Objectives	Endpoints
To evaluate the levels and specificity of any anti-drug antibodies formed following dosing with GSK3772847	• Incidence and titres of serum anti-GSK3772847 antibodies post dosing
To evaluate the health status of moderate to severe asthma participants with AFAD currently on SoC, and who are treated with GSK3772847 compared with placebo-treated participants	• Change from baseline (Week 0) in Asthma Control Questionnaire -5 (ACQ-5) absolute score at Weeks 2, 4, 8 and 12 • Change from baseline (Week 0) in Asthma Quality of Life Questionnaire (AQLQ) total and domain scores at Weeks 2, 4, 8 and 12 • Proportion of responders to ACQ-5. A responder to ACQ-5 will be defined as a subject who has a decrease from baseline in ACQ-5 score of 0.5 or more. • Proportion of responders to AQLQ. A responder to AQLQ will be defined as a subject who has an increase from baseline in AQLQ score of 0.5 or more.
To evaluate the effect on lung function of moderate to severe asthma participants with AFAD currently on SoC, treated with GSK3772847 compared with placebo	• Change from baseline (Week 0) in spirometry parameters over time including but not limited to pre-bronchodilator Forced expiratory volume in 1 second (FEV_1)
To evaluate the safety and tolerability of GSK3772847 compared with placebo in moderate to severe asthma participants with AFAD	Safety and tolerability parameters include: • Treatment emergent adverse events (AE) • Clinical Laboratory safety data • Vital signs (blood pressure, heart rate) • 12–Lead Electrocardiogram (ECG) monitoring • 24-hour Holter monitoring

Overall Design:

This is a randomised, multicentre, double blind (sponsor open), placebo-controlled, stratified, parallel group study evaluating 3 doses of 10 mg/kg GSK3772847 administered every 4 weeks versus placebo in addition to SoC. Participants who have been diagnosed as having moderate to severe asthma with allergic fungal airway disease shall be enrolled in the study. Moderate to severe asthmatics are defined as asthmatics who are well controlled with Step 3 or 4 treatment, respectively, based on Global Initiative for Asthma, 2017 Guidelines.

Number of Participants:

Approximately 46 participants with moderate to severe asthma will be randomised such that approximately 40 evaluable participants complete the study, where evaluable is

Procedure	Screening (±5days)	Run-in (±5days)	Treatment Period (Visit window ±3days)				End of Treatment / EW (±3days)	FU (±3days)	Notes
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**	**24**	
Pharmacogenetic (PGx) blood sample			X						PGx sample may be drawn any time from Visit 3 onwards, pre-dose. Informed consent must be obtained before collecting a sample.
Study Treatment and Questionnaires									
Randomisation			X						
Study treatment			X		X	X			
Dispense diary card		X							To be completed daily.
Diary card review			X	X	X	X	X		
Collect diary card							X		
Rescue medication dispensing		X	X[1]	X[1]	X[1]	X[1]			1. As needed
ACQ-5	X		X	X	X	X	X		Test to be performed before all other assessments
AQLQ			X	X	X	X	X		Test to be performed immediately after ACQ-5
Efficacy									
Haematology (including eosinophil count)	X		X[1]	X	X	X	X		1. Pre-dose
FeNO	X		X	X	X	X	X		Test to be performed pre-dose
Spirometry	X		X	X	X	X	X		Test to be performed pre-dose

Objectives	Endpoints
Exploratory	
To evaluate changes in exploratory biomarkers in the blood of moderate to severe asthma participants with AFAD who have been treated with GSK3772847 compared with placebo	• Change over time in levels of serum total Immunoglobulin E (IgE), fungal-specific IgE
To evaluate changes in IL-33 related and disease biology biomarkers in the sputum of moderate to severe asthma participants with AFAD who have been treated with GSK3772847 compared with placebo	• Difference from placebo in levels of sputum biomarkers including but not limited to interleukin (IL)-33, IL-13, IL-4, IL-5 and TNF-α • Difference from placebo including but not limited to levels of sputum eosinophils

- Attend a run-in visit (Visit 2) and enter the run-in period, approximately 14 days before the first treatment visit;
- Receive a total of 3 doses, each one on separate study visits (Visits 3, 5 and 6); doses will be every 4 weeks starting at Week 0;
- Attend treatment period study visits at Week 2 (Visit 4) and Week 12 (Visit 7) but not receive study treatment during these visits; and
- Have a follow-up visit (approximately 12 weeks after Visit 7).

Each participant will be involved in the study for approximately 28 weeks.

At specified visits, each participant will undergo the following procedures:

- Sputum inductions at baseline (Visit 2) and end of treatment period (Visit 7). The sputum inductions may each be repeated once: for baseline at Visit 3 and for end of treatment period at an extra visit after Visit 7;
- 24 h Holter monitoring at Visits 2 and 3 only.

During treatment period study visits, the participant will:

- Have blood drawn, for PD and/or PK assessments;
- Undergo FeNO measurement and spirometry;
- Have vital signs measured; and
- Complete 2 Quality of Life (QoL) questionnaires.

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, and complete the follow-up visit assessments.

5.2. Number of Participants

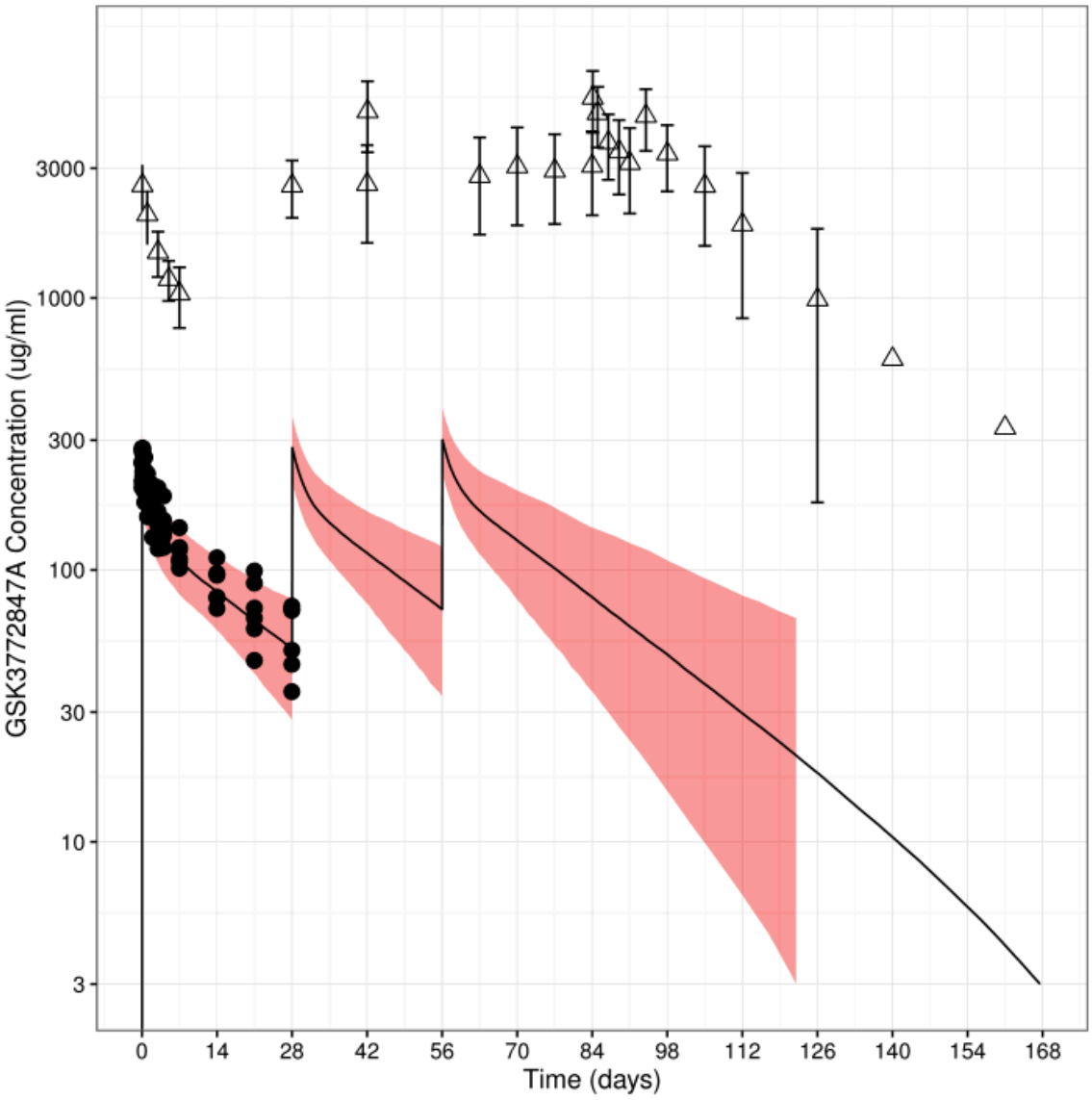
Approximately 46 participants with moderate to severe asthma will be randomised such that approximately 40 evaluable participants complete the study, where evaluable is defined as subjects with at least one post-baseline measurement for both FeNO and blood eosinophils.

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment (from Visit 1), at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

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

Figure 2 **Predicted clinical exposures at 10mg/kg at weeks 0, 4, and 8 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 (100 mg/kg weekly) in the 3-month GLP toxicology study in cynomolgus monkeys (T-2013-007)**



Open Triangles: Observed mean and standard deviation 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.

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

Further details will be provided in the SRM and third party vendor manual.

9.1.3. Questionnaires

The questionnaires should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participant should not be told the results of diagnostic tests prior to completing the questionnaires and it is recommended that the questionnaires be administered at the same time of day during each visit (as applicable).

Adequate time must be allowed to complete all items on the questionnaires; the questionnaires must be reviewed for completeness and, if necessary, the participant must be encouraged to complete any missing assessments or items.

Instructions for completing the questionnaires can be found in the SRM.

9.1.3.1. Asthma Control Questionnaire (ACQ-5)

The ACQ-5 is a five-item questionnaire that is as a measure of a participant's asthma control [Juniper, 2005]. The questions are self-completed by the participant, recalling over the previous 7 days, and enquire about the frequency and/or severity of symptoms (nocturnal awakening, activity limitation, shortness of breath and wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale.

The questions are equally weighted and the ACQ score is the mean of the 5 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

The ACQ-5 questionnaire shall be completed at the visits indicated in the SoA (Section 2).

9.1.3.2. Asthma Quality of Life Questionnaire (AQLQ)

The AQLQ is a disease-specific, self-administered quality of life questionnaire recalling over the previous 14 days. It was developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers [Juniper, 1993; Juniper, 2005]. The AQLQ contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (five items), and environmental stimuli (four items). In addition, the 32 items of the questionnaire are also averaged to produce one overall quality of life score. The response format consists of a seven-point scale where a value of 1 indicates 'total impairment' and 7 indicates 'no impairment'.

The AQLQ questionnaire shall be completed at the visits indicated in the SoA (Section 2).

9.1.4. Spirometry

Spirometry assessments will be performed from screening through the final visit as indicated in the SoA (Section 2). The following parameters will be assessed:

- Forced expiratory volume in one second (FEV_1)
- Forced vital capacity (FVC)

At least three acceptable spirometry manoeuvres (from a maximum of 8 attempts) should be achieved for each spirometry assessment, in accordance with ATS/ERS standards [Miller, 2005]. At each visit, spirometry assessments must be performed at the same time of day (±1 hour) as the assessment performed at Baseline (Visit 3).

Participants should withhold use of short-acting bronchodilators for ≥6 hours and LABAs, ICSs and OCSs for ≥12 hours prior to each clinic visit, if possible. Participants who take medications that contain once daily bronchodilators and once daily maintenance therapy medication should withhold use for ≥24 hours prior to each clinic visit.

Further details will be provided in the SRM and third party vendor manual.

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 Visit 3 until the follow-up visit at the time points specified in the SoA (Section 2). At Visits 1 and 2 SAE information will be collected only for any SAEs considered as related to study participation.
- All AEs will be collected from Visit 3 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 eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 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 AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is 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 according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific 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 Medical 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 follow-up visit.
- If a pregnancy is reported, the investigator should inform 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 GSK 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 (Section 2).

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 SoA (Section 2) prior to conducting ECG and spirometry. Blood pressure (systolic and diastolic), body temperature and pulse rate will be measured in the supine position after approximately 5 minutes rest. Body temperature will be collected in the participant's source documents only for site use. A single set of values for blood pressure and pulse rate 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 centralised 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 SoA (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 8.1.2). 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 centralised 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

9.6. Pharmacodynamics

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 (Section 2). 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 induced sputum 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, fungal specific IgE (*Aspergillus fumigatus, Penicillium chrysogenum (notatum)*) as well as sputum cell counts (e.g. percentage eosinophils) and sputum levels of IL-33, IL-13, IL-4, IL-5 and TNF-α. 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 (Section 2). Details of the sputum collection and processing methodology will be provided in the SRM.

Participants should not use their rescue medication for at least 6 hours before each sputum sampling visit, unless essential for clinical need. Participants should also withhold LABAs, ICSs and OCSs for ≥1 dosing interval (i.e. ≥12 or ≥24 hours based on the prescribed dosing interval of the product) before these visits.

9.8.2. Immunogenicity Assessments

Serum samples will be collected pre-dose and tested for the presence of antibodies that bind to GSK3772847, as specified in the SoA (Section 2). 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. Medical Resource Utilization and Health Economics

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

ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG2σ	human immunoglobulin G2 sigma isotype
IL-1RL1	Interleukin-1 receptor like-1
IL-33R	Interleukin-33 receptor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
iSRC	Internal safety review committee
IV	Intravenous
IWRS	Interactive web response system
LABA	Long-acting beta-2-agonist
LTRA	Leukotriene receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MM	Michaelis Menten
MMRM	Mixed model repeated measures analysis
MMRM	Mixed model repeated measures analysis
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamic
PGx	Pharmacogenetic
PK	Pharmacokinetic
PSVT	Paroxysmal supraventricular tachycardia
QoL	Quality of Life
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting Analysis Plan
SABA	Short acting β-2 agonist
SAE	Serious adverse event
SC	Subcutaneous
SoA	Schedule of activities
SoC	Standard of care
SRM	Study Reference Manual
(s) ST2	(soluble) Suppressor of tumorigenicity 2
T2	Type 2
ULN	Upper limit of normal
VT	Ventricular tachycardia
WOCBP	woman of childbearing potential

Laboratory Assessments	Parameters
	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology [(HIV antibody, 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

Blood eosinophils, total IgE and specific IgE from V3 only that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 (e.g., hospitalisation 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 hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation 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 hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation 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, diarrhoea, influenza, and accidental trauma (e.g., 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

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, stabilise 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, stabilise or return to within baseline	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 or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; 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.

defined as subjects with at least one post-baseline measurement for both FeNO and blood eosinophils.

Treatment Groups and Duration:

Participants who meet the eligibility criteria at Screening (Visit 1) will enter a two-week Run-in period during which they will undergo one 24h Holter monitoring session and fulfil paper Diary requirements. Participants who meet the pre-defined randomisation criteria, will be randomised in a 1:1 ratio to one of the following treatment groups:

- 10 mg/kg GSK3772847 administered intravenously
- Matching placebo administered intravenously

The randomisation will be stratified based on whether a participant is taking anti-fungal medication or not, determined at screening.

Both treatments will be administered on Week 0 (Day 1), Week 4 and Week 8.

Each participant will:

- Be screened;
- Attend a run-in visit (Visit 2) and enter the run-in period, approximately 14 days before the first treatment visit;
- Receive a total of 3 doses, each one on separate study visits (Visits 3, 5 and 6); doses will be every 4 weeks starting at week 0;
- Attend treatment period study visits at week 2 (Visit 4) and week 12 (Visit 7) but not receive study treatment during these visits; and
- Have a follow-up visit (approximately 12 weeks after Visit 7).

Each participant will be involved in the study for approximately 28 weeks.

At specified visits, each participant will undergo the following procedures:

- Sputum inductions at baseline (Visit 2) and end of treatment period (Visit 7). The sputum inductions may each be repeated once: for baseline at visit 3 and for end of treatment period at an extra visit after Visit 7;
- 24 h Holter monitoring at Visits 2 and 3 only.

During treatment period study visits, the participant will:

- Have blood drawn, for PD and/or PK assessments;
- Undergo FeNO measurement and spirometry;
- Have vital signs measured; and
- Complete 2 Quality of Life (QoL) questionnaires.

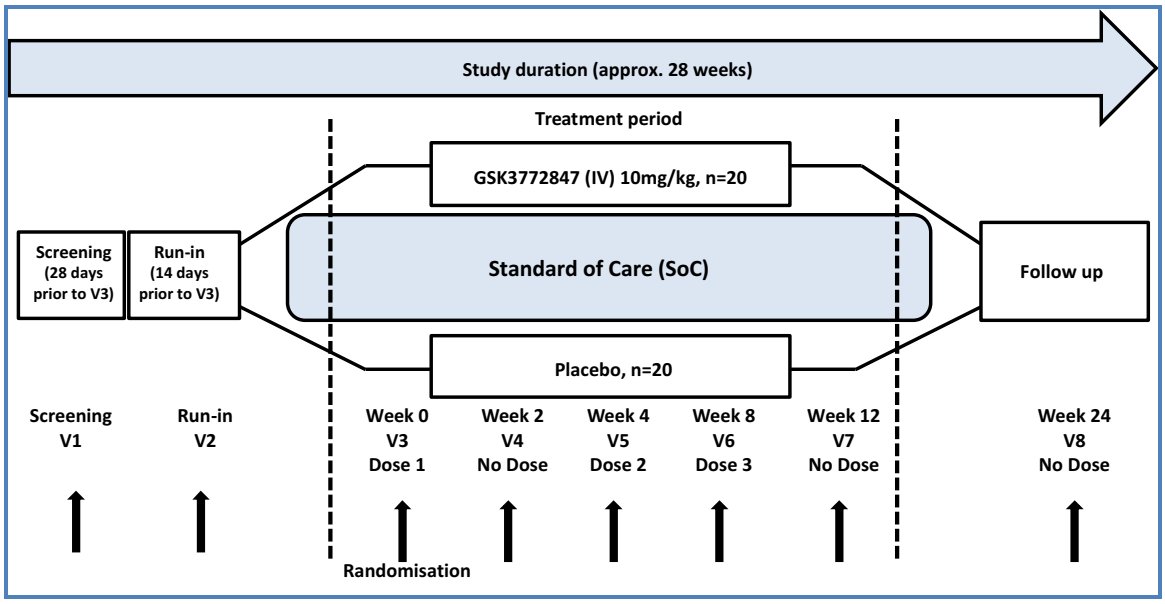
Procedure	**Screening (±5days)**	**Run-in (±5days)**	**Treatment Period (Visit window ±3days)**				**End of Treatment / EW (±3days)**	**FU (±3days)**	**Notes**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Week	**-4**	**-2**	**0**	**2**	**4**	**8**	**12**	**24**	
Free and total sST2 (serum)			X[1]	X	X[2]	X[1]	X[3]	X[3]	1. Pre and Post Dose 2. Pre Dose 3. Anytime (± 5 days) 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.
Total & fungal specific IgE	X[1]		X[2]	X	X	X	X		1. Fungal specific IgE only if no historical documented results available 2. Pre-dose

5. STUDY DESIGN

5.1. Overall Design

This is a randomised, multicentre, double blind (sponsor open), placebo-controlled, stratified, parallel group study evaluating 3 doses of 10 mg/kg GSK3772847 administered every 4 weeks versus placebo in addition to SoC. Participants who have been diagnosed as having moderate to severe asthma with allergic fungal airway disease shall be enrolled in the study.

Figure 1 Study Design Overview



Participants who meet the eligibility criteria at Screening (Visit 1) will enter a two-week Run-in period during which they will undergo one 24h Holter monitoring session and fulfil paper Diary requirements. Participants who meet the pre-defined randomisation criteria (Section 6.4), will be randomised in a 1:1 ratio to one of the following treatment groups:

- 10 mg/kg GSK3772847 administered intravenously
- Matching placebo administered intravenously

The randomisation will be stratified based on whether a participant is taking anti-fungal medication or not, determined at screening.

Both treatments will be administered on Week 0 (Day 1), Week 4 and Week 8.

Each participant will:

- Be screened;

The end of the study is defined as the date of the last visit (Visit 8) of the last participant in the study.

5.4. Scientific Rationale for Study Design

This study will use a randomised, multi-centre, double blind (sponsor open), placebo-controlled, parallel-group design. This is a well-established design to evaluate the efficacy, safety, PK and PD profile of an investigational medicinal product.

Use of a placebo arm is considered justified as all patients will be continuing on standard of care treatments and will also allow the absolute effect of GSK3772847 to be assessed.

The study will be sponsor open to allow selected sponsor study team members to be unblinded in order to perform interim analysis of in-stream data.

The dosing duration of 8 weeks is supported by pre-clinical study data. Dosing frequency of GSK3772847 every 4 weeks with endpoints assessments scheduled 4 weeks post final dose were determined by the available target engagement pharmacodynamic findings.

Participants 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 collected to characterise the pharmacokinetics, pharmacodynamics, and anti-drug antibody responses in this patient population.

5.5. Dose Justification

The dosing regimen of 10 mg/kg IV at Week 0 then Weeks 4 and 8 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 0-12 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 2.

The anticipated exposure margins of the dosing regimen of 10 mg/kg IV at Week 0 then Weeks 4, and 8 over the 3-month GLP toxicology study in cynomolgus monkeys (T-2013-007) are summarised in Figure 2.

Table 1 Predicted clinical exposures and safety margins for study 207972 following dosing of 10 mg/kg at weeks 0, 4, and 8.

Day 1 mean C_{max} (µg/mL)	Exposure margin[a]	Week 8 mean C_{max} (µg/mL)	Exposure margin[a]	0-28 weeks mean AUC (µg.day/mL)	Exposure margin[b]
245.3[c]	10.5	304.5[d]	17.9	12545.3[d]	24.4

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 (306900 ug.day/mL).
c. Mean observed exposures in study CNTO7160ASH1001.
d. Predicted exposures using preliminary MM model

As an additional approach to comparing exposure margins the AUC(τ) at steady state at 10 mg/kg every 4 weeks was estimated based on the preliminary population PK model. At this regimen, the contribution of the non-linear elimination is minimal and so AUC(inf) can be estimated as Dose/Clearance. Clearance was estimated at 2.38 mL/kg/day, therefore, mean predicted AUC(τ) at steady state is 4202 µg.day/mL.

The mean AUC(day85-92) at the no observed adverse effect level (NOAEL) (100 mg/kg, IV, weekly) in cynomolgus monkeys was 27408 µg.day/mL (T-2013-007). In order to correct for weekly dosing in the cynomolgus and dosing every 4 weeks in this study, this figure was multiplied by 4 and results in an estimated exposure margin of 26.

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

9.4.6. Diary assessments

Participants will be issued with a diary card at visit 2. Participants should complete their daily diary pages during the study duration to record the use of rescue (SABA) medication, AEs and concomitant medication usage.

9.5. Pharmacokinetics

- Whole blood samples of approximately 3 mL will be collected for measurement of serum concentrations of GSK3772847as specified in the SoA (Section 2). 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.

10. STATISTICAL CONSIDERATIONS

The primary objective of this study is to investigate the effect of treatment with GSK3772847 compared with placebo on blood eosinophils and FeNO levels in moderate to severe asthmatic participants with AFAD currently on SoC. There are no formal hypothesis tests associated with this objective and no formal significance tests. The information acquired from this study will be used to quantify the effects that GSK3772847 has on the selected efficacy endpoints, as measured by change in the co-primary endpoints; change from baseline in blood eosinophils and change from baseline in FeNO over time.

10.1. Sample Size Determination

To account for a 10% withdrawal rate, approximately 46 participants will be randomised in 1:1 ratio to active arm or placebo arm, to ensure approximately 40 will be evaluable in total.

The sample size is based on feasibility and no formal sample size calculation has been performed.

As described below, change from baseline in blood eosinophils and change from baseline in FeNO will be log-transformed.

Estimates of the variability for the ratio to baseline in blood eosinophils and the ratio to baseline in FeNO were obtained from [Anderson, 2012] and from studies in Mepolizumab in participants with severe asthma.

The half widths of the 95% confidence interval of the point estimate of the treatment ratio of active to placebo for the ratio to baseline in blood eosinophils and FeNO have been calculated and are displayed in Table 4 and Table 5.

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
    - Applicable International Conference on Harmonization (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 authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of

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 hospitalisation but may jeopardise 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 hospitalisation, 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

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.