. Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference for all safety parameters will be provided to the site by the laboratory responsible for the assessments.
- All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.
- Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit White Cell Count RDW	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin

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

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

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

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 eCRF 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.

Study and Site Closure

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

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

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

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

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

Definition of AE

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

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

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

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

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

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

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the 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.

- 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 eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

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

minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- 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 or to the

assigned SAE contact by telephone.

- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page

SAE Reporting to GSK via Paper eCRF

- Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the assigned SAE contact by telephone.
- 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 eCRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 6.

Table 6 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed during the treatment period as specified in the Table of Events
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

- Pregnancy testing, with a sensitivity of 5, 10, 25 mIU/mL will be performed and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female Participants who become pregnant

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

Any female participant who becomes pregnant while participating will discontinue study treatment

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for Deoxyribonucleic acid (DNA) analysis
- DNA samples will be used for research related to GSK3772847 or asthma and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3772847 or other treatments which may regulate neutrophils and eosinophils or other study treatments including, but not limited to, steroids, long-acting beta-agonists, and other drugs used in the treatment of asthma, or for asthma and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
- DNA samples may be analyzed 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 analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3772847 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3772847 (or study treatments of this class) or asthma and related diseases continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (see below) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, insert time interval recommended by clinical pharmacokinetics representative after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of

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

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