TITLE PAGE

Protocol Title: A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744

Protocol Number: 212895

Compound Number or Name: GSK3511294

Brief Title: A Study of **G**SK3511294 (Depemokimab) in participants who were previously enrolled **I**n 206713 or 213744; Open-**L**abel **E**xtension

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

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

Manufacturer: GSK

Regulatory Agency Identifying Number(s):

IND: 146742

EU CT number: 2023-505203-23

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

SPONSOR SIGNATORY:

David A. Lipson, M.D.
Vice President, Respiratory Disease Area Lead
GSK Development Clinical Sciences

Approval Date: 16 Jan 2025

Protocol Investigator Agreement

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the clinical study site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.

Study identifier	212895
EU CT number	**2023-505203-23**
IND number	**146742**
Approval date	16 Jan 2025
Title	A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	16 Jan 2025
Amendment 1	12 January 2023
Original Protocol	30 July 2021

Overall Rationale for the Amendment: This is an amendment for EU countries to include the EU CT number in accordance with EU CTR requirements. A description and rationale for all changes is provided below.

Section # and Name	**Description of Change**	**Brief Rationale**
Title page	Replaced EudraCT number with EU CTR number	Clarification

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744

Brief Title: A Study of GSK3511294 (Depemokimab) in participants who were previously enrolled in 206713 or 213744; Open-Label Extension

Rationale:

The efficacy and safety of GSK3511294 in participants with severe uncontrolled asthma with an eosinophilic phenotype will be evaluated in the placebo-controlled studies 206713 and 213744. The purpose of this open-label 12 month extension study is to continue to characterize the long-term safety, efficacy and immunogenic profile of GSK3511294 in participants with severe asthma with an eosinophilic phenotype following completion of clinical studies 206713 or 213744. Participants who have completed either of these prior studies will receive two doses (at Week 0 and Week 26) of add-on study intervention (either GSK3511294 100 mg or placebo) by subcutaneous (SC) injection over a 52-week treatment period. In this open-label extension study, all participants will receive two doses (at Week 0 and Week 26) of GSK3511294 100 mg SC over a study intervention period of 52 weeks.

Objectives and Endpoints

Primary (Safety)	
• To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12 month open label extension phase	• Incidence of adverse events (AEs)/ serious adverse events (SAEs) over 52 weeks • Incidence of immunogenicity as measured by the presence of anti-drug antibody (ADA)/ neutralising antibody (Nab) to GSK3511294 over 52 weeks
Secondary (Efficacy)	
• To evaluate the effects of long-term dosing of GSK3511294 100 mg (SC) every 26 weeks on a range of clinical markers of asthma control and additional efficacy assessments on top of existing asthma therapy over a 12 month open label extension phase	• Annualized rate of clinically significant exacerbations over 52 weeks • Change from Baseline in Asthma Control Questionnaire-5 (ACQ-5) score at discrete timepoints during the 52 week period • Change from Baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 26 and Week 52 • Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52

Overall Design:

This is a multicentre, single-arm, open-label 12-month extension study to evaluate the long-term safety of GSK3511294 100 mg administered SC, in addition to standard of care (SoC), in participants who have severe asthma with an eosinophilic phenotype. All participants who completed either study 206713 or 213744 will have the opportunity to participate in this study. The number of participants participating in this trial will not be greater than the combined number randomised into studies 206713 and 213744.

Brief Summary:

All participants who completed either study 206713 or 213744 will have the opportunity to enrol in this study, regardless of which treatment they were randomized to in the previous studies. Participants will be eligible to screen to enter the Open-label Extension (OLE) Study 212895 if he/she:

- has received both doses of study intervention (at Visit 2 and Visit 10), AND
- completed the scheduled Exit Visit of the parent protocol (Visit 17), AND
- did not meet any of the study intervention discontinuation conditions during the study.

The Exit Visit in 206713/213744 will serve as the Baseline Visit (Visit 1) for this study (212895). If the Exit Visit in 206713/213744 is on the same day or within 7 days of Visit 1 for study 212895 then some assessments from the Exit Visit will be used as the baseline for 212895. If the Visit 1 is performed >7 days (maximum 14 days) after the Exit Visit in 206713/213744 several of the assessments need to be repeated. A delayed administration of the study intervention may be considered (maximum 4 weeks) in consultation with the GSK Medical Monitor.

After giving informed consent for this study, eligibility will be assessed. The assessments at this baseline visit will include informed consent, updated medical history and change in smoking status.

Those participants meeting all the inclusion criteria and none of the exclusion criteria will receive their first open-label dose of GSK3511294 SC at Visit 1. Participants will receive a second dose of GSK3511294 SC approximately 26 weeks after Visit 1.

Number of Participants:

This study is an extension of Study 206713 and Study 213744. Participants must complete study 206713 or 213744 prior to entering this study. The maximum number of participants who are potentially eligible to take part in this study is not greater than the total number of participants enrolled in studies 206713 and 213744 (approximately 750 participants).

Intervention Groups and Duration:

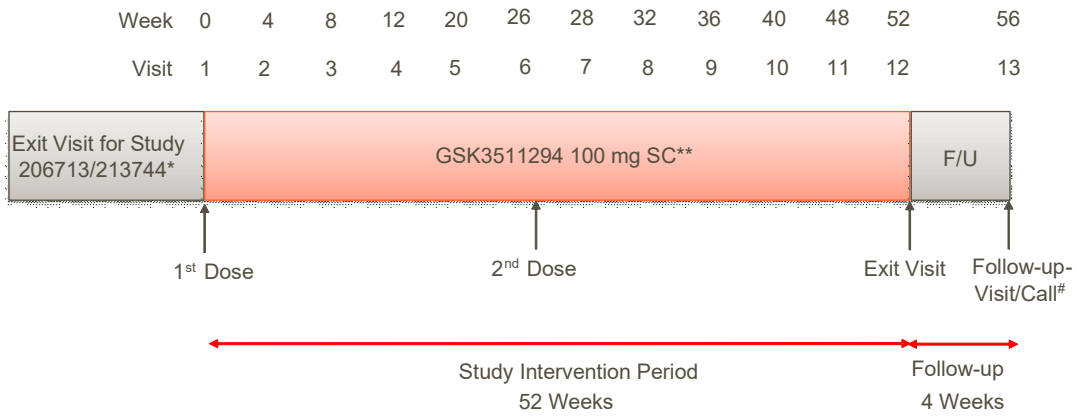
Eligible participants will be requested to participate in the study for a maximum of 56 weeks (Visit 1 to the Follow-up visit/call, inclusive). There will be a single treatment arm and all participants will receive open-label GSK3511294 100 mg SC at enrolment (Week 0) and at Week 26. The study consists of two phases described below:

- **Intervention Period**: (Duration - 52 weeks). Participants who meet the eligibility criteria will enter the open-label 52-week treatment period and receive GSK3511294 100 mg SC administered via a prefilled safety syringe, at enrolment (Week 0) and at Week 26. The Exit Visit will occur at Week 52. Following enrolment, visits will occur at Week 4 and approximately every 4 weeks (with some exceptions) thereafter with a visit at Week 26 for the administration of the second dose of GSK3511294 100 mg SC.
- **Follow-up Period:** (Duration – 4 weeks). Participants will be contacted 4 weeks after the Exit Visit. A participant will be regarded as having completed the study if they complete the treatment administration and Exit Visit and the Follow up visit/call, 4 weeks after the Exit Visit.

Study visits may be conducted remotely or virtually, however, in-person clinic visits are required for those visits with study drug administration, 12-lead ECG or spirometry assessments, as detailed in the Schedule of activities (SoA): Visit 1, Visit 2, Visit 6, Visit 7, Exit Visit 12 and Withdraw from Study (WS) Visit (if applicable). For WOCBP the follow up visit should be conducted as onsite visit or home visit (where applicable). Follow-up phone call is only applicable for male and WONCBP.

Data Monitoring/ Other Committee: Yes

1.2. Schema



**The Exit Visit in 206713/213744 will serve as the Baseline Visit (Visit 1) for this study (212895)*

*** Participants will remain on standard of care asthma therapy, which may be adjusted during the study at the discretion of their physician.*

 # Follow-up phone call is only applicable for male and WONCBP

1.3. Schedule of Activities (SoA)

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
Study Week	**0**	**4**	**8**	**12**	**20**	**26**	**28**	**32**	**36**	**40**	**48**	**52**	**56**		
Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
General Eligibility Assessments															
Informed Consent[a]	X														See footnote a.
Inclusion/Exclusion Criteria	X														
Demography data collection	X														
Medical history	X														Changes including cardiovascular (CV), CV risk factors, asthma including exacerbations, vasculitis, allergies and anaphylaxis
Smoking Status	X														
Parasitic screening	X														Parasitic screening should have been performed prior to treatment in the OLE only if the participant has travelled to high risk countries in the past six months. For details refer to study reference manual (SRM).
Safety assessments															
Concomitant Medication Assessment [c]	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X		X	See footnote c.
Physical Examination	(X)											X		X	

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
Study Week	**0**	**4**	**8**	**12**	**20**	**26**	**28**	**32**	**36**	**40**	**48**	**52**	**56**		
Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
Vital Signs	X[d]		X		X	X	X			X		X[d]		X[d]	See footnote d.
12-lead ECG	(X)	X				X	X					X		X	ECG must be performed and assessed pre-dose. Twelve-lead ECG central overread values should be used at all visits with the exception of Visit 1 and Visit 6 where 12-lead ECG machine read values should be used.
Adverse Events/Serious Adverse Event Assessment	X [e]	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X	X	See footnote e.
Laboratory Assessments															
Urine Pregnancy Test[f] (WOCBP only)	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X	X	See footnote f. All WOCBP as determined in prior study (206713/ 213744) must continue their highly effective contraceptive method without any interruptions between prior study and enrolment in this study. See Section 5.1 and Section 8.2.5 for additional details

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
Study Week	**0**	**4**	**8**	**12**	**20**	**26**	**28**	**32**	**36**	**40**	**48**	**52**	**56**		
Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
Urinalysis	(X)					X						X		X	Note: Urinalysis to be performed using dipstick test. If results are abnormal a second urine sample should be taken and sent to central laboratory. **China Only:** For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick.
Clinical Chemistry	(X)	X	X	X	X	X	X			X		X		X	Include liver chemistry.
Immunogenicity sample	(X)			X		X				X		X		X	
CCI [redacted]															CCI [redacted]
Efficacy Assessments															
Review of exacerbations	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X	X	

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
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Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
Spirometry (pre-bronchodilator FEV_1)	(X)					X						X		X	FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19
ACQ-5	(X)	X	X	X	X	X	X	X		X		X		X	ACQ-5=Asthma Control Questionnaire
Study Intervention															
Administer Study intervention	X					X									Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for hypersensitivity for at least 2 h after IP administration. For details refer to study reference manual (SRM).
Worksheets/eCRF															
Provide worksheet	X	X	X	X	X	X	X	X		X					The worksheet is a medical problems and healthcare utilisation worksheet
Review worksheet		X	X	X	X	X	X	X		X		X		X	
Dispense Rescue medication	X	X	X	X	X	X	X	X		X					
Register Visit in the IRT system	X					X								X	IRT=interactive response technology
Complete electronic Case Report Form (eCRF)	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X		X	
HRQoL: PRO and Health Outcomes Assessments															
SGRQ	(X)					X						X		X	SGRQ=St. George's Respiratory Questionnaire

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	V1 *	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Exit Visit V12	FU[i]	WS Visit [b]	FU=Follow-up visit WS=Withdrawn from study visit
Study Week	0	4	8	12	20	26	28	32	36	40	48	52	56		
Study Day	1	28	56	84	140	182	196	224	252	280	336	364	392		
CCI [redacted]															

*: If the Exit Visit in 206713/213744 is on the same day, or within 7 days of Visit 1 for study 212895 then the assessments in brackets above do not need to be performed and the assessments from the Exit Visit from 206713/213744 will be used as the baseline for 212895. Information will be transferred accordingly. If the Visit 1 performed greater >7 days (maximum 14 days) after the Exit Visit in 206713/213744 then the assessments in brackets needs to be performed (For details refer to Section 8). A delayed administration of the study intervention (maximum 4 weeks) may be considered in consultation with the GSK Medical Monitor.

a. Informed Consent must be obtained prior to initiating any study assessments.
b. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the participant withdraws before the second dose of study intervention, or at Week 52 if the second dose of study intervention was received.
c. Ensure maintenance asthma medications from the previous trial to Visit 1 and all current medications are reviewed.
d. Vital signs including height and weight should be conducted at Visit 1. Height can be omitted for subsequent visits.
e. SAEs must be collected after signing of Informed Consent.
f. Urine pregnancy testing is only required for women of childbearing potential (WOCBP). Serum pregnancy test is required at the Exit Visit of the parent protocols for all WOCBP.
g. For haematology samples CCI [redacted] the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will be blinded to site staff and sponsor to protect the blind from the previous study. Starting at CCI [redacted] haematology samples are no longer blinded. Sites will be sent total white blood counts throughout the study. Samples should be taken pre-dose on dosing days.
h. Week 36 and Week 48 are phone visits. In France, Week 36 and Week 48 are phone visits for all participants except WOCBP who will perform both visits, including the Follow Up visit, onsite.
i. A follow-up visit/call should be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing. For WOCBP the follow up visit should be conducted as onsite visit or home visit (where applicable). Follow-up phone call is only applicable for male and WONCBP.

2. INTRODUCTION

2.1. Study Rationale

Interleukin-5 (IL5) mediates the growth and differentiation of eosinophils in the bone marrow and their recruitment and activation within tissues [Corren, 2012]. Eosinophils circulate in the blood with a half-life of 8 to 18 hours and can persist in tissues for longer (days to weeks) [Kovalszki, 2016]. Therefore, inhibiting IL5 will remove a key eosinophil growth factor, and given the short half-life of eosinophils, will cause a rapid reduction in the circulating population. Reduction in eosinophils has been identified as a therapeutic strategy for numerous disorders with monoclonal antibodies (mAbs) targeting IL5, such as mepolizumab [Legrand, 2015]. Anti-IL5 therapies have an established efficacy and long-term safety profile and are a cornerstone of severe asthma management for patients with an eosinophilic phenotype. Three antagonists, of IL5 (mepolizumab and reslizumab) or its receptor (IL5R) (benralizumab) are approved for severe eosinophilic asthma, as an add-on treatment administered every 4 to 8 weeks.

GSK3511294 (Depemokimab) is being developed as a long-acting (LA) SC injectable anti-IL5 therapy and is anticipated to deliver an efficacy and safety profile similar to the current anti-IL5 therapies with a reduced dosing frequency (once every 26 weeks). The long-term safety, efficacy and immunogenic profile of GSK3511294 has not been characterised.

The aim of this study is to provide long-term safety data for GSK3511294 following completion of treatment in clinical trial 206713 or 213744. Participants in these prior studies will receive either GSK3511294 100 mg subcutaneously (SC) or placebo. In this open-label extension study, all participants will receive GSK3511294 100 mg SC for 52 weeks; therefore, participants that received GSK3511294 in clinical trial 206713 or 213744 will have received approximately 104 weeks of GSK3511294 exposure after completion of 212895.

2.2. Background

Persistent eosinophilic inflammation is a feature of more than 50% of the patients with severe asthma [Chung, 2014]. Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorisation for asthma with an eosinophilic phenotype, including 3 targeting either interleukin-5 (IL5) or its receptor (IL5R): mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra), respectively. All three, by utilizing blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations and improve lung function and health-related quality of life (HrQoL) in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL5/5R is provided by long-term extension studies of mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data of mepolizumab in real-world evidence settings [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence, have demonstrated that treatments targeting the IL5 pathway are both highly effective and well tolerated. Based on this established efficacy and safety, anti-IL5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimised care with Step 4 or Step 5 treatment (medium and high dose ICS) [GINA, 2020].

GSK3511294 is a humanised, affinity matured mAb that blocks human IL5 binding to its receptor and belongs to the established class of anti-IL5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid substitutions in the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region, and 3 amino acid changes (YTE) in the Fc region. The resulting antibody has increased affinity and half-life. Evidence to date indicate that these amino acid changes extend the PK and pharmacology of GSK3511294 to enable less frequent dosing with an anticipated similar safety and efficacy profile relative to mepolizumab (administered chronically).

Long-acting (LA) alternatives that can be administered on a less frequent basis are recognised as successful approaches for chronic indications. As a LA anti-IL-5 therapy, GSK3511294 is anticipated to deliver similar efficacy and safety as currently approved therapies in its class but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses).

A detailed description of the chemistry, pharmacology, efficacy and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GSK Document Number RPS-CLIN-044550 or later].

2.3. Benefit/Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and completed first time in humans (FTIH) study 205722 can be found in the current IB [GSK Document Number RPS-CLIN-044550 or later]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3511294		
• Allergic reactions including anaphylaxis.	• Allergic reactions, with the most severe form being anaphylaxis (see Appendix 8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity Standardised MedDRA Queries (SMQ) with preferred term of rash verbatim "localised rash both bends of arms", 82 days post 30 mg SC dose of GSK3511294. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator	• Daily monitoring of serious adverse events (SAEs) by medical monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. • Use of Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at Visit 1 and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care, if appropriate. • Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1 month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded to from enrolment if diagnosed (Section 5.2). • Daily monitoring of serious adverse events (SAEs) by medical monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies will be performed by a GSK safety review team. • Protocol guidance on early identification of vasculitis events is provided (see Section 7.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first open-label dose will not receive another dose of study intervention (see Section 7.1).
• Immunogenicity, anti-drug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and neutralising antibodies (NAb), which have the potential to modulate PK or PD, or to produce adverse reactions.	• Blood samples will be collected for detection of both ADA and Nab (See Section 8.8).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the GSK3511294 30 mg dose group (5 participants), which was also the group with the highest total serum IL5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the GSK3511294 plasma concentration profiles and blood eosinophil count-time profiles, as well as AE reporting between ADA positive and ADA negative participants. Neutralizing antibodies were not tested in this study.	
• Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies.	• Daily monitoring of SAEs by medical monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• In the GSK3511294 FTIH study (205722), injection site reactions were reported by one (3%) participant who received GSK3511294 and one (8%) participant who received placebo.	
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), a total of 2 participants had an elevated post-baseline QTcF value of potential clinical importance based on average from triplicate assessment: one on GSK3511294 100mg SC [Week 2: 467 msec (all subsequent assessments were <450 msec and Day 1 pre-dose was 450 msec)] and one on placebo [Week 36: 455 msec (last assessment on study and Day 1 pre-dose was 414 msec)]	• ECGs will be performed according to time points specified in SoA Section 1.3 and assessment will be done as specified in Section 8.2.3. • Participants with QTc prolongation at visit 1 will be excluded (criterion 6, Section 5.2). • Participants who meet QTc stopping criteria as specified in Section 7.1.3 after the first open-label dose will not receive the second open-label dose.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Risk of GSK3511294 affecting an unborn baby.	• Reproductive studies have not been conducted with GSK3511294; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages in sexually mature males. No cell or stage specific abnormalities were noted.	• Participants who are pregnant, breastfeeding, or plan to become pregnant during the study are excluded (criterion 10, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • For all female participants of childbearing potential continuation of highly effective contraceptive method between the previous study (206713/213744) and enrolment into this study without any interruptions is required and must continue until 30 weeks after the last dose. • In case the highly effective contraceptive method was interrupted prior to enrolment in this study, the reason must be discussed with medical monitor and the following must be done: ➢ Highly effective contraceptive method must be restarted and continued for at least 14 days prior to first dose

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• In addition, there is a low reproductive risk associated with the IL5 target mechanism (as shown in pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of monoclonal antibody (mAbs) into semen due to the inability of large molecular weight proteins such as GSK3511294 to access pivotal cells in the testes [Setchell, 1975; Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).

2.3.2. Benefit Assessment

Current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype. The safety profile of anti-IL5/5R mAbs is favourable. Based on the positive benefit: risk, anti-IL5/5R mAbs have been approved as add-on maintenance treatment for severe eosinophilic asthma.

As a long-acting anti-IL5 mAb, GSK3511294 is anticipated to provide the same clinical benefit with a similar safety profile compared with others in its class and with the added benefit of less frequent SC dosing (once every 6 months). As such, GSK3511294 may offer the convenience of an improved dosing schedule.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants enrolled in this study, the potential risks identified in association with GSK3511294 are justified by the anticipated benefits that may be afforded to participants with severe uncontrolled asthma with an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the safety and efficacy of GSK3511294 is justified in study 212895 with a positive benefit: risk ratio.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary (Safety)	
• To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12 month open label extension phase	• Incidence of AEs/SAEs over 52 weeks • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294 over 52 weeks
Secondary (Efficacy)	
• To evaluate the effects of long-term dosing of GSK3511294 100 mg (SC) every 26 weeks on a range of clinical markers of asthma control and additional efficacy assessments on top of existing asthma therapy over a 12 month open label extension phase	• Annualized rate of Clinically significant exacerbations over 52 weeks • Change from Baseline in Asthma Control Questionnaire-5 (ACQ-5) score at discrete timepoints during the 52 week period • Change from Baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 26 and Week 52. • Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52
Other	
• To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12 month open label extension phase	• ECG assessments at discrete timepoints during the 52 week period o Change from baseline in ECG values o Maximum QTc values post baseline o Maximum increase in QTc values post baseline o ECG findings • Change from baseline in vital signs including blood pressure (BP), body temperature, and pulse rate at discrete timepoints during the 52 week period

Objectives	Endpoints
	• Change from baseline in laboratory parameters (including haematological, clinical chemistry) and hepatobiliary laboratory abnormalities, at discrete timepoints during the 52 week period
CCI [redacted]	
Pharmacodynamic (PD)	
CCI [redacted]	

3.1. Primary Estimand

Treatment: open-label GSK3511294 + SoC

- open-label GSK3511294 + SoC and on GSK3511294 + SoC in previous study
- open-label GSK3511294 + SoC and on placebo + SoC in previous study

Population: Adult and adolescent participants with severe asthma with an eosinophilic phenotype following the strategy outlined for dealing with the main intercurrent events that are anticipated.

Endpoints:

- Incidence of AEs/SAEs
- Incidence of immunogenicity measured by the presence of ADA/NAb to GSK3511294

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on-treatment strategy i.e. using data up until 26 weeks after last dose of GSK3511294. This strategy is to summarise the events while the participants are exposed to the treatment.

- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on-treatment strategy i.e. using data up until 26 weeks after last dose of GSK3511294
- Change in maintenance therapy or use of prohibited medications: CCI [redacted]

Summary measures:

- Number and percentage of participants with any AEs and incidence rate of AEs
- Number and percentage of participants with incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294 and mean titre results

3.2. Secondary Estimands

Treatment: open-label GSK3511294 + SoC

- open-label GSK3511294 + SoC and on GSK3511294 + SoC in previous study
- open-label GSK3511294 + SoC and on placebo + SoC in previous study

Population: Adult and adolescent participants with severe asthma with an eosinophilic phenotype following the strategy outlined for dealing with the main intercurrent events that are anticipated.

Endpoints:

- Annualised rate of clinically significant exacerbations over 52 weeks
- Change from Baseline in ACQ-5 score at discrete timepoints during the 52-week period
- Change from Baseline in SGRQ total score at Week 26 and Week 52.
- Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: CCI [redacted]
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted]
- Change in maintenance therapy or use of prohibited medications: treatment CCI [redacted]

Summary measures:

- Annualised rate of clinically significant exacerbations
- Mean Change from Baseline in SGRQ total score, ACQ-5 score, pre-bronchodilator FEV_1 at discrete timepoints during the 52-weeks period

4. STUDY DESIGN

4.1. Overall Design

This is a multicentre, single-arm, open-label 12- month extension study to evaluate the long-term safety of GSK3511294 100 mg administered SC, in addition to standard of care, in participants who have severe asthma with an eosinophilic phenotype. Participants who completed either study 206713 or 213744 will have the opportunity to participate in this study, regardless of which treatment they were previously randomized. The number of participants enrolled in this trial will not be greater than the combined number randomised into Studies 206713 and 213744. Participants will be eligible to screen to enter the open-label extension (OLE) Study 212895 if he/she:

- has received both doses of study intervention (at Visit 2 and Visit 10) AND
- completed the scheduled Exit Visit (Visit 17) AND
- did not meet any of the study intervention discontinuation conditions during the study.

Visit 1 will serve as the Baseline Visit for this study (212895). If the Exit Visit in 206713/213744 is on the same day or within 7 days of Visit 1 for study 212895 then some assessments from the Exit Visit will be used as the baseline for 212895. If the Visit 1 is performed >7 days (maximum 14 days) after the Exit Visit in 206713/213744 several of the assessments need to be repeated (for details refer to Section 8). A delayed administration of the study intervention may be considered (maximum 4 weeks) in consultation with the GSK Medical Monitor.

After giving informed consent for this study, eligibility will be assessed. The assessments at this baseline visit will include informed consent, updated medical history, and change in smoking status.

Those participants meeting all the inclusion criteria and none of the exclusion criteria will receive their first open-label dose of GSK3511294 SC at Visit 1. Participants will receive a second open-label dose of GSK3511294 SC 26 weeks after Visit 1, providing up to 52 weeks of treatment. Participants who experience any of the study intervention discontinuation conditions (listed in Section 7.1) will not receive another dose of study intervention.

Participants will remain on standard of care asthma therapy, which may be adjusted during the study at the discretion of their physician. The use of any other anti-IL-5/5R therapy mepolizumab (Nucala), benralizumab (Fasenra), reslizumab (Cinqair/Cinqaero) or any other monoclonal antibody including omalizumab (Xolair) and dupilumab (Dupixent), will not be permitted during the course of the study.

Serum samples for anti-GSK3511294 antibody measurements will be obtained from all participants according to the time points specified in SoA (Section 1.3). Any sample obtained for anti-GSK3511294 antibody testing that tests positive will be tested for neutralizing antibody.

Participants will be monitored for a minimum of two hours after each dose and safety and efficacy will be assessed according to the time points specified in the SoA (Section 1.3). The Asthma Control Questionnaire-5 (ACQ-5) and SGRQ will be used to assist the investigator in assessing the participant's asthma status along with spirometry. As some subjects may have previously received placebo while participating in the 206713 and 213744 studies and are naïve to GSK3511294, safety lab monitoring will be more frequent after each dose administration. Participants will be regarded as having completed the current study if they complete the 52-week treatment administration, Exit Visit and an additional Follow-up visit/call, 4 weeks after the Exit Visit.

For WOCBP the follow up visit should be conducted as onsite visit or home visit (where applicable). Follow-up phone call is only applicable for male and WONCBP.

Study visits may be conducted remotely or virtually, however, in-person clinic visits are required for those visits with study drug administration, 12-lead ECG or spirometry assessments, as detailed in the SoA (Section 1.3): Visit 1, Visit 2, Visit 6, Visit 7, Exit Visit 12, and WS Visit (if applicable). Participants who are unable to attend their scheduled clinic visits due to COVID-19 restrictions or other unexpected events may complete some visits at home (see Appendix 9).

4.2. Scientific Rationale for Study Design

This study will allow participants that completed Study 206713 and Study 213744 to initiate GSK3511294 100 mg SC treatment if they were previously randomised to placebo, or continue with GSK3511294 if previously randomised to receive GSK3511294 100 mg SC. This will increase the overall number of participants exposed to GSK3511294 by permitting participants previously on placebo to be treated with GSK3511294 100 mg SC, while allowing exposure of up to a total of 104 weeks for participants previously receiving GSK3511294 in Study 206713 and 213744.

GSK3511294 100 mg SC will be administered as adjunctive therapy to the participant's usual treatment. Investigators should continue participants on their maintenance asthma therapy and adjust this therapy as needed in response to improving or worsening asthma. All changes in asthma therapy will be captured in the source and electronic case report form (eCRF).

Participants will be evaluated in the clinic after each dosing occasion and approximately every 4 weeks (with some exceptions) thereafter. The Asthma Control Questionnaire-5 (ACQ-5) and SGRQ will be used to assist the investigator in assessing the participant's asthma status along with spirometry.

4.2.1. Participant Input into Design

Participant involvement in the study design was obtained from 10 patients (6 in Italy, 1 in UK, and 3 in US [1 adolescent]) using 2 online qualitative surveys containing 17 questions over a period of 2 weeks. Based on the participant feedback, the following design elements will be implemented:

- Reduced number of laboratory samples and patient-reported outcomes (PRO) assessments
- A hybrid trial model, allowing for home visits and virtual/telemedicine visits at key assessments which will reduce the burden of onsite visits and offer some flexibility in visit timing for the participant's schedule.

4.3. Justification for Dose

The dose rationale for this study is supported by the FTIH Study 205722 [GSK Document Number RPS-CLIN-044550] that investigated single SC doses of GSK3511294 ranging from 2 mg to 300 mg. The FTIH study was designed to collect robust blood eosinophil pharmacology data (including washout) in a relevant population (mild to moderate asthma and a blood eosinophil count ≥200 cells/μL at screening) and inform dose selection in late-phase development using Model-informed drug development (MIDD) principles [Wang, 2019; Marshall, 2019]. The precedence of using blood eosinophil reduction as a predictor of efficacy in severe asthma with an eosinophilic phenotype was established in two mepolizumab Phase 3 studies, which consistently reduced annualised exacerbation rate by approximately 50%, for associated reductions in blood eosinophils of 84% in the MENSA trial [Ortega, 2014] and 78% in the MUSCA trial [Chupp, 2017], compared with placebo. Since GSK3511294 targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils as mepolizumab via the same IL-5 neutralisation is expected to generate the same clinical efficacy in the same patient population (i.e., severe asthma with an eosinophilic phenotype with a previous history of two or more exacerbations in the past 12 months). In addition, given the precedented safety profile of IL-5 neutralisation comparable to placebo, targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of GSK3511294.

A comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils from Study 205722 was therefore conducted to identify the dose and frequency of dosing that match previous Phase 3 mepolizumab target pharmacology most closely. To this end, a Bayesian non-linear mixed-effects dose-time response model was used to analyse blood eosinophil data. This model was then used to calculate the posterior probability of achieving reductions of 78% for the MUSCA trial [Chupp, 2017] and 84% for the MENSA trial [Ortega, 2014] compared with placebo. Doses deemed suitable were defined as having a probability of exceeding MUSCA in excess of 80% while doses deemed unsuitable as having a probability of exceeding MENSA of less than 10%.

Based on the comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils, a dose of 100 mg SC GSK3511294 administered every 26 weeks has been selected to match the pharmacology seen with mepolizumab in two Phase 3 studies at the approved therapeutic dose, but over an extended period of 26 weeks [GSK Document Number 2019N418119_00].

4.4. End of Study Definition

The end of the study is defined as the date of the last follow-up visit/call for the last participant in the trial.

Participants will be considered to have completed the study if he/she has completed the Exit Visit and the Follow-up visit/call, 4 weeks after the Exit Visit, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
1. **Participants:** Participants who completed the double-blind study intervention treatment during Study 206713 or Study 213744. 2. Age: Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent. CCI [redacted].

SEX
CCI [redacted]

SEX
CCI [redacted]

INFORMED CONSENT
4. **Informed Consent:** Capable of giving signed informed consent/assent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
5. **French participants**: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. **Health Status:** Clinically significant change in health status during Study 206713 or Study 213744 which in the opinion of the investigator would make the participant unsuitable for participation in this study.

MEDICAL CONDITIONS

2. **Malignancy:** A current malignancy or a malignancy that developed during Study 206713 or Study 213744 (participants who had localised carcinoma of the skin that was resected for cure will not be excluded).
3. Participants who have other clinically significant medical conditions uncontrolled with SoC therapy not associated with Asthma, e.g., uncontrolled cardiovascular disease or ongoing active infectious disease which in the opinion of the investigator makes them unsuitable for the study.
4. Participants with known parasitic (helminth) infections within 6 months prior to Visit 1 will be excluded from the study or required to be adequately treated for helminth infections before initiation of GSK3511294.
5. Liver chemistry test: Participants who meet the following based results of week 48 assessment from Study 206713 or Study 213744 or from a later result:
    a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
    b) Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
    c) Liver Disease: Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice.

    NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome,

    asymptomatic gallstones, and chronic stable hepatitis B or C) are acceptable if participant otherwise meets eligibility criteria.
6. Vasculitis: Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment.
7. ECG Assessment: QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block in the 12-lead ECG machine read at Visit 1.

OTHER EXCLUSIONS

8. Smoking status: Current smokers
9. Hypersensitivity: Participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1, a monoclonal antibody, or biologic.
10. Pregnancy: Participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation. Requirements for pregnancy testing are located in Section 8.2.5.

OTHER EXCLUSIONS
11. Permanent Discontinuation of study intervention in Previous Study: Participants who for any reason permanently discontinued study treatment in the previous study 206713/213744 will be excluded from this study. 12. Other investigational product/clinical study: • Participants who have received treatment with an investigational agent (biologic or non-biologic) within the past 30 days or 5 drug half-lives whichever is longer, prior to the first dose, other than Study 206713/213744 study treatment. The term "investigational" applies to any drug not approved for sale for the disease/indication to treat in the country in which it is being used or investigational formulations of marketed products • Participants who are currently participating in any other interventional clinical study

5.3. Lifestyle Considerations

No Lifestyle restrictions are required.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying Enrolment/ Administration of Study Intervention Administration

A delayed administration of the study intervention (>14 days after the Exit Visit in 206713/213744 and up to a maximum of 4 weeks) may be considered in consultation with the GSK Medical Monitor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention will only be administered in the clinic; hence, Visit 1 (Week 0) and Visit 6 (Week 26) are required to be in-clinic visits.

6.1. Study Intervention(s) Administered

GSK3511294 is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. GSK3511294 liquid drug product will be supplied by GSK in Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex-free rubber plunger). The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each device enables SC delivery of 100 mg GSK3511294 in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, disodium edetate (EDTA), water for injection and polysorbate 80.

An overview of study intervention is provided in Table 1.

Table 1 Overview of Study Intervention

ARM Name	GSK3511294 100 mg
Intervention Name	GSK3511294 100 mg SC
Type	Biologic
Dose Formulation	Sterile liquid formulation in single-use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)
Route of Administration	SC injection
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product

6.1.1. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices:

- A pre-filled syringe contained within a safety syringe device. The devices used in the study are representative of the devices planned to be marketed for the product.
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) are sourced from Becton Dickinson. The pre-filled syringe is filled and assembled at GSK, Barnard Castle.
- The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.

The Instruction for use (IFU) of the injection device will be provided. The instructions were developed and optimised as a result of formative human factors studies for mepolizumab and are representative of those that are planned for GSK3511294.

All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by GSK.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study, randomization is not applicable. In order to maintain the blind from previous studies, WBC differential (% and total) will be blinded at screening CCI [redacted]. Sites to continue the blinding strategy from 206713 and 213744 studies CCI [redacted]

6.4. Study Intervention Compliance

GSK3511294 will be administered under medical supervision via SC injection to participants by the investigator or designee at the study site. Dose administration details (date and time) will be recorded in the source documents and reported in the CRF.

Participants will be monitored in clinic for a minimum of 2 hours post-dose to monitor for immediate hypersensitivity and any other untoward event (For details refer to SRM). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of GSK3511294, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate.

6.5. Dose Modification

Dose modification is not allowed.

6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study. The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

6.7. Treatment of Overdose

The dose of GSK3511294 that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 [GSK Document Number RPS-CLIN-044550 or later], single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS will enable the delivery of a single dose of study intervention (see Section 6.1).

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the patient with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of GSK3511294.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding discontinuation or delay of another dose of study intervention will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

At enrolment, information on the participant's baseline SoC asthma therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Permitted Medications and Non-Drug Therapies

Throughout the study, participants are to be maintained on SoC asthma treatment. During the study, adjustments may be made to participant's asthma maintenance therapy based on the investigator's judgment.

If uncertain whether a medication is permitted, please confirm with the Medical Monitor.

Albuterol/salbutamol is permitted throughout the study but should, if possible, be withheld in the 6-hour period prior to spirometry assessments.

LABAs, LAMAs, ICS/LABA or ICS/LABA/LAMA fixed dose combinations should be withheld for ≥12 hours prior to spirometry, if possible.

Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) for the treatment of obstructive sleep apnoea is permitted. This treatment must be captured in the eCRF.

Participants can be vaccinated against SARS-CoV-2 infection using authorized COVID-19 vaccines in line with local/national guidelines for COVID-19 vaccines. Experimental COVID-19 vaccines are not permitted.

COVID-19 vaccination is permitted and should follow local regulations. COVID-19 vaccine administration and the study site injection should be separated by 14 days if possible, in order to be able to properly assess study injection site/treatment reactions.

6.8.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed during the study:

Medication

Monoclonal antibodies and Investigational drugs

- Any investigational drug/vaccine.
- Mepolizumab [Nucala], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra], Omalizumab [Xolair], dupilumab [Dupixent]
- Other monoclonal antibodies
- Experimental anti-inflammatory drugs (non-biologicals)

Immunosuppressive medications such as those listed below (not all inclusive)

- Regular systemic (oral or parenteral) and intramuscular, long-acting depot corticosteroids if used to treat a condition other than asthma
- Methotrexate, cyclosporin, azathioprine
- Oral gold
- Chemotherapy used for conditions other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded throughout the study.

6.8.3. Rescue Medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication throughout the study. Albuterol/salbutamol will be sourced for all centres. Low dose ICS-formoterol as rescue medication is not allowed.

Participants will be dispensed an MDI at Visit 1 to be used primarily to treat asthma symptoms on an as needed basis (see Section 8.4.3). The MDI should be replaced as needed.

Although the use of rescue medications is allowable (at any time during the study), the use of rescue medications should be delayed, if possible, for at least 6 hours prior to the spirometry assessments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

No further doses of study intervention will be administered to participants who meet any of the following permanent treatment discontinuation conditions at any time during the study treatment period:

- Meets any of the protocol-defined liver chemistry stopping criteria, (see Section 7.1.1)
- ECG: meets any of the protocol-defined QTc stopping criteria (see Section 7.1.3)
- Pregnancy: Positive pregnancy test (see Section 8.2.5)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 8)
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.4).

If a participant meets any of the treatment discontinuation conditions or chooses (for any reason) not to receive an additional dose of study intervention before the end of the protocol specified intervention period:

- The Investigator will make every effort to encourage the participant to remain in the study **and** to continue with all remaining study visits, including the Exit Visit and Follow-up Visit/call.
- The primary reason for discontinuation of study intervention (e.g., AE, lack of efficacy, protocol deviation, investigator discretion, consent withdrawn etc.) must be recorded in the eCRF.
- Participants will be provided with the option to continue to have regularly scheduled in-clinic visits or to have regularly scheduled phone visits. The required study assessments will depend on whether the participant is attending an in-clinic visit or a scheduled phone visit. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed.
- If for any reason, the participant later chooses to withdraw from the study, a Withdraw from Study Visit (see Section 7.2) should be conducted according to the SoA (Section 1.3).

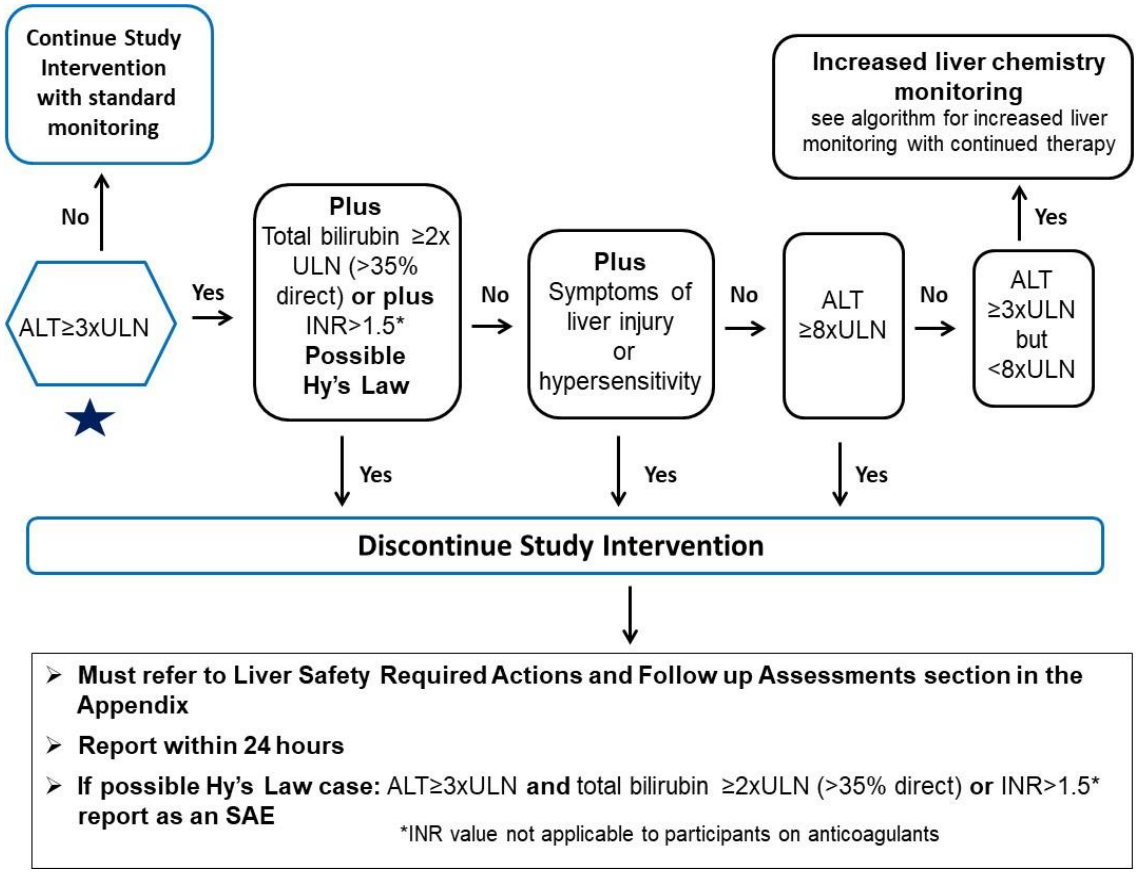
7.1.1. Liver Chemistry Stopping Criteria

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

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

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

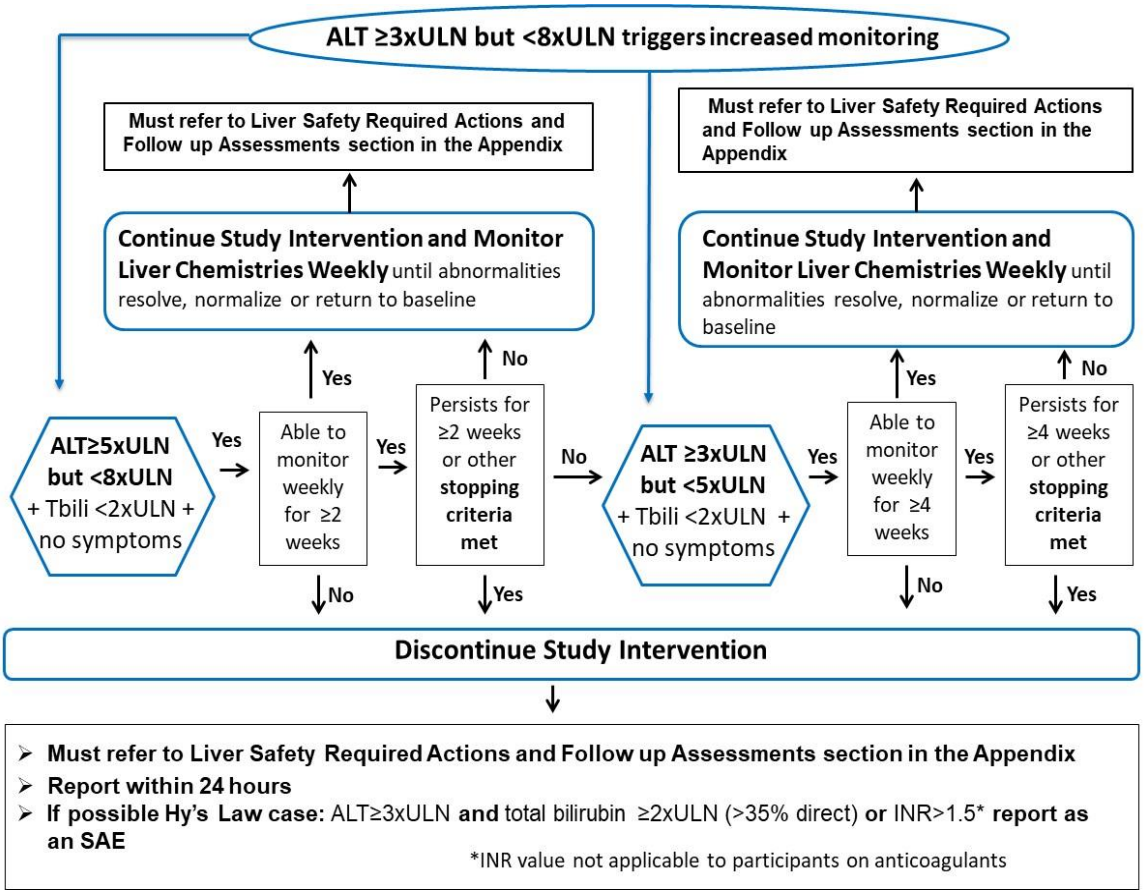
Liver Chemistry Stopping Criteria Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Refer to Appendix 6, for required Liver Safety Actions, Monitoring and Follow up Assessments.

Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN and do not meet any of the liver stopping criteria



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Appendix 6, for required Liver Safety Actions, Monitoring and Follow up Assessments.

7.1.2. Rechallenge

7.1.2.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.3. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.2.3.

The QT interval corrected using Fridericia's formula (QTcF) must be used for each individual participant to determine eligibility for and discontinuation from the study intervention. This formula may not be changed or substituted once the participant has been enrolled. For this study, the following QTc stopping criteria will apply:

- QTcF >500 msec OR Uncorrected QT >600 msec
- Change from Baseline of QTcF >60 msec

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

Baseline QTcF with Bundle Branch Block	**Discontinuation QTcF with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The QTcF value from the 12-lead ECG central over-read at Visit 1 should be used as baseline QTcF value for any changes from baseline calculations during the study. Twelve-lead ECG central overread values should be used at all visits with the exception of Visit 1 and Visit 6 where 12-lead ECG machine read values should be used. After Visit 1 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 6 (Week 26) where 12-lead ECG machine read values should be used.

7.1.4. Temporary Discontinuation

For this study, a temporary discontinuation refers to a delayed administration of the second open-label dose of study intervention at Week 26.

A delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor due to clinical or safety reasons (eg. If a participant becomes infected [parasitic infection] during the study intervention period before receiving the second dose of study intervention and does not respond to anti helminth treatment).

7.2. Participant Discontinuation/Withdrawal from the Study

- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely discontinue study intervention product and withdraw from the study at any time at his/her own request, at the request of their legally authorised representative (LAR), or at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
    - a Withdraw from Study (WS) Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
    - a Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy assessment. WOCBP will need to perform the follow up visit as onsite visit or home visit.

  Note: This includes any participants who initially discontinue IP and remain in the study (Section 7.1) but later decide to withdraw from the study.
- Participants who permanently discontinue IP are not required to withdraw from the study. If a participant must permanently discontinue IP, every effort should be made by the Investigator/site staff to keep the participant in the study to collect important safety and efficacy data. Participants who have permanently discontinued IP and have not withdrawn consent may continue in the study to complete all remaining protocol specified visits by continued in-clinic visits or by phone contact.
- For participants who discontinue IP and withdraw from the study, the Withdraw from Study Visit should be conducted as per SoA.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (or scheduled phone calls, if applicable) 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. A final attempt will be made to contact the participant for a safety follow-up 30 weeks after the last administered dose of study intervention.

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

7.4. Reasons for Study Intervention Discontinuation and/or Study Withdrawal

The primary reason for a study intervention discontinuation and/or study withdrawal will be recorded in the eCRF. When a participant withdraws consent, the investigator must document the reason (if specified by the participant) in the eCRF.

7.5. Criteria for Follow-up of Potential Type III Hypersensitivity (Immune Complex Disease /Vasculitis)

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not 6-month, nonclinical toxicology studies, events potentially representing type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the medical monitor is encouraged. Treatment for the event will be given as medically required. If possible, ADA, C3, and C4 samples may be taken at the time of the event along with haematology, clinical chemistry and urinalysis.

Symptoms potentially suggestive of vasculitis include but are not limited to:

- persistent* fever (*where persistent is considered to be a duration of ≥ 2 days)
- persistent* muscle and joint pain
- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, like numbness or weakness

- laboratory abnormalities, e.g., decreased platelets, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

Participants who experience any of the above events should be monitored until the event resolves and/or a diagnosis is established.

The symptoms and clinical features are often non-specific and heterogeneous with respect to the time course over which they develop, organ involvement and the constellation of symptoms and severity. Early recognition of potential events of vasculitis is important to timely diagnosis and subsequent treatment.

The precise management will depend on the clinical evaluation at the time of presentation and ongoing assessment including consideration of relevant differential diagnoses. Given that there is often a differential for presenting symptoms such as infection, and indeed such factors may also precipitate immune related AEs, these factors (infectious, neoplastic, metabolic, toxic) should be given due consideration and ruled out.

Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis and consultation with the GSK medical monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.

Unscheduled ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., ANA, anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [PR3] antibody), may also be conducted using the frozen baseline serum samples from the preceding study 206713 or 213744 (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.7.2). Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

If clinically indicated, the patient may be referred to a specialist for further management, which may include organ biopsy.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA 1.3.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All enrolment evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- For haematology samples CCI [redacted], the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will be blinded to site staff and sponsor to protect the blind from the previous study.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants should be provided a quiet space in which to complete patient-reported outcomes (PRO), prior to other assessments and procedures. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. Family or friends should not influence the answers. Site staff should encourage participants to complete all questions.

8.1. Screening and Critical Baseline Assessments

8.1.1. Critical Assessments performed at Enrolment (Visit 1)

The following assessments must be performed for all participants at Visit 1:

- Informed consent
- Assessment of inclusion/exclusion criteria
- Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF. Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.
- Review and document any changes in Medical History

- Review of prior/concomitant medication
- Review and document any change in Smoking Status
- Review for exacerbations. If Visit 1 for 212895 is not on the same day as the exit visit for the preceding study (206713 or 213744) then any asthma exacerbations that occurred between the two studies should be recorded as historical asthma exacerbations for study 212895.
- Urine pregnancy test for females of childbearing potential
- Provide medical problems and healthcare utilisation worksheet (see Section 8.9)

8.1.2. Assessments performed if the time between the Exit Visit from the prior study (206713/213744) and Visit 1 is >7 days

The following assessments need only be performed if the time between the Exit Visit from the prior study (206713/213744) and Visit 1 is >7 days:

- Physical Examination
- 12-lead ECG
- Urine analysis
- Blood sampling for:
  - Complement C3/C4
  - Hematology
  - Clinical chemistry
  - Immunogenicity
- Spirometry (pre-bronchodilator FEV_1)
- ACQ-5
- SGRQ

All clinic visits from Visit 1 to the Exit Visit (or if applicable, the WS Visit or the Follow-up Visit) should be completed in the relevant eCRF form. Visit 1, 6 and WS visit must be registered in the IRT.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3) – where possible, these should be aligned with standard of care.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, eyes, cardiovascular, respiratory, gastrointestinal and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.
- Vital signs including height and weight should be conducted at Visit 1. Height can be omitted for subsequent visits.

8.2.3. Electrocardiograms

- Twelve-lead ECGs will be obtained at the time points specified in the SoA (see Section 1.3) using an ECG machine, provided by GSK via a designated central laboratory, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The QTcF formula must be used for *each* individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled. Refer to Section 7.1.3 for the QTcF formula.
- If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the patient should be enrolled or discontinued from the study intervention (but not from the study). Refer to Section 5.2 for exclusion criteria related to ECG assessment and Section 7.1.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method.

- Paper ECG traces are required to be maintained at the site with other source documents.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA Section 1.3 for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, 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 until the Exit Visit (or Follow-up if applicable) 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 clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.
- For haematology samples [redacted], the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will be blinded to site staff and sponsor to protect the blind from the previous study.

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Urine pregnancy testing should be conducted as per SoA (Section 1.3) during study intervention period.
- For all WOCBP, serum pregnancy test should be done at Exit Visit of 206713/213744 study and urine pregnancy testing must be performed at Visit 1 prior to receiving first dose.
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last dose of study intervention
- Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the WS Visit

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3. Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]) can be found in Section 10.7. Device deficiencies are covered in Section 10.7.

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

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the start of intervention until the Follow-up Visit/call at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the Follow-up Visit/call at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions (in the eCRF) not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to GSK within 24 hours of it being available.

- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.3.2. 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.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 30 weeks after the last study drug administration.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within **24 hours** of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 in the study will discontinue study intervention and if possible, remain in the study and continue with all remaining study visits.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

The Death CRF page 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.

8.3.7. Adverse Events of Special Interest

Adverse events of special interest include:

- Allergic reactions including anaphylaxis
  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 8).
- Type III hypersensitivity (immune complex disease/vasculitis)

- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.3.8. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.3.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the sponsor by email. If email is unavailable, then fax should be utilised.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.3.8.4. Regulatory Reporting Requirements for Medical Device Incidents

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

8.4. Efficacy Assessments

8.4.1. Efficacy Endpoints

Efficacy endpoints are listed in Section 3.

8.4.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by worsening of asthma which requires:

- use of systemic CSs or
- hospitalisation or Emergency Department (ED) visit**,** requiring systemic steroids.

For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM corticosteroid dose is required. For participants on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Details of each asthma exacerbation, including medications used to treat exacerbations should be recorded in the eCRF.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of a SAE.

The time period for collection of exacerbation information in the eCRF will be from the time that the ICF is signed until the Exit Visit or Follow-up Visit/call or Withdraw from Study Visit as applicable.

8.4.3. Spirometry

Spirometry lung function assessments will be performed for all participants at specified visits to assess FEV_1. At least 3 valid spirometry efforts should be attempted (with no more than 8 attempts) using the ATS guidelines [Miller, 2005]. Spirometry includes FEV_1, percent predicted FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC. Spirometry assessments will be performed at screening (Visit 1), and at scheduled in clinic- visits according to the SoA (Section 1.3). At each visit where spirometry is performed, spirometry should be performed at the same time of the day (±1 hour) as the assessment performed at Visit 1 (the baseline assessment). Participants should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs/LAMAs for ≥12 hours prior to the clinic visit, if possible.

Spirometry should not be conducted for participants with confirmed/suspected COVID-19 infection.

8.4.4. Asthma Control Questionnaire (ACQ-5)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze) over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. This will be completed according to the SoA (Section 1.3).

8.4.5. St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well-established instrument, comprising 50 items designed to measure Quality of Life in participants with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered as per guidance from the measure developers and completed according to the SoA (Section 1.3).

CCI

8.5. Pharmacokinetics

Not applicable.

8.6. Genetics and Pharmacogenomics

Not applicable.

8.7. Biomarkers/Pharmacodynamic Markers

CCI

8.8. Immunogenicity Assessments

Antibodies to GSK3511294 will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. Processing, storage and shipping procedures are provided in the SRM.

In the immunogenicity assessment for GSK3511294, a tiered analyses approach will use a validated binding ADA assay (screening, confirmation and titration assays) and a validated neutralization antibody (NAb) assay. If necessary, further immune response characterization may be performed as needed.

CCI

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Because the study has a single treatment arm, statistical analyses of treatment effect will not be performed. Therefore, no hypotheses have been defined for this study.

9.2. Sample Size Determination

There is no sample size calculation for this study since this is an estimation study with the primary aim to estimate long-term safety outcomes. The sample size will be determined by the number of available participants who were randomised into Study 206713 and Study 213744 and are eligible for the current study based on inclusion and exclusion criteria.

This study is an extension of Study 206713 and Study 213744. Participants must have completed the study intervention during Study 206713 or 213744 prior to entering this study. The maximum number of participants who are potentially eligible to take part in this study is approximately 750. Assuming 15% drop out rate, 637 will be enrolled into this open label safety study.

The primary endpoints are incidence of AE/SAE and incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294. Table 2 gives the probability of observing various numbers of events over an averaged on-treatment observation period, e.g., AE, for different anticipated population risks given a sample size of 637. For example, for a risk of an AE of 1/1000, we would have approximately 50% chance of observing at least one AE over an averaged on-treatment observation time period. Also, for a risk of 1/10,000, would have 6.5% chance of seeing at least one AE over an averaged on-treatment observation time period

Table 2 Probabilities of observing a given number of adverse events or more (k)

	Risk of an Event					
k	0.0200	0.0100	0.0050	0.0020	0.0010	0.0001
1	>0.9999	0.9983	0.9590	0.7206	0.4713	0.0617
2	>0.9999	0.9877	0.8276	0.3640	0.1342	0.0019
3	0.9997	0.9534	0.6176	0.1368	0.0269	<0.0001
4	0.9988	0.8801	0.3942	0.0404	0.0041	
5	0.9958	0.7628	0.2164	0.0098	0.0005	
6	0.9879	0.6128	0.1032	0.0020	0.0001	
7	0.9711	0.4532	0.0433	0.0004	<0.0001	
8	0.9400	0.3079	0.0162	0.0001		
9	0.8901	0.1923	0.0054	<0.0001		
10	0.8190	0.1107	0.0016			

9.3. Analysis Sets

Analysis Set	Description
Screened	All participants who were screened for eligibility
Enrolled	All participants who entered the study (who received study intervention or underwent a post screening study procedure). Note screening failures and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.
Safety	All participants who receive at least one dose of open-label GSK3511294.

9.4. Statistical Analyses

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

9.4.1. General Considerations

9.4.2. Primary Endpoints

Treatment	• open-label GSK3511294 + SoC Results will also be summarised according to treatment group in studies 206713/213744: • open-label GSK3511294 + SoC and on GSK3511294 + SoC in previous study • open-label GSK3511294 + SoC and on placebo + SoC in previous study
Target Patient Population	Adult and adolescent participants with severe asthma with an eosinophilic phenotype following the strategy outlined for dealing with the main intercurrent events that are anticipated
Primary Endpoints	• Incidence of AEs/SAEs • Incidence of immunogenicity measured by the presence of ADA/NAb to GSK3511294

Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on-treatment strategy i.e. using data up to 26 weeks after last dose of GSK3511294 b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on-treatment strategy, i.e. using data up to 26 weeks after last dose of GSK3511294. c) Change in maintenance therapy or use of prohibited medications: CCI [redacted]
Summary measures	• Number and percentage of participants with any AE/SAE will be summarized and incidence rate of AE/SAE will also be summarized. • Number and percentage of participants with positive anti-GSK3511294 binding anti-body status will be summarized. Summary statistics for titre results will also be presented.

9.4.3. Secondary Endpoints

Treatment	open-label GSK3511294 + SoC Results will also be summarised according to treatment group in studies 206713/213744: • open-label GSK3511294 + SoC and on GSK3511294 + SoC in previous study • open-label GSK3511294 + SoC and on placebo + SoC in previous study
Target Patient Population	Adult and adolescent participants with severe asthma with an eosinophilic phenotype following the strategy outlined for dealing with the main intercurrent events that are anticipated
Endpoint	Annualized rate of clinically significant exacerbations. Clinically significant exacerbations are defined in Section 8.4.2
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: CCI [redacted] b) Study intervention discontinuation due to reasons related to the COVID-19

	pandemic: CCI [redacted] c) Change in maintenance therapy or use of prohibited medications: CCI [redacted]
Summary measure	Annualized exacerbation rate and 95% confidence interval (CI)
Analysis Method	The primary analysis of the number of clinically significant exacerbations will use a negative binomial model. Covariates included will be region, and treatment group during 206713/213744 with loge(time in study in years) as an offset variable.
Handling of missing data and data to be excluded due to intercurrent events	a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, CCI [redacted]. b) For participants that withdraw from the study, preventing assessment of the endpoint, CCI [redacted]

Treatment	• open-label GSK3511294 + SoC Results will also be summarised according to treatment group in studies 206713/213744: • open-label GSK3511294 + SoC and on GSK3511294 + SoC in previous study • open-label GSK3511294 + SoC and on placebo + SoC in previous study
Target Patient Population	Adult and adolescent participants with severe asthma with an eosinophilic phenotype the strategy outlined for dealing with the main intercurrent events that are anticipated
Endpoints	• Change from Baseline in ACQ-5 score at discrete timepoints during the 52 week period • Change from Baseline in SGRQ total score at Week 26 and Week 52.

	• Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: CCI [redacted] b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted] c) Change in maintenance therapy or use of prohibited medications: CCI [redacted]
Summary measure	Mean and 95% CIs.
Analysis Method	The analysis will be performed using a repeated measures mixed model. Covariates included will be region, treatment group during 206713/213744 and visit, plus interaction terms for visit by treatment group during 206713/213744 group. Baseline values for each assessment (unless otherwise specified) will be the Visit 1 pre-dose assessment.
Handling of missing data and data to be excluded due to intercurrent events	a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, CCI [redacted] b) For participants that withdraw from the study, preventing assessment of the endpoint, CCI [redacted]).

9.4.4. Other Endpoint(s)

The statistical analysis plan will provide a detailed description of the planned analyses for other endpoints.

9.5. Interim Analysis

As the study will be still ongoing at the time of regulatory submission, interim analyses will be performed in order to provide open-label safety and efficacy data in an interim Clinical Study Report (CSR) to inform the risk-benefit assessment of GSK3511294 in severe asthma. The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their 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 informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- For participants 12-17 years old, written informed assent must be obtained in addition to the legally authorized representative(s)' consent. Assent will be obtained in accordance with applicable country or IRB/Ethics Committee regulations. Written informed consent will be obtained from participants turning 18 years of age to continue participation in the study.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented/re-assented 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 their legally/ authorised representative.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3511294 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3511294 approved for medical use or approved for payment coverage.

In case of unexpected pregnancy, participant must be informed that personal information such as [year of birth, sex] of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by GSK. Any participant records or datasets that are transferred to GSK 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 GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An IDMC will review safety data from Studies 206713, 213744 and 206785 and Study 212895 until sponsor unblinding of Studies 206713, 213744 and 206785. After sponsor unblinding of Studies 206713, 213744 and 206785, safety data from Study 212895 will be reviewed by GSK and not by the IDMC.

The IDMC will not issue recommendations for the conduct of Study 212895. GSK will evaluate if IDMC recommendations from Studies 206713, 213744 and 206785 will require changes to Study 212895

An Independent IDMC comprised of clinical experts external to GSK will review unblinded data from the parent studies (studies 206713 and 213744) and 206785 at defined timepoints during the study. Data from Study 212895 is being provided for information to the IDMC as potential supporting data for the overall assessment of safety for use of GSK3511294 in the 206713, 213744 and 206785 study population.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request.

In addition to the IDMC, the GSK SRT will review Study 212895 safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- GSK or a designee is responsible for the data management of this study including quality checking of the data.
- GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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 GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

The tests detailed in Table 3 will be performed by the central laboratory.

Local laboratory results may be required in the event that the central laboratory results are not available in time – for example: at any time when a participant is unwell and results are required urgently. CCI [redacted]

If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick.

Table 3 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters		
Hematology[1]	Platelet Count	*RBC Indices:*	*WBC count with Differential:* *(post-dose results blinded* CCI [redacted] *as described in footnote 1)*
	RBC Count	MCV	WBC
	Haemoglobin	MCH	Neutrophils
	Haematocrit	%Reticulocytes	Lymphocytes
			Monocytes
			Eosinophils
			Basophils

Laboratory Assessments	Parameters			
Clinical Chemistry[2]	BUN	Potassium	AST(SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase[3]	Albumin
		Magnesium	GGT	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥1+])			
Pregnancy testing	• Highly sensitive urine pregnancy test at Visit 1 and as per SoA (Section 1.3) during study intervention period and at the Follow up Visit for WOCBP[4] ; Highly sensitive serum pregnancy test at Exit Visit of 206713/213744 study for all WOCBP.			

NOTES:
ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BUN = Blood urea nitrogen; FSH = Follicle-stimulating hormone; GGT= Gamma glutamyl transferase; hBsAg – hepatitis B surface antigen; hBc = hepatitis B core antibody; hCG = human chorionic gonadotropin; hsCRP = highly sensitive C-reactive protein; MPO=myeloperoxidase; PR3=proteinase 3; RBC = red blood cell; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; UACR = urinary albumin-creatinine ratio; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1. To maintain the treatment blind, the following post-dose results will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils (Unblinded at CCI [redacted]
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total 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 to GSK as an SAE.
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "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 fulfil the definition of 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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 admitted (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 fulfils 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.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
d) Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, 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
f) Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalised ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

Assessment of Causality
• The investigator will also consult the current IB, 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 recognised 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 submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours and send/fax it to the Medical Monitor. • The site will enter the SAE data into the electronic system as soon as it becomes available.

SAE Reporting to GSK via Electronic Data Collection Tool
• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical monitor or the SAE coordinator. • 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 data collection tool 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.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

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

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

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   a. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   b. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female participants:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• *Implantable progestogen-only hormone contraception associated with inhibition of ovulationc*
• *Intrauterine device (IUD)*
• *Intrauterine hormone-releasing system (IUS)c*
• *Bilateral tubal occlusion*
• *Azoospermic partner (vasectomised or due to a medical cause)* • *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of*

contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • *oral* • *intravaginal* • *transdermal* • *injectable*
Progestogen-only hormone contraception associated with inhibition of ovulation • oral • injectable
• 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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

Male participants: As GSK3511294 is a monoclonal antibody that is not anticipated to interact directly with Deoxyribonucleic acid (DNA) or other chromosomal material and minimal exposure through semen is expected, male participants will not be required to use contraception during the study.

10.5. Appendix 5: Genetics

Not applicable.

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

Liver Chemistry Stopping criteria and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event aetiology.

Liver Chemistry Stopping criteria and Required Follow-up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks

ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks

ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention

• Report the event to GSK within 24 hours

• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]

• Perform follow-up assessments as described in the Follow-up Assessment column.

• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:</td><td>• Viral hepatitis serology[4]

• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend

• Obtain blood sample for pharmacokinetic (PK) analysis, within a week of meeting increased liver monitoring criteria.[5]

• Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilise or return to within baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **it is not allowed per protocol;** continue participant in the study for any protocol specified follow-up assessments.	• Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia. Also note that the mechanism of action of GSK3511294 leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • 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 assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease: complete Liver Imaging form

Liver Chemistry Stopping Criteria	
	• Liver biopsy may be considered and discussed with local specialist if available, for instance: ○ In patients when serology raises the possibility of autoimmune hepatitis (AIH) ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), must be reported to GSK as an SAE ; the INR 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 Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal , 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the 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

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **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 intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) 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 ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a) Led to death
b) Led to serious deterioration in the health of the participant, that either resulted in: A life-threatening illness or injury. 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.

A Medical Device SAE is any serious adverse event **that:**
A permanent impairment of a body structure or a body function. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect
d) Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- 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.
- For device deficiencies, it is very important that the investigator describe any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs 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.
- Other measures to evaluate AEs and SAEs may be utilised (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the current IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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/SAE/device deficiency

- 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor or SAE coordinator by telephone. • Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the [GSK medical monitor or the SAE coordinator]. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper 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 paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in SRM.

10.8. Appendix 8: Anaphylaxis Criteria

Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarised as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline.

10.9. Appendix 9: Recommended Measures Related to COVID-19 Pandemic

Overall Rationale for this Appendix:

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

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

STUDY PROCEDURES DURING COVID-19 PANDEMIC

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

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

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.
- Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

Protocol Defined Procedures/Visits:

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

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then the medical evaluation of the participant's asthma may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.
- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.
- The revised schedule of study activities is provided in.

Note: If the Investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures. Refer to and follow most recent local guidance and regulations if available or refer to FDA or EMA guidance available at time.

Study Intervention:

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Interventions and Concomitant Therapy), a maximum dose interval CCI [redacted] may be used.
- In-clinic visits are required for administration of the study intervention (Week 0 and Week 26).
- In some cases, trial participants who no longer have access to study intervention or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

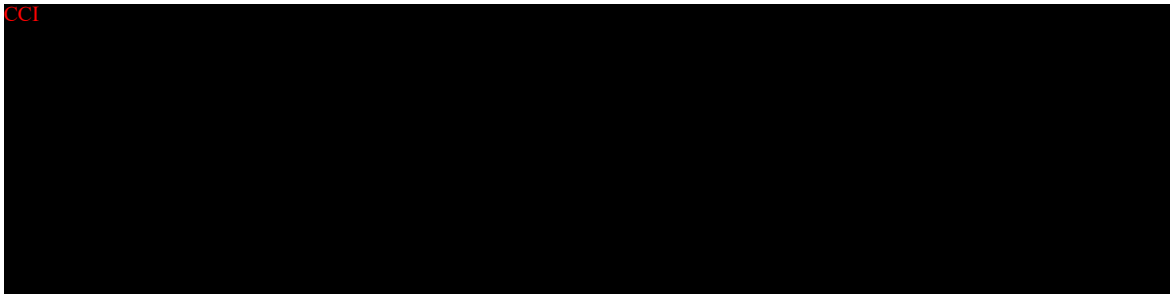
Data Management/Monitoring:

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

Assessments that can be Conducted Outside Clinical Study Site:

Activities/assessments that may be conducted outside of a clinical study site are indicated in.

CCI



- The FU Visit may be conducted as a remote/home visit or as a phone call.
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.

Table 4 Schedule of Activities (SoA) Indicating Assessments that may be Conducted Outside of a Clinical Study Site

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	V1 *	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Exit Visit V12	FU[i]	WS Visit [b]	FU=Follow-up visit WS=Withdrawn from study visit
Study Week	0	4	8	12	20	26	28	32	36	40	48	52	56		
Study Day	1	28	56	84	140	182	196	224	252	280	336	364	392		
General Eligibility Assessments															
Informed Consent[a]	X														See footnote a.
Inclusion/Exclusion Criteria	X														
Demography data collection	X														
Medical history	X														Changes including cardiovascular (CV), CV risk factors, asthma including exacerbations, vasculitis, allergies and anaphylaxis
Smoking Status	X														
Parasitic screening	X														Parasitic screening should have been performed prior to treatment in the OLE only if the participant has travelled to high risk countries in the past six months. For details refer to study reference manual (SRM).
Safety assessments															
Concomitant Medication Assessment [c]	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X		X	See footnote c.
Physical Examination	(X)											X		X	
Vital Signs	X[d]		X		X	X	X			X		X[d]		X[d]	See footnote d.

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
Study Week	**0**	**4**	**8**	**12**	**20**	**26**	**28**	**32**	**36**	**40**	**48**	**52**	**56**		
Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
12-lead ECG	(X)	X				X	X					X		X	ECG must be performed and assessed pre-dose. Twelve-lead ECG central overread values should be used at all visits with the exception of Visit 1 and Visit 6 where 12-lead ECG machine read values should be used.
Adverse Events/Serious Adverse Event Assessment	X [e]	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X	X	See footnote e.
Laboratory Assessments															
Urine Pregnancy Test[f] (WOCBP only)	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X	X	See footnote f. All WOCBP as determined in prior study (206713/ 213744) must continue their highly effective contraceptive method without any interruptions between prior study and enrolment in this study. See Section 5.1 and Section 8.2.5 for additional details

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
Study Week	**0**	**4**	**8**	**12**	**20**	**26**	**28**	**32**	**36**	**40**	**48**	**52**	**56**		
Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
Urinalysis	(X)					X						X		X	Note: Urinalysis to be performed using dipstick test. If results are abnormal a second urine sample should be taken and sent to central laboratory. **China Only:** For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick.
Clinical Chemistry	(X)	X	X	X	X	X	X			X		X		X	Include liver chemistry.
Immunogenicity sample	(X)			X		X				X		X		X	
CCI [redacted]															
Efficacy Assessments															
Review of exacerbations	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X	X	.
Spirometry (pre-bronchodilator FEV_1)	(X)					X						X		X	FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	**V1 ***	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Exit Visit V12**	**FU[i]**	**WS Visit [b]**	**FU=Follow-up visit WS=Withdrawn from study visit**
Study Week	**0**	**4**	**8**	**12**	**20**	**26**	**28**	**32**	**36**	**40**	**48**	**52**	**56**		
Study Day	**1**	**28**	**56**	**84**	**140**	**182**	**196**	**224**	**252**	**280**	**336**	**364**	**392**		
ACQ-5	(X)	X	X	X	X	X	X	X		X		X		X	ACQ-5=Asthma Control Questionnaire
Study Intervention															
Administer Study intervention	X					X									Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for hypersensitivity for at least 2 h after IP administration. For details refer to study reference manual (SRM).
Worksheets/eCRF															
Provide worksheet	X	X	X	X	X	X	X	X		X					The worksheet is a medical problems and healthcare utilisation worksheet
Review worksheet		X	X	X	X	X	X	X		X		X		X	
Dispense Rescue medication	X	X	X	X	X	X	X	X		X					
Register Visit in the IRT system	X					X								X	IRT=interactive response technology
Complete electronic Case Report Form (eCRF)	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X		X	
HRQoL: PRO and Health Outcomes Assessments															
SGRQ	(X)					X						X		X	SGRQ=St. George's Respiratory Questionnaire
CCI															

Protocol Activity		Intervention Period and Exit Visit (visit window is ±7 days)											Follow-up visit/call or Withdrawal Visit (±7 days		Notes
Visit	V1 *	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Exit Visit V12	FU[i]	WS Visit [b]	FU=Follow-up visit WS=Withdrawn from study visit
Study Week	0	4	8	12	20	26	28	32	36	40	48	52	56		
Study Day	1	28	56	84	140	182	196	224	252	280	336	364	392		

*: If the Exit Visit in 206713/213744 is on the same day, or within 7 days of Visit 1 for study 212895 then the assessments in brackets above do not need to be performed and the assessments from the Exit Visit from 206713/213744 will be used as the baseline for 212895. Information will be transferred accordingly. If the Visit 1 performed greater >7 days (maximum 14 days) after the Exit Visit in 206713/213744 then the assessments in brackets needs to be performed (For details refer to Section 8). A delayed administration of the study intervention (maximum 4 weeks) may be considered in consultation with the GSK Medical Monitor.

a. Informed Consent must be obtained prior to initiating any study assessments.
b. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the participant withdraws before the second dose of study intervention, or at Week 52 if the second dose of study intervention was received.
c. Ensure maintenance asthma medications from the previous trial to Visit 1 and all current medications are reviewed.
d. Vital signs including height and weight should be conducted at Visit 1. Height can be omitted for subsequent visits.
e. SAEs must be collected after signing of Informed Consent.
f. Urine pregnancy testing is only required for women of childbearing potential (WOCBP). Serum pregnancy test is required at the Exit Visit of the parent protocols for all WOCBP.
g. For haematology samples CCI [redacted], the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will be blinded to site staff and sponsor to protect the blind from the previous study. CCI [redacted]. Sites will be sent total white blood counts throughout the study. Samples should be taken pre-dose on dosing days.
h. Week 36 and Week 48 are phone visits. In France, Week 36 and Week 48 are phone visits for all participants except WOCBP who will perform both visits, including the Follow Up visit, onsite.
i. A follow-up visit/call should be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing. For WOCBP the follow up visit should be conducted as onsite visit or home visit (where applicable). Follow-up phone call is only applicable for male and WONCBP.

10.10. Appendix 10: Country-specific requirements

Czech Republic specific requirements:

1. Protocol Section 8.4.2 is supplemented with following requirement: Asthma exacerbations should be treated in accordance with current clinical practice in the Czech Republic and with the current GINA recommendations.
2. The Protocol 10.9 Appendix 9 with Recommended Measures Related to COVID-19 Pandemic is supplemented with following requirement: These recommendations apply only if they are in accordance with national laws and the opinions of the State Institute for Drug Control- SUKL.

10.11. Appendix 11: Protocol amendment history

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

Amendment 1: 12 January 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the Amendment:

The protocol was amended in response to France EC recommendation and to include country specific changes in Germany, UK and Czech Republic and to provide added clarity to the ECG process. Additionally, it provides clarification on the use of a central lab for urinalyses in China.

The Key changes are:

- Clarification on urinalysis in China
- Country specific changes in Germany, UK, France and Czech Republic
- Follow up visit should be conducted as onsite visit or home visit (where applicable) for WOCBP. Administrative change to SOA table to be clear on assessment that can be done at home vs site
- ECG updates
- AGILE safety data will be included in the Independent Data Monitoring Committee (IDMC) review as supporting data.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 and Schema	Added footnote # Follow-up phone call is only applicable for male and WONCBP.	Clarification
Section 1.1 and Synopsis, Section 1.3 and Schedule of Activities (SoA), Section 4.1 and Overall design, Section 5.5 and Criteria for Temporarily Delaying Enrolment/ Administration of Study Intervention Administration, Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Existing text: A delayed administration of the study intervention may be considered (maximum 4 weeks) due to clinical or safety reasons in consultation with the GSK Medical Monitor. Revised text: A delayed administration of the study intervention may be considered (maximum 4 weeks) in consultation with the GSK Medical Monitor.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 4.1 Overall design	Removed reference to week 0, week 26 and week 52 from the parent studies (206713 or 213744) and added reference to Visits 2, 10 and 17 instead.	Clarification
Section 1.3 and Schedule of Activities (SoA), Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Moved note (see footnote d) from Physical examination to Vital signs.	Clarification
Section 1.3 and Schedule of Activities (SoA), Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Administer Study intervention: Modified the text in notes as follows: Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for hypersensitivity for at least 2 h **after IP administration. For details refer to study reference manual (SRM).**	Clarification
Section 1.3 and Schedule of Activities (SoA), Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Add notes to SoA referencing for ECG and new wording as below, ECG must be performed and assessed pre-dose. Twelve-lead ECG central overread values should be used at all visits with the exception of Visit 1 and Visit 6 where 12-lead ECG machine read values should be used.	Clarification on ECG to be performed at pre-dose and to give clarification on usage of twelve-lead ECG central overread and machine read values for QTcF exclusion and discontinuation criteria.
Section 1.1 and Synopsis, Section 1.3 and Schedule of Activities (SoA), Section 4.1 Overall design, Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Added new footnote “i” with new wording as below: For WOCBP the follow up visit should be conducted as onsite visit or home visit (where applicable). Follow-up phone call is only applicable for male and WONCBP.	Clarification
Section 1.3 and Schedule of Activities (SoA), Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Updated footnote “h” with new wording as below: In France, Week 36 and Week 48 are phone visits for all participants except WOCBP who will need to perform both visits, including the Follow Up visit, onsite.	France EC recommendations
Section 1.3 and Schedule of Activities (SoA), Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Removed follow up visit/call conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing from footnote “b” and added as a new footnote “i”.	Clarification
Section 5.1 and Inclusion Criteria	Added note to Germany and UK participants. Note: German and UK Participants: In Germany and UK only adult participants (≥18 years) are to be	Country requirements

Section # and Name	Description of Change	Brief Rationale
	included in this clinical trial.	
Section 5.2 and Exclusion Criteria	Criteria 7 revised as follows: ECG Assessment: QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block **in the 12-lead ECG machine read** at Visit 1.	Clarification
Section 6.3 and Measures to Minimize Bias: Randomization and Blinding	Added the following text: Sites to continue the blinding strategy from 206713 and 213744 studies up to [redacted]	Clarification
Section 6.4 and Study Intervention Compliance	Modified the below text Participants will be monitored in clinic for a minimum of 2 hours post-dose to monitor for immediate hypersensitivity and any other untoward event **(For details refer to SRM).**	Clarification
Section 7.1.3 and QTc Stopping Criteria	Added the following text: The QTcF value from the 12-lead ECG central over-read at Visit 1 should be used as baseline QTcF value for any changes from baseline calculations during the study. Twelve-lead ECG central overread values should be used at all visits with the exception of Visit 1 and Visit 6 where 12-lead ECG machine read values should be used. After Visit 1 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 6 (Week 26) where 12-lead ECG machine read values should be used.	Clarification
Section 7.2 and Participant Discontinuation/Withdrawal from the Study	Added the text to follow-up visit as follows: WOCBP will need to perform the follow up visit as onsite visit or home visit.	Clarification
Section 8.1.1 and Critical Assessments performed at Enrolment (Visit 1)	Added below point: Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF. Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.	As per audit findings from other studies

Section # and Name	Description of Change	Brief Rationale
Section 8.1.2 and Assessments performed if the time between the Exit Visit from the prior study (206713/213744) and Visit 1 is >7 days	Added new section heading for existing text. Removed below assessments: • SAEs/AEs • Vital Signs	Clarification
Section 8.2.1 and Physical Examination	Removed below text: Height (screening only) and weight will also be measured and recorded	Clarification
Section 8.2.2 and Vital Signs	Added below text: Vital signs including height and weight should be conducted at Visit 1. Height can be omitted for subsequent visits.	Clarification
Section 8.2.3 and Electrocardiograms	If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the patient should be **enrolled or** discontinued from the study intervention (but not from the study). Refer to **Section 5.2 for exclusion criteria related to ECG assessment** and Section 7.1.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.	Clarification
Section 8.4.2 and Asthma Exacerbations	**Existing text:** Clinically significant exacerbations of asthma are defined by: Worsening of asthma that requires use of systemic corticosteroids[1] and/or hospitalization and/or Emergency Department (ED) visits. **Revised text:** Clinically significant exacerbations of asthma are defined by worsening of asthma which requires: •use of systemic CSs or •hospitalisation or Emergency Department (ED) visit, requiring systemic steroids.	Clarification
Section 10.1.3 and Informed Consent Process	**Added text:** In case of unexpected pregnancy, participant must be informed that personal information such as [year of birth, sex] of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.	As per new protocol template instructions
Section 10.1.5 and Committees Structure	Structure of IDMC included.	Study data provided as supporting data for the IDMC review.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 and Schedule of Activities (SoA), Section 10.2.Appendix 2: Clinical Laboratory Tests, Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Note: Urinalysis to be performed using dipstick test. If results are abnormal a second urine sample should be taken and sent to central laboratory. For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick.	Country specific procedure
Section 1.3 and Schedule of Activities (SoA), Section 10.2.Appendix 2: Clinical Laboratory Tests, Section 10.9 Appendix 9: Recommended Measures Related to COVID-19 Pandemic (Table 4)	Haematology with white blood cells count: Added Note: Site should continue with the blinding strategy from 206713 and 213744 studies up to [redacted]	Clarification
Section 10.10 Appendix 10: Country-specific requirements	Added Czech Republic specific requirements: 1. Protocol Section 8.4.2 is supplemented with following requirement: Asthma exacerbations should be treated in accordance with current clinical practice in the Czech Republic and with the current GINA recommendations. 2. The Protocol 10.9 Appendix 9 with Recommended Measures Related to COVID-19 Pandemic is supplemented with following requirement: These recommendations apply only if they are in accordance with national laws and the opinions of the State Institute for Drug Control- SUKL.	Country requirements
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized.

10.12. Appendix 12: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
ADE	Adverse device events
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
cm	Centimeter
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein
CS	Corticosteroid
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
ED	Emergency department
FAAN	Food Allergy and Anaphylaxis Network
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FTIH	First Time in Humans
FVC	Forced vital capacity
g	Grams
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline

h	Hours
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
IUS	Intrauterine hormone-releasing system
IV	Intravenous
K	Probabilities of observing a given number of adverse events or more
kg	kilogram
L	Litre
LA	Long-acting
LABA	Long acting β-agonist
LAMA	Long acting muscarinic antagonist
LDH	Lactate dehydrogenase
LFT	Liver function test
mAb	Monoclonal antibody
MAR	Missing at random
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody

NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OLE	Open-label extension
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
CCI	[redacted]
PK	Pharmacokinetics
PR3	Proteinase 3
PRO	Patient-reported outcomes
QTcF	QTc corrected by Fridericia's formula
QTL	Quality tolerance limits
RNA	Ribonucleic acid
RBC	Red blood cell
SABA	Short acting beta-2-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SC	Subcutaneous
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of assessments
SoC	Standard of care
SOC	System organ class
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
UACR	Urinary albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
w/v	Weight/volume
µL	Microlitre

Trademark Information

Trademarks of the GSK group of companies
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