TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, double-dummy, parallel group, multi-centre, non-inferiority study assessing exacerbation rate, additional measures of asthma control and safety in adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with GSK3511294 (depemokimab) compared with mepolizumab or benralizumab

Protocol Number: 206785

Compound Number or Name: GSK3511294 (Depemokimab)

Primary Study Intervention: Depemokimab

Other Study Intervention(s): Mepolizumab, Benralizumab, placebo

Brief Title: Non-inferiority study of GSK3511294 (depemokimab) compared with mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

GSK Research & Development Limited
980 Great West Road
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Manufacturers: GSK (GSK3511294 and mepolizumab**); AstraZeneca** (benralizumab) (details in Pharmacy Manual)

Regulatory Agency Identifying Number(s):

IND: 146742

EU CT number: 2023-510230-84-00

Approval Date: 23 Aug 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 4	23 Aug 2024	TMF-19702519
Amendment 3	07 Dec 2023	TMF-17429313
Amendment 2	09 August 2023	TMF-16130759
Amendment 1	01 December 2020	2020N441323_01
Original Protocol	08 October 2020	2020N441323_00

Amendment 4: 23 Aug 2024

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	Added EU CT number	To fulfil EU requirements.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, randomised, double-blind, double-dummy, parallel group, multi-centre, non-inferiority study assessing exacerbation rate, additional measures of asthma control and safety in adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with GSK3511294 (depemokimab) compared with mepolizumab or benralizumab

Brief Title: Non-inferiority study of GSK3511294 (depemokimab) compared with mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype

Rationale:

GSK3511294 is being developed as a long-acting (LA) subcutaneous (SC) injectable anti-interleukin-5 (anti-IL-5) therapy and is expected to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate whether switching participants who have benefitted from mepolizumab or benralizumab to GSK3511294 100 mg SC (once every 26 weeks**)** is non-inferior to maintaining current treatment on the annualised rate of clinically significant exacerbations in participants with severe asthma with an eosinophilic phenotype over a 52-week treatment period.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on health-related quality of life (HRQoL) and additional efficacy assessments	• Weighted mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks • Weighted mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks

Objectives	Endpoints
	• Weighted mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) calculated over 52 weeks

a. Clinically significant exacerbations will be defined as worsening of asthma requiring systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Overall Design:

This is a multi-centre, randomised, double-blind, double-dummy, parallel group non-inferiority trial of GSK3511294 100 mg SC compared with continuation of mepolizumab or benralizumab treatment in participants with severe asthma with an eosinophilic phenotype.

Brief Summary:

At Visit 2 (Week 0) those participants who meet the randomisation eligibility criteria will be randomised in a 1:1 ratio to either remain on their existing anti-IL-5/5R therapy (mepolizumab or benralizumab) or switch to GSK3511294 100 mg. Participants remaining on active comparator treatment (mepolizumab or benralizumab) will be combined into a single arm with a minimum of 40% of the participants on each treatment. Throughout the study, all participants will continue their baseline standard of care (SoC) asthma treatment consisting of inhaled corticosteroid (ICS) plus at least one other controller, e.g. long-acting beta-2-agonist (LABA), long-acting muscarinic antagonist (LAMA), with or without maintenance oral corticosteroids (OCS). Assessments will include the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety.

Number of Participants:

Approximately 2,650 participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy (mepolizumab or benralizumab) will be screened to achieve a target global randomisation of approximately 1,700 participants (850 participants per arm).

Intervention Groups and Duration:

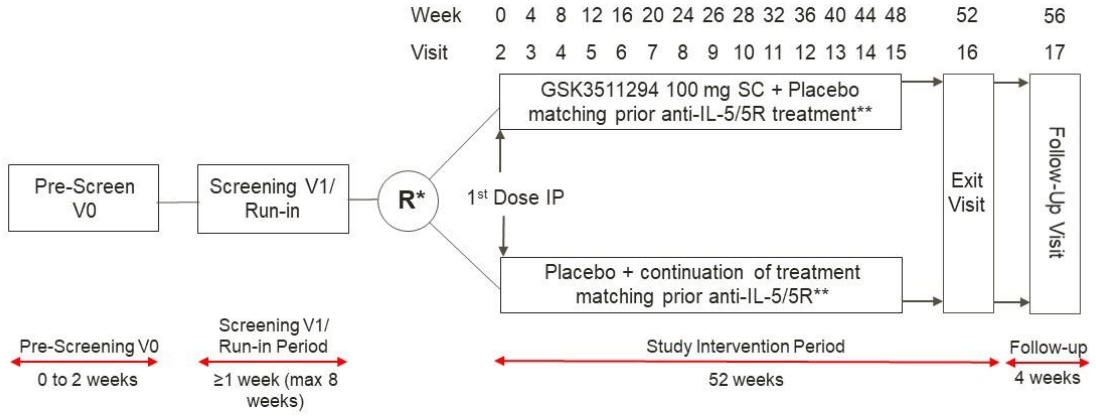
Eligible participants will be requested to participate in the study for a maximum of 66 weeks (Visit 0 to the Follow-Visit, inclusive). The study consists of four phases: Pre-screening (0-2 weeks); Screening/Run-in (1 to 8 weeks); Intervention Period (52 weeks); and Follow-up Period (4 weeks). After the screening/run-in period, participants will be randomised in a 1:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either:

- **GSK3511294** 100 mg SC administered every 26 weeks plus placebo SC treatment matching the active comparator (participant's anti-IL-5/5R treatment prior to randomisation: either placebo matching mepolizumab every 4 weeks or placebo matching benralizumab every 8 weeks). All injections will be administered via a pre-filled safety syringe (PFS).
- **Active comparator** (either mepolizumab every 4 weeks or benralizumab every 8 weeks) according to the participant's treatment prior to randomisation plus placebo SC matching GSK3511294 administered every 26 weeks. All injections will be administered via a PFS.

Participants will be assessed at each scheduled visit during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 5, Visit 9, Visit 13, Exit Visit 16, and WS Visit (if applicable).

Independent Data Monitoring Committee: Yes

1.2. Schema



** R = Randomisation*
*** Participants randomised to GSK3511294 will receive placebo treatment matching their prior anti-IL-5/5R medication while subjects randomised to receive placebo matching GSK3511294 will receive active treatment matching their prior anti-IL-5/5R (either mepolizumab 100 mg every 4 weeks or benralizumab 30 mg every 8 weeks). All injections will be administered by a prefilled safety syringe (PFS)*

1.3. Schedule of Activities (SoA)

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)															Follow-up /Withdraw (±7 days)		Notes
Visit	**V0** [a]	**Visit 1** [a]	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																				
Informed consent [a]	X	(X)																		Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [b]	X	(X)																		Conduct at Visit 1 if not completed at Visit 0; See footnote b.
Demography and childbearing status	X	(X)																		Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Screening Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																		
Medical history		X																		Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																		
Parasite screening		X																		Only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months. Use local laboratories for the parasitic test.
eDiary registration and training		X																		Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																	Assess prior to randomisation.

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)															Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Efficacy Assessments																				
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry (pre-bronchodilator FEV_1)			X			X				X				X			X	X		FEV_1=Forced expiratory volume in 1 second. Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (See Section 8.2.3).
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
ACQ-5		(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5; (ACQ-5 may be conducted at Screening if needed to meet inclusion criterion 3).
HRQoL: PRO and Health Outcomes Assessments																				
SGRQ			X	X		X				X							X	X		SGRQ=St. George's Respiratory Questionnaire
CCI [redacted]																				

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**															**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Safety Assessments																				
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		In addition to entry criteria related to confirming either mepolizumab or benralizumab for at least 12 months prior to entry, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X															X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X		X			X		X		X		X		X	X	X		
12-lead ECG		X	X							X							X	X		The 12-lead ECG central over-read values should be used at all visits with the exception of Visit 2 (randomisation) and Visit 9. At Visit 2 and Visit 9, the 12-lead ECG machine values should be used. Note: ECGs at Visit 2 and Visit 9 must be performed and assessed pre-dose
AE/SAE Assessment	X [e]	X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote e.
Laboratory Assessments [f]																				
Haematology with differential [d]		X [d]	X	X	X	X		X		X	X			X		X	X	X	X	For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnote d.
Clinical Chemistry		X	X	X	X	X		X		X	X			X			X	X		Include liver chemistry.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**															**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Pregnancy Test (WOCBP only)		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; Pregnancy test must be performed prior to administration of any dose of study intervention. See Section 8.3.5 for additional information.
Urinalysis		X	(X)														X	X		Conduct at Visit 2 if not completed at Visit 1; Note: dipstick, send for analysis if abnormality is identified by dipstick.
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																	ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X			X				X				X			X	X		
Immunogenicity sample			X	X		X				X				X			X	X		
Genetics sample [b]			←==========							The genetics sample can be collected at Visit 2 or any visit after							==========→			See footnote b.
Study intervention [f]																				
Administer GSK3511294 or matching placebo			X							X										Conduct for all participants; GSK3511294/placebo will only be administered in the clinic. Monitor participant for at least 2h after administration (see Section 6.5).
Administer mepolizumab or matching placebo			X	X	X	X	X	X	X		X	X	X	X	X	X				Conduct for participants who were receiving mepolizumab prior to randomisation.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**															**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Administer benralizumab or matching placebo			X		X		X		X			X		X		X				Conduct for participants who were receiving benralizumab prior to randomisation.
eCRF/worksheets/other																				
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				IRT=interactive response technology The initial IRT registration can be performed either at V0 or V1 but is preferred to be completed at V1. IRT visit registration is only needed for IP dispensation after V2. Benralizumab patients – not required to register dispensing visit at V3, V5, V7, V10, V12, V14 NOTE: Ensure that at least 7 days have passed from Visit 1 (Screening) before proceeding with Randomization
eDiary close out																	X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	eCRF=electronic Case Report Form

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Informed Consent for optional genetics research must be obtained before collecting a sample.
c. 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 GSK3511294/placebo, i.e., at Week 26 if the second dose of GSK3511294/placebo was not received, or at Week 52 if the second dose of GSK3511294/placebo was received. A follow-up visit should also be conducted 4 weeks after the WS visit for AE/SAE assessments and pregnancy testing.

d. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken pre-dose on dosing days.
e. SAEs must be collected from signing of Informed Consent if considered related to study procedures.
f. Any scheduled assessments or sample draws should be performed prior to administration of study intervention.

2. INTRODUCTION

2.1. Study Rationale

Anti-IL-5 therapies have an established efficacy and long-term safety profile and are a cornerstone of severe asthma management for patients with an eosinophilic phenotype [GINA, 2023]. Three antagonists of IL-5 (mepolizumab and reslizumab) or its receptor (IL-5R) (benralizumab) are approved in multiple markets for severe asthma with an eosinophilic phenotype, as an add-on treatment administered every 4 to 8 weeks.

Long-acting (LA) alternatives that can be administered on a less frequent basis are recognised as successful approaches for chronic indications. GSK3511294 is being developed as a LA SC injectable anti-IL-5 therapy. As a LA anti-IL-5 therapy, GSK3511294 is anticipated to have an efficacy and safety profile similar to those of the current-approved therapies in its class but with a reduced dosing frequency of 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).

The aim of this study is to investigate whether GSK3511294 100 mg SC given every 26 weeks is non-inferior to maintaining current treatment on the rate of clinically significant exacerbations in participants with severe asthma with an eosinophilic phenotype, over a 52-week treatment period.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of 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 (IL-5) or its receptor (IL-5R): mepolizumab [Summary of Product Characteristics for Mepolizumab] (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab [Summary of Product Characteristics for Benralizumab] (Fasenra). All three, by utilising 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 IL-5/5R is provided by long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data in real-world evidence settings for mepolizumab [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 IL-5 pathway are both highly effective and well-tolerated. Based on this established efficacy and safety, anti-IL-5/5R 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, 2023].

GSK3511294 is a humanised, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid substitutions to 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 pharmacokinetics (PK) and pharmacology of GSK3511294 to enable less frequent dosing with an anticipated similar efficacy and safety profile relative to mepolizumab (administered chronically).

A detailed description of the chemistry, pharmacology, and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GSK Document Number 2016N295843_03 or later].

2.3. Benefit: Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and completed FTIH study 205722 can be found in the current IB [GSK Document Number 2016N295843_03 or later]. Safety information for mepolizumab and benralizumab can be found in their respective product labels. The following section outlines the risk assessment and mitigation strategy for this protocol. For mepolizumab and benralizumab, the approved country product labels should be referenced.

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 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 NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8). • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours after the first dose of GSK3511294 or matching placebo (at Week 0) and after the dose 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals. • Participants with severe allergic reaction/anaphylaxis with no alternative explanation at any time after the first dose of study intervention will not receive another dose.
• Type 3 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 3 hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed (Section 5.2). • Daily monitoring of SAEs will be done 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. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a rheumatologist (member of the IDMC).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK3511294; 12 participants received placebo).	• 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 at any time after the first dose of study intervention will not receive another dose (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 pharmacodynamics (PD), or to produce adverse reactions. • 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 IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the GSK3511294 plasma concentration-time and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants.	• 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
	Neutralising 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. • 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.	• 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. • The IDMC will review unblinded safety data at regular intervals.
• 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), no treatment effect for ECG parameters including corrected QT interval (QTcF) was observed across the GSK3511294 treatment groups (n=36). No participants met QTcF protocol specified criteria (QTcF >500 msec or increase from baseline >60 msec, or uncorrected QT >600 msec) that would require additional monitoring.	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.3.3. • Participants with QTc prolongation on screening will be excluded (criterion 13, Section 5.2). • Participants with a clinically significant cardiac abnormalities that are uncontrolled with standard treatment are excluded (criterion 7, Section 5.2). • Participants who meet QT stopping criteria as specified in Section 7.1.2 will not receive another dose of study intervention.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Analysis of the relationship between GSK3511294 plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study did not reveal any clinically or statistically significant trends of concern with increasing GSK3511294 dose up to 300 mg. The predicted increase in mean QTcF change from baseline with GSK3511294 plasma concentrations point estimates remained below 10 msec [FDA, 2005] up to concentrations of 100 ug/mL, with a 95% lower CI consistent with zero change from baseline (i.e., the 95% lower bound of the CI is below zero) [GSK Document Number 2020N457410_00].	• The IDMC will review unblinded safety data at regular intervals.
• 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. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (criterion 17, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing potential must be using a highly effective contraceptive method from at least 14 days

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	(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 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.	prior to first dose and until at least 30 weeks after either: • the first dose of GSK3511294 or matching placebo (if study intervention was permanently discontinued prior to Week 26), or • the dose at Week 26. (see Section 10.4.2).
Study Intervention mepolizumab and benralizumab: Detailed information about the established benefits and risks of mepolizumab and benralizumab may be found in the local mepolizumab and benralizumab approved product labels.		
• Hypersensitivity reactions including anaphylaxis Refer to mepolizumab and benralizumab labelling for additional safety information	• This risk is described in the Warnings and Precaution section of benralizumab and mepolizumab labelling.	• Refer to mitigation strategy for GSK3511294 above.
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.

As a LA anti-IL-5 mAb, GSK3511294 is anticipated to provide the same clinical benefit with a similar safety profile compared with mepolizumab and benralizumab and with the added benefit of an extended duration of action requiring 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

Although no additional clinical benefit is expected for recruited participants who are already receiving anti-IL-5/5R therapy, the overall benefit: risk balance of this study for participants with severe asthma with an eosinophilic phenotype is considered acceptable. Potential risks will be minimised with the risk mitigation strategy. Therefore, the Sponsor considers that the investigation of the efficacy and safety of GSK3511294 is justified in this study with a positive benefit: risk ratio.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on health-related quality of life (HRQoL) and additional efficacy assessments	• Weighted mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks • Weighted mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks • Weighted mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) calculated over 52 weeks

Objectives	Endpoints
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on incidence of hospitalisation and/or Emergency Department (ED) visit and measures of asthma control, night sleep and lung function	• Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks • Time to first clinically significant exacerbation[a] • Change from baseline in the percentage of nights free from awakenings due to asthma symptoms requiring rescue medication use over 2-week periods • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in percentage of rescue medication-free 24-hour periods over 2-week periods • Mean number of days with OCS usage over 52 weeks • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • Change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294

a. Clinically significant exacerbations will be defined as worsening of asthma requiring systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

3.1. Primary Estimand

Population: Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with active comparator (mepolizumab or benralizumab) + SoC

Endpoint: Annualised rate of clinically significant exacerbations over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e., regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e., had the intercurrent event not occurred
- Change in maintenance therapy (excluding prohibited medications listed in Section 6.9.2): to be handled with a treatment policy strategy i.e., regardless of the intercurrent event occurring

- Use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy strategy i.e., regardless of the intercurrent event occurring

Summary measures: Ratio of the rates of clinically significant exacerbations between GSK3511294 + SoC and the active comparator (mepolizumab or benralizumab) + SoC

For further details see Section 9.4.

3.2. Secondary Estimands

Population: Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with active comparator (mepolizumab or benralizumab) + SoC

Endpoints:

- Weighted mean change from baseline in SGRQ total score calculated over 52 weeks
- Weighted mean change from baseline in ACQ-5 score calculated over 52 weeks
- Weighted mean change from baseline in pre-bronchodilator FEV_1 calculated over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e., regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e., had the intercurrent event not occurred
- Change in maintenance therapy (excluding prohibited medications listed in Section 6.9.2): to be handled with a treatment policy strategy i.e., regardless of the intercurrent event occurring
- Use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy strategy i.e., regardless of the intercurrent event occurring

Summary measures:

- Difference in mean weighted mean change from baseline in SGRQ total score calculated over 52 weeks
- Difference in mean weighted mean change from baseline in ACQ-5 score calculated over 52 weeks
- Difference in mean weighted mean change from baseline in pre-bronchodilator FEV_1 calculated over 52 weeks

between GSK3511294 + SoC and the active comparator (mepolizumab or benralizumab) + SoC.

For further details see Section 9.4.

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, randomised, double-blind, double-dummy, parallel group, non-inferiority trial (see schema in Section 1.2). The study will recruit adults and adolescents (≥12 years) with a confirmed diagnosis of severe asthma with an eosinophilic phenotype, who are currently:

a. receiving either mepolizumab 100 mg SC or benralizumab 30 mg SC for at least 12 months prior to Screening. Eligible participants must have a documented benefit to their anti-IL-5/5R therapy (see inclusion criterion 3, Section 5.1)

   AND

b. on a SoC regimen of medium to high dose ICS and at least one other controller medication (see inclusion criteria 4 and 5, Section 5.1).

Participants will attend a Pre-screen Visit (Visit 0) to provide informed consent. Participants who are eligible/able to complete the Screening Visit (Visit 1) may do so, on the same day as the Pre-screen visit. Participants, who meet all eligibility criteria (see Section 5.1 and Section 5.2) at Visit 1 (Screening), will enter the run-in period for a minimum of 1 week and a maximum of 8 weeks. At the conclusion of the run-in period (Visit 2), participants who meet the randomisation eligibility criteria (Section 5.3) will be randomised in a 1:1 ratio to receive 1 of the following treatments:

- **GSK3511294** 100 mg SC administered every 26 weeks and placebo SC treatment matching the active comparator (participant's anti-IL-5/5R treatment prior to randomisation: either placebo matching mepolizumab every 4 weeks or placebo matching benralizumab every 8 weeks). Injections related to GSK3511294/placebo at randomisation and Week 26 will be administered in the clinic via a PFS.
- **Active comparator** according to the participant's treatment prior to randomisation (either mepolizumab every 4 weeks or benralizumab every 8 weeks) and placebo SC matching GSK3511294 administered every 26 weeks. All injections will be administered via a PFS.

Study interventions will be administered according to the SoA (Section 1.3). Throughout the study, all participants will continue their baseline SoC asthma therapy (see inclusion criteria 4 and 5, Section 5.1). Participants will receive GSK3511294/placebo at Visits 2 and 9 **and either** mepolizumab/placebo (at Visit 2 and then every 4 weeks) **or** benralizumab/placebo (at Visit 2 and then every 8 weeks) according to the treatment they were receiving prior to entry into the study (see Section 6.4.1). The last dose of mepolizumab/placebo or benralizumab/placebo will be administered at Week 48.

Participants will attend an Exit Visit at Week 52 and a final Follow-up Visit at Week 56. See Section 4.1.1 for additional details on the study phases, duration and treatment arms.

The primary outcome measure will be the annualised rate of clinically significant exacerbations (i.e., exacerbations requiring systemic CSs and/or hospitalisation and/or ED visit [see Section 8.2.2]). Additional efficacy assessments will include lung function (pre-bronchodilator FEV_1), asthma control (ACQ-5), HRQoL measured with the SGRQ, and daily electronic diary (eDiary) parameters including peak flow, rescue use, daily symptoms and nocturnal awakening due to asthma (see Section 8.2).

The study will include safety (see Section 8.3 and Section 8.4) and immunogenicity (see Section 8.8) assessments to characterise the safety profile of GSK3511294 following repeat dosing. In addition, blood samples will be collected for assessment of PD effects (blood eosinophils) (see Section 8.7).

After randomisation, all participants will be encouraged to remain in the study and complete all scheduled visits regardless of whether they have discontinued their study intervention.

Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 5, Visit 9, Visit 13, Exit Visit 16, and WS Visit (if applicable). Participants may complete some visits at home even if there is no Covid restrictions or other unexpected events (see Appendix 11). Note: at Week 0 and Week 26 visits, study intervention will only be administered in the clinic.

4.1.1. Study Phases, Duration, and Study Intervention Groups

Eligible participants will be requested to participate in the study for a maximum of 66 weeks (Visit 0 to the Follow-Visit, inclusive). The study consists of 4 periods described in Table 1.

With the exception of the anti-IL-5/5R therapy provided as study intervention, all other components of the participant's maintenance SoC asthma therapy (including the medium to high dose ICS plus at least one additional controller medication as per inclusion criteria 4 and 5, Section 5.1) should remain constant throughout the study.

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening (Visit 0)	0-2 weeks	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
2	Screening (Visit 1) and Run-in	1-8 weeks	Participants who meet all the eligibility criteria at Screening (Visit 1) will enter the run-in period for a minimum of 1 week and a maximum of 8 weeks. The run-in is intended to assess the participant's compliance (with study-related procedures) and continued eligibility for the study as well as to collect baseline eDiary data. During the run-in phase, participants will remain on their current asthma therapy and receive their last dose of **pre-study** anti-IL-5/5R therapy: 4 weeks prior to randomisation for mepolizumab; or 8 weeks prior to randomisation for benralizumab. Participants who experience an asthma exacerbation during the run-in period should receive treatment for their exacerbation and remain in the run-in period until the investigator considers that the participant has returned to their baseline asthma status for at least one week. Run-in may be extended after consultation with the Medical Monitor. The participants that are not eligible to continue in the study at the end of the run-in period will be deemed run-in failures, but may be rescreened after consultation with the Medical Monitor (Section 5.5).
3	Study Intervention (Visit 2-Visit 16)	52 weeks	Participants who meet the randomisation criteria will enter the 52-week treatment period and will be randomised in a 1:1 ratio to receive **EITHER**: • GSK3511294 100 mg SC (at Week 0 and Week 26) and placebo SC matching the participant's prior anti-IL-5/5R medication (either placebo matching mepolizumab [at Week 0 and every 4 weeks thereafter] or placebo matching benralizumab [at Week 0 and every 8 weeks thereafter])

Phase	Phase Title	Duration	Description
			OR • Active comparator matching the participant's prior anti-IL-5/5R medication (either active mepolizumab 100 mg SC [at Week 0 and every 4 weeks thereafter] or active benralizumab 30 mg SC [at Week 0 and every 8 weeks thereafter]) and placebo SC matching GSK3511294 (at Week 0 and Week 26) All study interventions will be administered via a PFS according to the SoA (Section 1.3). For further details, see Section 6.4.1. All participants will continue their baseline SoC asthma therapy throughout the study (see inclusion criteria 4 and 5, Section 5.1). Clinic visits will occur at Week 0 and every 4 weeks thereafter, with an additional clinic visit at Week 26. The study intervention period will conclude with the Exit Visit at Week 52 (Visit 16).
4	Follow-up	4 weeks	All participants should be monitored carefully for worsening of their asthma during the Follow-up Period. Participants will complete a Follow-up visit 4 weeks after the Exit Visit; this visit will capture AE/SAE assessments and a urine pregnancy test result.

Note: Participants who experience any of the study intervention discontinuation conditions listed in Section 7.1 will not receive another dose of study intervention but will be encouraged to remain in the study and complete their remaining scheduled visits/assessments.

4.1.2. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective review of the data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

Population: To demonstrate the non-inferior efficacy of switching to GSK3511294 compared to continuation of current anti-IL-5/5R therapy, this study will recruit asthmatic participants who have received mepolizumab or benralizumab for ≥12 months and who show a clinical benefit as documented by **either**:

- a ≥50% reduction in exacerbation frequency since initiating anti-IL-5/5R therapy, **or**
- a ≥50% reduction in maintenance OCS use since initiating anti-IL-5/5R therapy, **or**

- no exacerbations in the past 6 months whilst receiving anti-IL-5/5R therapy and an ACQ-5 score of ≤1.5 at screening.

These criteria were selected to identify a population responsive to anti-IL-5/5R treatment who have demonstrated a clinical benefit. The first 2 criteria are similar to those recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) as evidence of a treatment response to mepolizumab/benralizumab [NICE, 2017; NICE, 2019]. The third criterion allows for the enrolment of participants for whom the treating physician may not have access to historical records of exacerbation frequency or long-term maintenance OCS use but who, nonetheless, have demonstrated a benefit to their asthma control since initiating anti-IL-5/5R treatment.

Current anti-IL-5/5R therapy: Given the large number of participants required for a non-inferiority study, it is not considered feasible to recruit solely participants receiving only mepolizumab or benralizumab. The exacerbation reduction in Phase 3 studies has been shown to be broadly consistent and generally comparable between mepolizumab [Pavord, 2012; Ortega, 2014; Chupp, 2017] and benralizumab [Bleecker, 2016] with the exception of 1 of the benralizumab studies [FitzGerald, 2016] which had a lower exacerbation rate reduction than seen in the other Phase 3 studies. Hence, participants may enter the study on either mepolizumab or benralizumab therapy. To ensure balance, a minimum of 40% on any 1 treatment (i.e., mepolizumab or benralizumab) will be enrolled. Participants who are on reslizumab therapy will not be included in this study due to the complications of blinding an IV medication that uses a weight-based dosing regimen and the relatively few patients on this medication.

Non-inferiority design: The study design (1:1 randomised, double-blind, double-dummy, parallel group, non-inferiority) is appropriate for confirming the non-inferiority of an investigational agent (GSK3511294 100 mg SC every 26 weeks) compared with an active comparator (either mepolizumab 100 mg SC every 4 weeks or benralizumab 30 mg SC every 8 weeks) on the annualised rate of clinically significant exacerbations. The double-blind, double-dummy design requires only 2 additional SC injections (GSK3511294/placebo) to be administered to each participant over the 52-week study period compared with their pre-study treatment.

Primary efficacy endpoint: A primary efficacy endpoint of annualised rate of clinically significant exacerbations has been selected as a robust and clinically relevant measure of the benefit of an anti-IL-5/5R therapy. In this study, the definition of clinically significant exacerbations (see Section 8.2.2), i.e., exacerbations treated with systemic CSs (intramuscular [IM], intravenous [IV], or oral) for 3 or more days and/or hospitalisation and/or ED visit, is consistent with previous trials with mepolizumab [Pavord, 2012; Ortega, 2014] and benralizumab [Bleecker, 2016; FitzGerald, 2016].

Study Duration: The treatment duration of 52 weeks should allow sufficient time to demonstrate the non-inferior efficacy of switching to GSK3511294 100 mg SC every 26 weeks compared with continuation of mepolizumab 100 mg SC every 4 weeks or benralizumab 30 mg SC every 8 weeks. The study will also provide 12-month safety data with repeat dosing.

Run-in Period: The minimum 1-week Run-in period allows for the assessment of participant understanding and compliance with the daily eDiary to establish Baseline symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Blood eosinophil count and follow-up period: The 4-week Follow-up period at the end of the study is to monitor safety 4 weeks after the end of treatment and to collect blood eosinophil data to track the blood eosinophil profile after the end of the 26-week treatment period with GSK3511294. It is expected that blood eosinophils will continue to be adequately suppressed with GSK3511294 100 mg SC relative to the baseline throughout the Follow-up period. Therefore, the data will give useful information as to the likely level of blood eosinophil suppression were a participant to be late for their 6-monthly injection once the drug is commercially available. Participants receiving active benralizumab will be covered during the follow-up period as the last dose of active treatment will be received at Week 48, giving 8-week coverage until the end of the Follow-up period at Week 56.

Participants on active mepolizumab will be missing a dose (based on the indicated 4 week administration schedule) as their last dose will be given at Week 48, with the next dose being due at Week 52. However this is expected to be of minimal clinical significance as blood eosinophil levels should remain suppressed until the end of the Follow-up (as observed in the MEA112997 mepolizumab study [Pavord, 2012] where the last dose was also administered at Week 48 but blood eosinophils were still suppressed at the Week 56 Follow-up visit). Nevertheless, at the discretion of the PI, commercial mepolizumab **may** be given at the Week 52 visit if they feel the participant is at undue risk of adverse events (AEs) from missing a mepolizumab dose per their medical judgement.

Data collection after discontinuation of study intervention: The objective is to collect data over the full study period, regardless of whether participants continue on randomised study intervention or prematurely discontinue. If a participant discontinues randomised study intervention they will be encouraged to remain in the study, however the decision to continue in the study following discontinuation remains the choice of the participant. Participants who agree to continue in the study after premature discontinuation from randomised study intervention (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned 56-week participation, to enable capture of post-intervention information.

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 to the participant's schedule

4.3. Justification for Dose

The dose rationale for Study 206785 is supported by the FTIH Study 205722 [GSK Document Number 2019N411063_00] 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 2 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 2 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 2 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 and Study Completer Definition

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

A participant is considered to have completed the study if he/she has completed the Exit Visit (at Week 52) and the FU visit (at Week 56), regardless of whether all doses of study intervention were 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:

AGE
1. **Age:** Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent. [For countries where local regulations or the regulatory status of study medication permit enrolment of adults only, participants recruited will be ≥18 years of age]- **Note for Germany, UK and Norway Participants**: In Germany, UK and Norway, **only** adult participants (≥18 years) are to be included in this clinical trial. **Note for Austrian Participants**: In Austria, participants who are ≥16 years are to be included in this clinical trial.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. **Asthma**: Participants who have a documented physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung, and Blood Institute guidelines [NHLBI, 2007] or GINA guidelines [GINA, 2023]. 3. **Anti-IL-5/5R Therapy:** Receiving either mepolizumab 100 mg SC or benralizumab 30 mg SC for ≥12 months prior to Screening and have a documented benefit to therapy assessed by **either**: – ≥50% reduction in exacerbation frequency since initiating treatment, **OR** – ≥50% reduction in maintenance OCS use since initiating treatment, **OR** – no exacerbations in the past 6 months whilst receiving anti-IL-5/5R therapy and an ACQ-5 score of ≤1.5 at Screening. 4. **Inhaled Corticosteroid:** A well-documented requirement for regular treatment with medium to high dose ICS in the 12 months prior to Visit 1 with or without

maintenance OCS. The maintenance ICS dose must be ≥440 mcg fluticasone propionate [FP] hydrofluoroalkane product [HFA] daily, or clinically comparable [GINA, 2023; see Appendix 10]. Participants who are treated with medium dose ICS will also need to be treated with a LABA to qualify for inclusion.

5. **Additional Controller Medication:** Current treatment with at least one additional controller medication, besides ICS [e.g., LABA, LAMA, leukotriene receptor antagonist (LTRA), or theophylline].

SEX

6. Male or eligible female.

Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1.

    OR
  - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.2 from at least 14 days prior to the first dose of study intervention until at least 30 weeks after either: the first dose (if study intervention was permanently discontinued prior to Week 26), or the dose at Week 26.
- A WOCBP must have a negative highly sensitive serum pregnancy test at screening Visit 1 and a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method

of contraception. If reproductive status is questionable, additional evaluation should be considered.
INFORMED CONSENT
7. **Informed Consent:** Capable of giving signed informed consent/assent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. **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. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically important lung condition other than asthma. This includes (but is not limited to) current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer. 2. **Eosinophilic Diseases:** Participants with other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) or Eosinophilic Esophagitis. 3. **Parasitic Infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are to be excluded. 4. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of CSs taken as therapy for asthma. 5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Participants that had localised carcinoma of the skin which was resected for cure will not be excluded). 6. **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 entry criteria. 7. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.

8. **Vasculitis**: Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis excluded prior to enrolment.
9. **COVID-19:** Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection should be excluded. Participants with known COVID-19 positive contacts within the past 14 days should be excluded for at least 14 days following the exposure during which the participant should remain symptom-free.

PRIOR/CONCOMITANT THERAPY

10. **Other mAbs used in the treatment of asthma:** Participants who have received omalizumab (Xolair), dupilumab (Dupixent), reslizumab (Cinqair/Cinqaero) or Tezepelumab (Tezspire) within 130 days prior to Visit
11. **Other mAbs not used for the treatment of asthma:** Participants who have received any mAb within 5 half-lives of Visit 1. Authorised treatments for COVID-19 are permitted and should be used in line with local regulatory guidance.
12. **Investigational Medications:** Participants who have received treatment with an investigational drug within the past 30 days or 5 terminal phase half-lives of the drug whichever is longer, prior to visit 1 (this also includes investigational formulations of marketed products).

DIAGNOSTIC ASSESSMENTS

13. **ECG Assessment**: QTcF ≥450msec or QTcF ≥480 msec for participants with Bundle Branch Block in the central over-read 12-lead ECG at screening Visit 1.

OTHER EXCLUSIONS

14. **Smoking history:** Current smokers or former smokers with a smoking history of ≥20 pack years (number of pack years = (number of cigarettes per day / 20) x number of years smoked). A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1. Pipes and/or cigars and/or electronic cigarettes/vaping use cannot be used to calculate pack-year history. Current and former use of these is exclusionary.
15. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.
16. **Hypersensitivity:** Participants with allergy/intolerance to a mAb or biologic or any of the excipients of the investigational products listed in Section 6.1.
17. **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 8.3.5.

18. **Adherence:** Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

5.3. Randomisation Criteria

At the end of the run-in period, study participants must fulfil all of the following additional inclusion/exclusion criteria in order to be randomised to study intervention.

5.3.1. Randomisation Inclusion Criteria

RANDOMISATION INCLUSION CRITERIA
1. **eDiary compliance:** Compliance with completion of the eDiary defined as completion of all questions on 4 or more days out of the 7 days immediately preceding Visit 2.

5.3.2. Randomisation Exclusion Criteria

RANDOMISATION EXCLUSION CRITERIA
1. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator. 2. **Liver chemistry test:** Participants who meet the following based on results from sample taken at Screening Visit 1: – Alanine aminotransferase (ALT) >2x upper limit of normal (ULN) – Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated a nd direct bilirubin <35%) – Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice. **NOTES:** Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria. **3. ECG:** Evidence of a clinically significant abnormality in the 12-lead ECG central over-read conducted at Screening Visit 1, based on the evaluation of the investigator, **OR** QTcF ≥450msec or QTcF ≥480 msec for participants with Bundle Branch Block, at randomisation Visit 2 (12-lead ECG machine read QTcF value). 4. **Unstable Asthma:** Participants with a clinically significant asthma exacerbation in the 7 days prior to randomisation should have their randomisation visit delayed until the investigator considers the participant's asthma to be stable (see

Section 5.6). If the 8-week screening period has elapsed, then the participant should be considered a run-in failure.

5. **Maintenance Asthma Therapy:** Any changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period.

5.4. Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.5. Pre-screen/Screen/Run-in Failures

Pre-screen/screen/run-in failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. 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 SAEs.

For the purposes of this study, pre-screen/screen/run-in failures will be defined as follows:

Pre-screen Failures	Screen Failures	Run-in Failures
Participants who are assigned a study number at the time of signing the informed consent (pre-screen visit) but do not progress to the screening visit.	Participants who complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period.	Participants who enter the run-in period but are not subsequently randomised.

Re-screening of participants will be permitted; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor.

Re-screened participants should be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Randomisation

Participants who experience a clinically significant asthma exacerbation during the run-in period should receive treatment for their exacerbation, have their randomisation visit delayed and remain in the run-in period (up to 8 weeks) until the investigator considers the participant to have returned to their baseline asthma status for at least 7 days. The run-in period may be extended after consultation with the Medical Monitor.

A clinically significant exacerbation is defined as worsening of asthma requiring the use of systemic CS and/or hospitalisation and/or ED visit (Section 8.2.2).

A participant who is not eligible to continue in the study at the end of the run-in period, should be considered a run-in failure but may be rescreened after consultation with the Medical Monitor (Section 5.5).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

GSK3511294/placebo will only be administered in the clinic; hence Visit 2 (Week 0) and Visit 9 (Week 26) are required to be in-clinic visits.

Mepolizumab/placebo or benralizumab/placebo may be administered in the clinic or during home visits by a home healthcare professional.

6.1. Study Interventions Administered

GSK3511294 or Placebo

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 a Type 1 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.

The placebo in this study will be 0.9% sodium chloride solution contained in a PFS also supplied by GSK.

An overview of GSK3511294 and placebo study interventions is provided in Table 2.

Table 2 Study Interventional Products (GSK3511294/placebo)

ARM Name	GSK3511294 100 mg	Placebo
Intervention Name	GSK3511294 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloride solution in single-use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)	Placebo once every 26 weeks (Week 0 and Week 26)
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	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.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, N/A=not applicable

Mepolizumab or Placebo

Mepolizumab is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab liquid drug product will be supplied by GSK in Type 1 glass syringes with staked needles (1/2-inch x 29-gauge thin wall), sealed with latex-free rubber plungers. Mepolizumab liquid will be assembled in single use, disposable safety syringes to enable delivery of the drug product. Each device will deliver 100 mg mepolizumab in 1.0 mL sterile liquid formulation. The formulation contains sodium phosphate, citric acid, sucrose, ethylene diamine tetra acetic acid (EDTA), water for injection and polysorbate 80.

The placebo to match mepolizumab will be supplied as solution for injection with the same mepolizumab injection formulation but without the active drug substance.

An overview of mepolizumab and placebo study interventions is provided in Table 3.

Table 3 Study Interventional Products (Mepolizumab/placebo)

ARM Name	Mepolizumab 100 mg	Placebo
Intervention Name	Mepolizumab 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation	Sterile liquid formulation
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 4 weeks	Placebo once every 4 weeks
Route of Administration	SC injection	SC injection
Use	Active comparator	Placebo
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	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.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, N/A=not applicable

Benralizumab or Placebo

Benralizumab is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Benralizumab liquid drug product will be supplied by AstraZeneca as a liquid in a pre-filled syringe that contains 30 mg benralizumab in 1 mL (30 mg/mL) sterile liquid formulation. The pre-filled syringe is comprised of a type 1 glass barrel with a staked 29-gauge 12.7 mm stainless steel needle, rigid needle shield and FluoroTec-coated plunger stopper in a safety device. The formulation contains L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, polysorbate 20, and water for injection.

The study will start with commercial benralizumab in a PFS manufactured by AstraZeneca and then may transition later to clinical-supply benralizumab in a PFS. The study will start with placebo that will be 0.9% sodium chloride solution contained in a PFS supplied by GSK and then may transition later to placebo supplied by AstraZeneca.

An overview of benralizumab and placebo study interventions is provided in Table 4 (using commercial supplies) and Table 5 (using clinical supplies).

Table 4 Study Interventional Products (Benralizumab/placebo) Using Commercial Supplies

ARM Name	Benralizumab 30 mg	Placebo
Intervention Name	Benralizumab 30 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation	Sterile 0.9% (w/v) sodium chloride solution
Unit Dose Strength(s)	30 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	30 mg once every 8 weeks	Placebo once every 8 weeks
Route of Administration	SC injection	SC injection
Use	Active comparator	Placebo
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Commercial: Manufactured by AstraZeneca	Clinical Product: Manufactured by GSK
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, N/A=not applicable

Table 5 Study Interventional Products (Benralizumab/placebo) Using Clinical Trial Supplies

ARM Name	Benralizumab 30 mg	Placebo
Intervention Name	Benralizumab 30 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation	Placebo formulation
Unit Dose Strength(s)	30 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	30 mg once every 8 weeks	Placebo once every 8 weeks
Route of Administration	SC injection	SC injection
Use	Active comparator	Placebo
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Clinical Product: Supplied by AstraZeneca	Clinical Product: Supplied by AstraZeneca
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, N/A=not applicable

6.1.1. Medical Devices

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

- A Safety Syringe device comprised of pre-filled syringe contained within a passive safety device to prevent needle stick injuries. The devices used in the study are representative of the devices either currently marketed or planned to be marketed for the product.
- The components that comprise the pre-filled syringe, including glass barrel with pre-staked needle and plunger are sourced from Becton Dickinson. The pre-filled syringe (for GSK3511294 or matching placebo and mepolizumab or matching placebo) is filled and assembled at GSK, Barnard Castle. The pre-filled syringe for benralizumab or matching placebo is filled and assembled at AstraZeneca.
- The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle or at AstraZeneca.

The Instruction for use (IFU) of these injection devices will be provided. The instructions for GSK3511294 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 8.4.8) and appropriately managed by GSK.

6.2. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.3. 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 SRM.
- 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.

6.4. Measures to Minimise Bias: Randomisation and Blinding

The contents of the label will be in accordance with all applicable regulatory requirements.

6.4.1. Treatment Assignment

- Eligible participants will be centrally randomised using an IRT system.
- The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. Separate randomisation schedules will be created for each country. Participants will be assigned to study intervention in accordance with the randomisation schedule. Once a randomisation number has been assigned to a participant, it cannot be reassigned to any other participant in the study.
- At Visit 2 (Week 0), those participants who meet the randomisation eligibility criteria will be randomised in a 1:1 ratio to receive one of the following study interventions in addition to their SoC asthma treatment:
  - GSK3511294 100 mg SC and placebo SC treatment matching the participant's anti-IL-5/5R treatment prior to randomisation (either placebo matching mepolizumab or placebo matching benralizumab).
  - Either active mepolizumab or active benralizumab according to the participant's treatment prior to randomisation and placebo SC matching GSK3511294.
- Study interventions will be administered via a PFS as per the SoA (Section 1.3), as follows:
  - GSK3511294 100 mg or placebo matching GSK3511294, at Visit 2 (Week 0) and Visit 9 (Week 26), for a total of 2 injections **AND:**

    EITHER

    - Active mepolizumab or placebo matching mepolizumab, at Visit 2 (Week 0) and then every 4 weeks up to/including Visit 15 (Week 48), for a total of 13 injections

      OR

    - Active benralizumab or placebo matching benralizumab, at Visit 2 (Week 0) and then every 8 weeks up to/including Visit 15 (Week 48), for a total of 7 injections.

6.4.2. Blinding

- The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

- The Blinding Plan will provide both a generic and site-specific overview of the procedures and documentation necessary to maintain a regulatory acceptable level of blinding. Detailed blinding procedures are provided in the SRM.
- The participant, and the blinded study staff (responsible for evaluating the participants for safety and efficacy and for making decisions about participant care) must remain blinded to the study intervention assignment at all times.
- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, GSK3511294, mepolizumab, benralizumab, and matching placebo for each active study intervention will be administered from PFSs. For participants previously receiving benralizumab, for a period at the start of the study, commercial benralizumab may be supplied with a placebo from GSK. To maintain the treatment blind during this period, it is important that the person administering the injection of commercial benralizumab/matching placebo is an unblinded member of staff who is not involved in the assessment or management of study participants. Further information will be provided in the SRM.
- Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomisation/dispensing has been done accurately.
- A participant will be withdrawn from study intervention if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- To maintain the blind, haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomisation samples will not be reported to the site or the central study team.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study Intervention Compliance

GSK3511294, mepolizumab, benralizumab, and placebo 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. Separate unblinded site staff/personnel will administer commercial benralizumab/matching placebo.

Participants will be monitored in clinic for a minimum of 2 hours post-first dose of GSK3511294/placebo and post-dose at Week 26 to monitor for immediate hypersensitivity and any other untoward effects. In the event of an acute severe reaction (e.g., anaphylaxis), 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.

6.6. Dose Modification

Dose modification is not allowed.

6.7. Continued Access to Study Intervention after the End 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 whether or not GSK is providing specific post- study intervention. At the end of the study, participants may be prescribed appropriate alternative asthma therapy if needed and as determined by the study investigator.

6.8. Treatment of Overdose

GSK3511294: 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 (refer to the current IB [GSK Document Number 2016N295843_03 or later]), single SC doses of GSK3511294 up to 300 mg were well tolerated in 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 a potential overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the participant 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 of GSK3511294/placebo (either at randomisation [Week 0] or Visit 9 [Week 26]).
- 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 GSK3511294/placebo will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Mepolizumab: The dose of mepolizumab considered to be an overdose has not been defined. There are no known antidotes and GSK does not recommend a specific treatment in the event of a suspected overdose. However, the investigator should use clinical

judgement in treating the symptoms of a suspected overdose, inform the Medical Monitor and record the overdose in the eCRF.

Benralizumab: There is no specific treatment for an overdose with benralizumab. If a potential overdose occurs, the participant should be treated with supportive care with appropriate monitoring as necessary. However, the investigator should use clinical judgement in treating the symptoms of a suspected overdose, inform the Medical Monitor and record the overdose in the eCRF.

6.9. Concomitant Therapy

At pre-screening and/or screening, 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 in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency (dose changes are to be recorded for OCS)

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

6.9.1. Permitted Medications and Non-Drug Therapies

Throughout the study, participants are to be maintained on their baseline SoC asthma treatment consisting of ICS plus at least 1 other controller, e.g. LABA, LAMA, with or without maintenance OCS. It is recognised that in a year-long study, changes may need to be individualised if clinically crucial for a participant. The investigator is encouraged to discuss any cases with the Medical Monitor before initiating changes to a participant's maintenance asthma medication.

Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted provided that they have been taken regularly in the 3 months prior to screening (Visit 1). If uncertain whether a medication is permitted, please confirm with the Medical Monitor.

Anti-inflammatory reliever therapy using either an ICS/LABA (e.g., ICS/formoterol) as part of maintenance and reliever therapy (MART) treatment or as an ICS/SABA is permitted if already using that regimen at the time of screening. ICS/SABA and ICS/LABA should be withheld for ≥ 6 and 12 hours, respectively, prior to spirometry, if possible. Study-provided albuterol/salbutamol use should not be recorded in the eCRF,

only in the eDiary. The use of MART or ICS/SABA should be recorded in the eCRF and eDiary.

LABAs, LAMAs, and fixed dose combinations of ICS/LABA or ICS/LABA/LAMA 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, if initiated prior to the Screening Visit (Visit 1). This treatment must be captured in the eCRF.

Allergen-specific immunotherapy is permitted provided that it has been taken regularly in the 6 months prior to screening (Visit 1).

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

COVID-19 vaccine administration and the administration of the study intervention should be separated by 14 days if possible, in order to be able to properly assess study injection site/treatment reactions.

Participants can be treated for SARS-CoV-2 infection using authorised COVID-19 treatments (including monoclonal antibodies) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted.

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening (Visit 1), according to the following schedule, or during the study:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab (Xolair), dupilumab (Dupixent), reslizumab (Cinqair/Cinqaero), Tezepelumab (Tezspire)	130 days
Other monoclonal antibodies, with the exception of authorised monoclonal antibody treatments for COVID-19, which are permitted and should be used in line with local regulatory guidance.	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Immunosuppressive medications such as those listed below (not all inclusive)
Corticosteroids if used to treat a condition other than asthma • Intramuscular, long-acting depot • Regular systemic (oral or parenteral) Note: Hydrocortisone used to treat/prevent adrenal crisis when tapering off steroids (used for asthma) is permitted after discussion with the Medical Monitor Note: short term use of corticosteroid (≤5 days up to and including 4 short courses throughout the study) is permitted.
Methotrexate, troleandomycin, cyclosporin, azathioprine
Oral gold
Chemotherapy used for conditions other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study. CPAP, BiPAP, and oxygen therapy should not be initiated during the run-in period.

6.9.3. Rescue Medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication (auxiliary medication) throughout the study. Albuterol/salbutamol will be sourced locally for all centres.

Participants will be dispensed an MDI at Screening Visit 1 to be used primarily to treat asthma symptoms on an as needed basis. The MDI should be replaced as needed.

Furthermore, anti-inflammatory reliever either as part of a MART regimen (i.e., ICS/LABA [e.g. ICS/formoterol]) or as ICS/SABA is permitted for participants who are already using this therapy at screening. Participants should use their own anti-inflammatory reliever therapy as needed, throughout the study. **NOTE**: If a participant uses MART or ICS/SABA therapy as rescue, they **should not** use the study provided albuterol/salbutamol. **NOTE**: *MART is only permitted in participants who are newly recruited. Those who are already participating in the study should continue to use the study provided rescue medication.*

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 intervention period:

- Liver Chemistry: 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 7.1.2)

- Pregnancy: Positive pregnancy test (see Section 8.4.5)
- 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 7.5)
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant (see Section 6.4.2).

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 randomised 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 and Follow-up Visits.
- 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 their scheduled visits in-clinic, at home, or by phone. The required study assessments will depend on whether the participant is attending the visit in-clinic, at home, or by phone. 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).

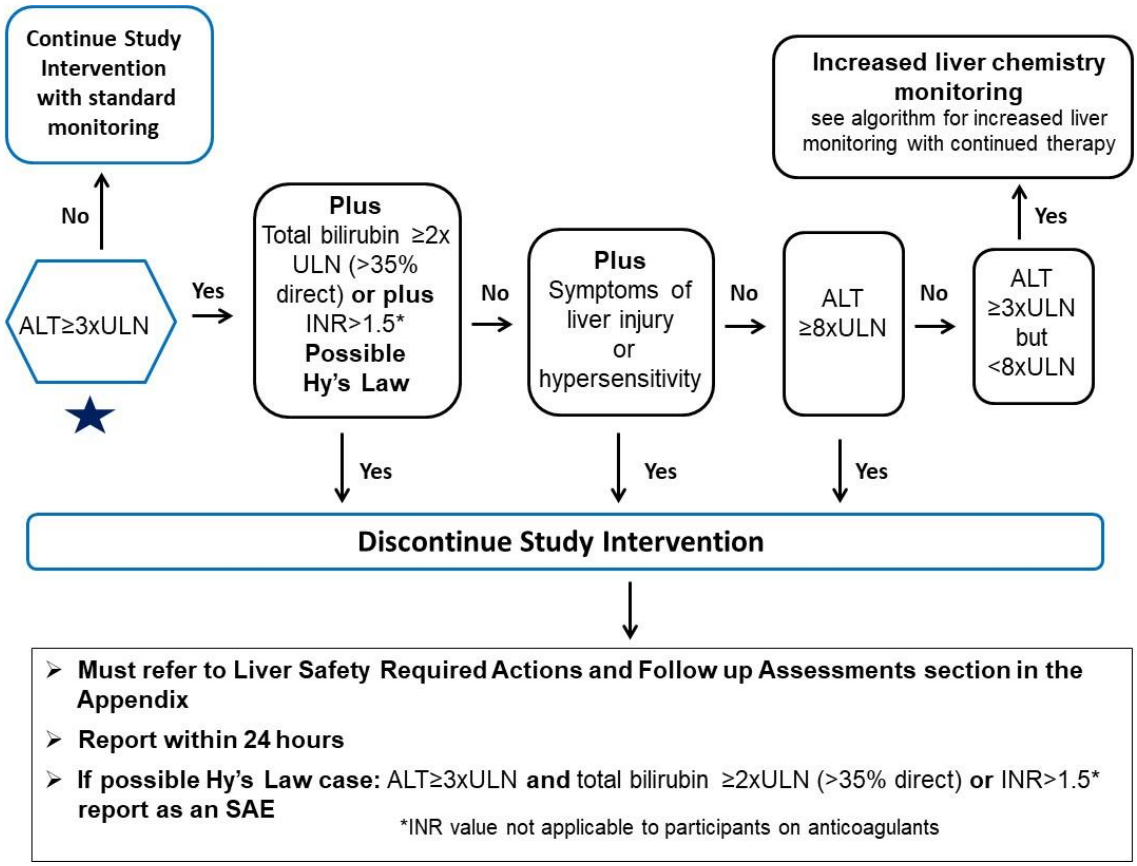
7.1.1. Liver Chemistry Stopping Criteria

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

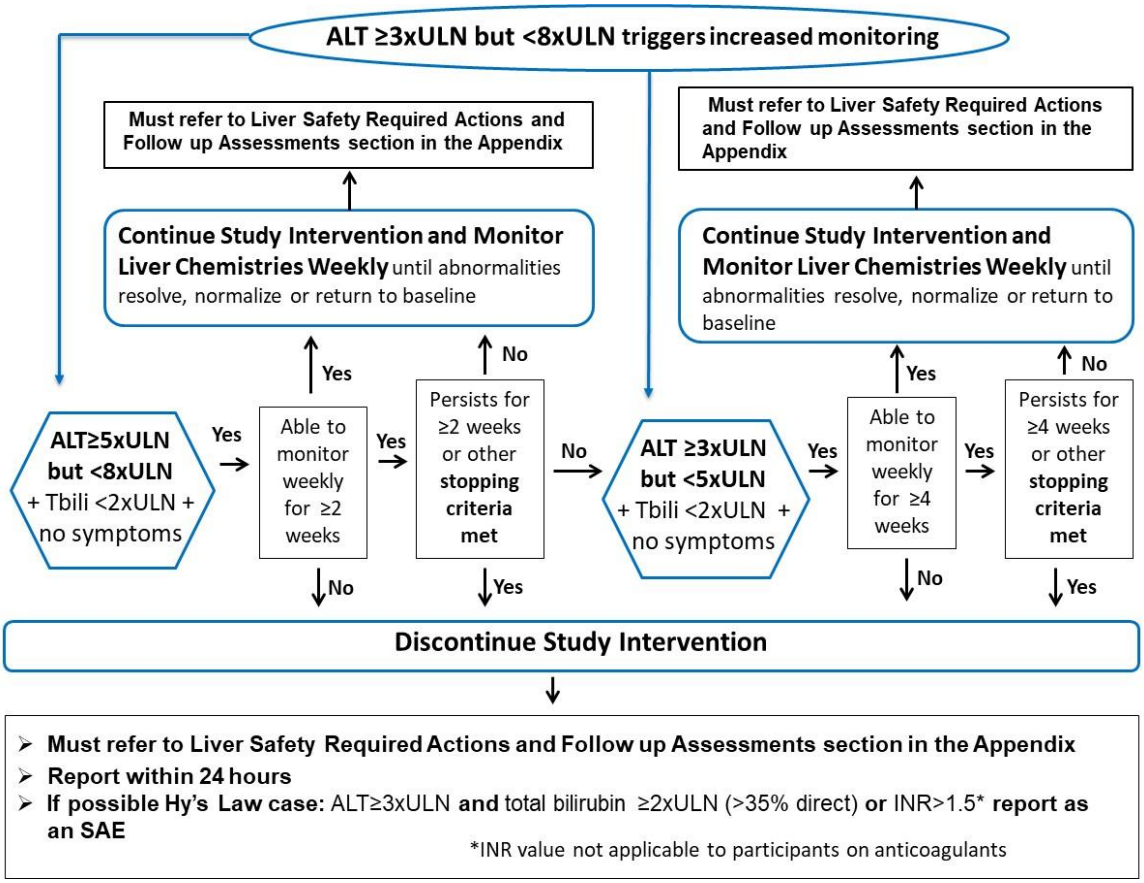
Liver Chemistry Stopping Criteria Algorithm



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 Section 10.6 (Appendix 6) for required Liver Safety Actions, Monitoring and Follow-up Assessments.

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

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by a participant in this study will not be permitted.

7.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.3.3.

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 randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study. At Visit 9, the 12-lead ECG machine-read values should be used and assessed against QTc Stopping Criteria, before administration of the study intervention. The 12-lead ECG central over-read values should be used at the remaining visits.

7.1.3. Temporary Discontinuation

For this study, a temporary discontinuation refers to a delayed administration of study intervention.

If a participant becomes infected (parasitic infection) during the study intervention period and does not respond to anti-helminth treatment, a delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorised representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
  - a Withdraw from Study (WS) Visit. This visit should be conducted 26 weeks after the last administered dose of GSK3511294/placebo (i.e., WS Visit at Week 26 if last dose of GSK3511294/placebo was at Week 0; WS Visit at Week 52 if last dose of GSK3511294/placebo was at Week 26) **AND**
  - a Follow-up Visit. This visit should be conducted 30 weeks after the last administered dose of GSK3511294/placebo for AE/SAE and pregnancy assessments.

  Note: this includes any participants who initially discontinue study intervention and remain in the study (Section 7.1) but later decide to withdraw from the study.

- All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses 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.
- The primary reason for participant discontinuation/withdrawal from the study will be documented in the eCRF.
- Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 8.4.3).

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/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 GSK3511294/placebo.

Discontinuation of specific sites or of 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 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 3 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 3 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, PK, 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 heterogenous 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 PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [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 done on frozen baseline serum samples (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 participant 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 (Section 1.3).
- As detailed in the SoA (Section 1.3), the follow-up visit may be completed within 7 days of the scheduled time-point, but every effort should be made to complete the visit on the scheduled day.
- Every effort should be made to reduce missing data throughout the study.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue to receive the second scheduled dose of study intervention, if applicable.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be 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.
- Laboratory results that could unblind the study (e.g., haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- 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. Pre-screening Visit (Visit 0)

Informed consent should be obtained at the Pre-screening Visit or the Screening Visit, prior to initiating any study assessments. A participant number will be assigned at the time the ICF is signed. Participants can conduct the Pre-screening Visit (Visit 0) up to 2 weeks prior to the Screening Visit (Visit 1).

The pre-screening procedures will include a review/assessment of:

- Inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Demographic data such as year of birth, sex, race, and ethnicity, which should be recorded in the participant's eCRF. Collection of sex, race and ethnicity data (if permitted based on country legislation) 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. Demographic data review and collection can be done at Visit 1 instead, if necessary).
- Childbearing status for all women (can be conducted at Visit 1 instead, if necessary); for WOCBP contraception should be started at least 14 days prior to receiving the first dose study intervention (see Appendix 4).
- Therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications.

All clinic visits as indicated in the SOA must be registered in the IRT and the relevant eCRF form completed.

Serious adverse events must be collected from signing of Informed Consent if considered related to study procedures.

8.1.2. Critical Assessments performed at Screening (Visit 1)

- Inclusion/Exclusion criteria (see Section 5.1 and Section 5.2)
- Therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications.
- ACQ-5 (see Section 8.2.5) if needed to meet inclusion criterion 3 (see Section 5.1)

- Medical history including:
  - Asthma including current treatment, duration of asthma, courses of rescue CSs, history of previous intubations, asthma exacerbation history in previous year, asthma triggers
  - Cardiovascular (CV) medical history/risk factors (as detailed in the eCRF)
  - Vasculitis, allergies and anaphylaxis history
  - Smoking history and current status
- CCI [redacted]
- Safety Assessments including:
  - Physical exam (see Section 8.3.1)
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Clinical chemistry (including liver chemistry)
  - Serum pregnancy test – for all WOCBP (childbearing potential for all women will be assessed at pre-Screening) (see Section 8.3.5)
  - Urinalysis (can be conducted at Visit 2 instead, if necessary)
  - Parasitic screening (only in regions with high-risk or for participants who have visited a high-risk region in the past 6 months)
- eDiary registration and training

8.1.3. Critical Assessments performed at Randomisation (Visit 2)

The following critical assessments will be conducted at randomisation Visit 2:

- Review of randomisation criteria (see Section 5.3), and data collected at Visit 1.
- Review of concomitant medications
- Spirometry (see Section 8.2.3)
- SGRQ (see Section 8.2.4)
- ACQ-5 (see Section 8.2.5)
- Review eDiary asthma symptoms and PEF summary report
- CCI [redacted]
- Safety assessments including:
  - Vital signs (see Section 8.3.2)

  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Clinical chemistry (including liver chemistry)
  - Urine pregnancy test – for all WOCBP (see Section 8.3.5)
  - Complement C3 and C4
  - Baseline immunogenicity (see Section 8.8)
  - Storage of a baseline sample that may be analysed for the presence of ANCA (anti-MPO antibody and anti-PR3 antibody tests), ANA, and anti-dsDNA antibody, if necessary (see Section 7.5)

8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

8.2.1. Efficacy Endpoints

Efficacy endpoints are listed in Section 3.

8.2.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by:

Worsening of asthma which requires use of systemic CSs[1] and/or hospitalisation and/or Emergency Department (ED) visit.

[1]*For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, 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.

Additional details on the process for determination of clinically significant exacerbations can be found in the Statistical Analysis Plan (SAP).

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 start of study intervention until the Follow-up Visit.

8.2.3. Pulmonary Function Testing/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 randomisation (Visit 2), and at scheduled in-clinic visits according to the SoA (Section 1.3). At each visit, spirometry should be performed at the same time of day (±1 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should try to withhold short-acting beta-2-agonists (SABAs) and/or ICS/SABA ≥6 hours and LAMAS/LABAs and/or MART for ≥12 hours prior to the clinic visit, if possible.

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

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

The SGRQ is a well-established instrument, comprising 51 questions 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 electronically according to the SoA (Section 1.3).

8.2.5. Asthma Control Questionnaire-5 (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 5 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 6 (total impairment/ limitation) scale. This will be completed according to the SoA (Section 1.3). After Screening Visit 1, ACQ-5 responses will be collected electronically.

CCI

CCI

[redacted]

8.2.8. eDiary Asthma Parameters and Alerts

The participant will be asked to record the following parameters daily in the eDiary from Visit 1 onwards:

- Morning peak expiratory flow (best of 3), before rescue medication usage (L/min).
- Occasions of rescue usage over the previous 24-hours.
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 9).
- Frequency of awakening due to asthma symptoms requiring rescue medication use.

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

- Decrease in morning PEF ≥30% on at least 2 of 3 successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least 2 of 3 successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least 2 of 3 successive nights.
- A symptom score of 5 for at least 2 of 3 successive days.

8.3. 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.

8.3.1. Physical Examinations

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

8.3.2. Vital Signs

- Oral or skin 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.

8.3.3. Electrocardiograms (ECGs)

- 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 7.1.2 for the QTcF formula.
- If a routine ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTcF values of the 3 ECGs to determine whether the participant should be screened/randomised/discontinued from the study intervention (but not from the study). Refer to Section 5.2 for exclusion criteria related to ECG assessment and Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the participant 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 2 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.

8.3.4. 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 Follow-up visit 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.
- 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), then the results must be recorded.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from any visits post-randomisation.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- A serum pregnancy test should be conducted for all WOCBP at the screening visit (Visit 1) and the Exit visit. In addition, a urine pregnancy test should be performed for all WOCBP prior to randomisation (Visit 2), on a monthly basis at the specified scheduled study visit, and at the Follow-up Visit as per the SoA (Section 1.3). WOCBP must perform the pregnancy test before the administration of any dose of study intervention.

- Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- A final urine pregnancy test should be conducted for all WOCBP, at least 30 weeks after either the first dose of GSK3511294 or matching placebo (if study intervention was permanently discontinued prior to Week 26), or the dose at Week 26 (Follow-up Visit at Week 56) (see Section 7.2).
- 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.

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

The definitions of AEs or 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.

AEs 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.

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

- All SAEs will be collected from the start of intervention (Visit 2) until the follow-up visit 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 contact 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.

8.4.2. 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.

8.4.3. 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 8.4.7), 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.

8.4.4. 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.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report.
- 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 IB 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.

8.4.5. Pregnancy

- Any female participant who becomes pregnant while participating in the study will not receive another dose of study intervention.
- Details of all pregnancies in female participants will be collected from the start of study intervention until at least 30 weeks after either the first dose of GSK3511294/placebo (if study intervention was permanently discontinued prior to Week 26), or the dose at Week 26 (Follow-up Visit at Week 56).
- 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, 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 8.4.4. 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.

8.4.6. Cardiovascular and Death Events

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

The CV CRF pages are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV 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.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) 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 3 hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.8. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294 or matching placebo injections. 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.

8.4.8.1. 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.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.4.8.2. 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.

8.4.8.3. 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.

8.4.8.4. 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.

8.5. Pharmacokinetics

Pharmacokinetic samples will not be collected in this study.

8.6. Genetics and Pharmacogenomics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5. Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.

8.7. Biomarkers/ Pharmacodynamic Markers

8.7.1. Blood Eosinophil Counts

In order to investigate the PD effects of GSK3511294, blood eosinophil counts will be measured as part of the standard haematological assessments according to the SoA (Section 1.3). The site staff and central study team will be blinded to each participant's blood eosinophil count (as well as overall haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomisation visits. Total white blood cell counts will be provided throughout the study.

8.7.2. Complement, and Inflammatory Markers

Blood samples will be collected to measure complement (C3 and C4), according to the SoA (Section 1.3).

A baseline serum sample will be collected at Visit 2 and stored. If necessary, this sample may be analysed for the presence of ANCA (using anti-MPO antibody and anti-PR3 antibody tests), and ANA, including anti-dsDNA antibodies. After dosing, additional inflammatory markers and tests may be considered on an ad-hoc basis should there be clinical concerns regarding an immune-mediated AE (see Section 7.5).

8.8. Immunogenicity Assessments

Antibodies to GSK3511294 will be evaluated in serum samples collected from participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the Exit Visit or the final in-clinic visit for participants who withdraw early 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 neutralisation antibody (NAb) assay. If necessary, further immune response characterisation may be performed as needed.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The treatment comparison of GSK3511294 + SoC with active comparator (mepolizumab or benralizumab) + SoC on the primary endpoint of annualised rate of clinically significant exacerbations will be made in order to assess the primary objective of non-inferiority. The null hypothesis that the exacerbation rate ratio for GSK3511294 + SoC compared with active comparator (mepolizumab or benralizumab) + SoC is at least 1.28 will be tested at the one-sided 2.5% significance level i.e., non-inferiority will be met if the upper bound for the 95% confidence interval (CI) is less than 1.28 (see Section 9.2.2.1). Should non-inferiority be met, the primary endpoint will then be tested for superiority at the 5% 2-sided significance level.

9.2. Sample Size Determination

Approximately 2,650 participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy (mepolizumab or benralizumab) will be screened to achieve a target global randomisation of approximately 1,700 participants (850 participants per arm).

9.2.1. Sample Size Assumptions

The sample size of 850 participants per arm (equal allocation) is based on sufficient power to conclude non-inferiority with a margin of 1.28 using a one-sided 2.5% significance level.

The assumption of 0.8 for the dispersion parameter was observed in 2 mepolizumab phase 3 studies [Pavord, 2012; Ortega, 2014]. The assumption of 0.7 for the annual exacerbation rate for GSK3511294 and the active comparator arm was estimated from 2 mepolizumab open-label extension (OLE) studies [Khatri, 2019; Lugogo, 2016] when taking into account the inclusion criteria for this study. Missing/excluded data (based on the estimand strategy described in Section 3.1 and Section 3.2) is assumed at 10% of participant-years data (proportion of missing data observed in the first year of a mepolizumab OLE study [Lugogo, 2016]). An exacerbation rate ratio of 1 is assumed (GSK3511294 and comparator therapies are equally efficacious). Based on these assumptions, the power of the study is 91% [PASS, 2020].

Based on the assumptions above, the maximum treatment effect (i.e., observed rate ratio of GSK3511294 + SoC compared to active comparator (mepolizumab or benralizumab) + SoC estimated to result in a conclusion of non-inferiority is 1.11.

9.2.2. Sample Size Sensitivity

The power calculation is based on assumptions. Table 6 illustrates how changes in assumptions for 2 parameters (annualised exacerbation rate of the active comparator [mepolizumab or benralizumab] + SoC and exacerbation rate ratio for GSK3511294 + SoC compared with active comparator + SoC) affect the power.

Table 6 Estimates of Power for Assumed Active Comparator + SoC Exacerbation Rate and True Exacerbation Rate Ratio (GSK3511294 + SoC Compared with Active Comparator + SoC)

Annualised exacerbation rate of active comparator + SoC	Exacerbation rate ratio for GSK3511294 + SoC compared with active comparator (mepolizumab or benralizumab) + SoC				
	0.9	0.95	**1**	1.05	1.1
0.6	99	96	88	72	50
0.7	>99	98	**91**	76	54
0.8	>99	98	93	79	57
0.9	>99	99	95	82	60
1	>99	99	96	84	63

9.2.2.1. Determination of Non-inferiority Margin

The choice of non-inferiority margin is based on the application of the fixed margin approach (Non-Inferiority Clinical Trials to Establish Effectiveness) [FDA, 2016]. The active control treatment effect was estimated by conducting a random-effects meta-analysis of competitor anti-IL-5 therapies (mepolizumab, benralizumab, reslizumab) compared with placebo. The rate ratio was estimated as 0.51 (95% CI: 0.42, 0.61). Based on an assumption of constancy (the effect of the active control compared with placebo would be similar in this study to that observed in the historical studies), the rate ratio for GSK3511294 compared with the active comparator arm (mepolizumab or benralizumab) that would result in a placebo-like efficacy for GSK3511294 is 1/0.61 = 1.64. The upper bound is used because this represents a conservative estimate of the effect the active comparator (mepolizumab, benralizumab) is expected to have. A non-inferiority margin of 1.28 preserves 50% of the active control treatment effect (exacerbation rate ratio) on the $\log_e$ scale.

9.3. Analysis Sets

For the purpose of analyses, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure) Note: Screening failures (who never passed screening even if rescreened) 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.
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention. Data will be analysed according to randomised study intervention.

9.4. Statistical Analyses

The SAP will be finalised prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section. Full details of the analysis methods and non-inferiority margins will be provided in the SAP.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Endpoint

9.4.1.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Primary Endpoint	Annualised rate of clinically significant exacerbations over 52 weeks. Clinically significant exacerbations are defined in Section 8.2.2.
Intercurrent events	The anticipated intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e., regardless of the intercurrent event occurring b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e., had the intercurrent event not occurred c) Change in maintenance therapy (excluding prohibited medications listed in Section 6.9.2): treatment policy strategy i.e., regardless of the intercurrent event occurring d) Use of prohibited medications listed in Section 6.9.2): treatment policy strategy i.e., regardless of the intercurrent event occurring
Summary measure	Ratio of the rate of exacerbations between GSK3511294 + SoC and the active comparator (mepolizumab or benralizumab) + SoC.
Analysis Method	The primary analysis of annualised rate of clinically significant exacerbations will use a negative binomial model. Covariates included will be region, number of exacerbations in the year prior to the study, baseline % predicted FEV_1, pre-study biologic treatment for asthma and treatment group with $\log_e$(time in study in years) as an offset variable. The rate ratio and 95% CI will be provided for the comparison between GSK3511294 + SoC and the active comparator (mepolizumab or benralizumab) + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for this period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (i.e., based on all data included in the analysis under the current estimand strategy).

	b) For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for this period will be assumed MAR (i.e., based on all data included in the analysis under the current estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. Missing/excluded data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing/excluded data based on a plausible range of values for the rate of exacerbations per year. The imputed exacerbation rates will be varied independently for treatment arms to determine which value for imputation changes the conclusion of non-inferiority. Further details will be provided in the SAP.

9.4.1.2. Supplementary Estimands

A supplementary estimand will be conducted by handling both the intercurrent event of study intervention discontinuation (for any reason) and the intercurrent event of prohibited medication use with a hypothetical strategy. All other details remain the same as those described in the main estimand. In the spirit of a per protocol analysis, this estimand targets the treatment effect in the absence of study intervention discontinuation and use of prohibited medication. If other potential major intercurrent events, currently not foreseen, emerged during the study these would also be dealt with using a hypothetical strategy. Data for the period following the intercurrent event will be excluded and assumed MAR. Sensitivity analyses would be conducted as described in the main estimand.

Full details of the analysis methods will be provided in the SAP.

9.4.2. Secondary Endpoints

9.4.2.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Secondary Endpoints	• Weighted mean change from baseline in SGRQ total score over 52 weeks • Weighted mean change from baseline in ACQ-5 score over 52 weeks • Weighted mean change from baseline in FEV_1 over 52 weeks
Intercurrent events	The anticipated intercurrent events and corresponding strategies: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e., regardless of the intercurrent event occurring b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e., had the intercurrent event not occurred c) Change in maintenance therapy (excluding prohibited medications listed in Section 6.9.2): treatment policy strategy i.e., regardless of the intercurrent event occurring

	d) Use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e., regardless of the intercurrent event occurring
Summary measure	Difference in mean weighted mean change from baseline between GSK3511294 + SoC and the active comparator (mepolizumab or benralizumab) + SoC.
Analysis Method	The analysis will be performed using an analysis of covariance (ANCOVA) model. Covariates included will be treatment group, baseline, region, number of exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV_1, pre-study biologic treatment for asthma. The differences in means and 95% CI will be provided for the comparison between GSK3511294 + SoC and the active comparator (mepolizumab or benralizumab) + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for this period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (i.e., based on all data included in the analysis under the current estimand). b) For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for this period following withdrawal will be assumed MAR (i.e., based on all data included in the analysis under the current estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. Missing/excluded data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. Further details will be provided in the SAP.

9.4.2.2. Supplementary Estimands

A supplementary estimand will be conducted by handling both the intercurrent event of study intervention discontinuation (for any reason) and the intercurrent event of prohibited medication use with a hypothetical strategy. All other details remain the same as those described in the main estimand. In the spirit of a per protocol analysis, this estimand targets the treatment effect in the absence of study intervention discontinuation and use of prohibited medication. If other potential major intercurrent events, currently not foreseen, emerged during the study these would also be dealt with using a hypothetical strategy. Data for the period following the intercurrent event will be excluded and assumed MAR. Sensitivity analyses would be conducted as described in the main estimand.

Full details of the analyses methods will be provided in the SAP.

9.4.3. Other Endpoints

Full details of analysis methods to be used for other endpoints will be provided in the SAP.

9.4.4. Safety Analysis

All safety analyses will be performed on the Safety Population. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of AEs, SAEs, AESIs, laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system organ class (SOC). AEs will be summarised by frequency and percentage of participants, by SOC and preferred term within each treatment group (summaries will be presented separately for mepolizumab and benralizumab and also combined for the active comparator arm). Separate summaries will be presented for all AEs, drug-related AEs, serious AEs (SAEs), AEs leading to permanent discontinuation of study intervention or withdrawal from study and for any AEs of special interest.

9.5. Interim Analysis

As the study will be ongoing at the time of regulatory submission, an interim analysis will be performed in order to provide unblinded safety data in an interim Clinical Study Report (CSR) to inform on the risk-benefit assessment of GSK3511294 in asthma. Further details will be provided in the Blinding Plan for NIMBLE Interim Analysis and the Statistical Analysis Plan.

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 authorised 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.

Participants who are rescreened are required to provide consent/assent and sign a new ICF/assent form.

GSK (alone or working with others) may use a 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 GSK3511294 approved for medical use or approved for payment coverage.

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.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties**.**
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. If using HHS, DTP/DFP, or TM: GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.5. Committees Structure

An Independent Data Monitoring Committee (IDMC) comprised of clinical experts external to GSK will review unblinded data at defined timepoints during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional timepoints for review may be added.

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 blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. An SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information. 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

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report (CSR). 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 patients 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 patient 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.

- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- 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 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 CSR.
- 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 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 the SRM.
- 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.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

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, including stopping for safety reasons

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
- Total number of participants included earlier than expected
- 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 multicentre 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).

Local laboratory results may be required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation to be performed – for example: when results from screening Visit 1 should be available before dosing on Visit 2, or at any time when a participant is unwell and results are required urgently.

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.

To maintain the blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.

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.

Table 7 Protocol-Required Safety Laboratory Tests

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

Laboratory Assessments	Parameters
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 serum pregnancy test at Screening Visit 1 and Exit Visit; urine pregnancy tests for all other scheduled visits (as needed for WOCBP)[4]
Other Screening Tests	• FSH and oestradiol (if required to confirm postmenopausal status) • Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories. • Serum samples collected at baseline will be frozen and stored for later analyses if necessary, anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody

NOTES:
ALT = Alanine Aminotransferase; ANA = anti-nuclear antibody; AST = Aspartate Aminotransferase; BUN = Blood urea nitrogen; FSH = Follicle-stimulating hormone; GGT = gamma glutamyl transferase; MPO=myeloperoxidase; PR3=proteinase 3; 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-randomisation results will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils. Total white blood cell counts will be provided throughout the study.
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 normalised 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 Meeting 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., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation – In general, hospitalisation signifies that the participant has been 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 hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. – Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent 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.

– 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
- Revascularisation

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.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a 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. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study intervention/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor 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 in the SRM.

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-oestrogen 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 sterilisation 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):
   - 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.
2. Postmenopausal female

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt 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 ovulation[c]
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 (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence *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 mAb 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

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3511294 or asthma with an eosinophilic phenotype and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3511294 or study interventions of this drug class, and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3511294 or study interventions of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3511294 (or study interventions of this class) or asthma with an eosinophilic phenotype continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

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)</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>

MONITORING: **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. This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's treatment assignment is required. Also note that the mechanism of action of GSK3511294, mepolizumab and benralizumab 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 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 central laboratory manual.

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 permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalisation. Planned hospitalisation 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 describes 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 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 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 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 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 the 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 at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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:
   - Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - 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):
   - Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.9. Appendix 9: Daily Asthma Symptom Score

Each morning, participants will record an asthma symptom score using the following scale:

Daily Symptom Score:

- 0 = No symptoms during the previous 24-hours.
- 1 = Symptoms for one short period during the previous 24-hours.
- 2 = Symptoms for two or more short periods during the previous 24-hours.
- 3 = Symptoms for most of the previous 24-hours which did not affect my normal daily activities.
- 4 = Symptoms for most of the previous 24-hours which did affect my normal daily activities.
- 5 = Symptoms so severe that I could not go to work/school or perform normal daily activities.

10.10. Appendix 10: Low, Medium and High Daily Doses of Inhaled Corticosteroids

Daily medium and high dose ICS options for adults and adolescents (12 years and older) are shown in Figure 1.

Figure 1 Low, medium and high daily doses of inhaled corticosteroids

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options for adults/adolescents, p.54 and children 6–11 years, p.55, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.153)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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- The medium to high dose for Japanese adolescent participants 15 years or younger will be ≥ 200 µg/day of FP or other ICSs of equivalent dose) as per the Japanese asthma pediatric guidelines.
- Updates as per GINA 2023:
  - Beclometasone dipropionate (pMDI, extrafine particle, HFA) changed to Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)
  - Budesonide (DPI) changed to Budesonide (DPI, or pMDI, standard particle, HFA)
  - Mometasone Furoate (DPI) Low, Medium and High total daily ICS doses reference to product information as it depends on DPI device

10.11. Appendix 11: 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 enrolment 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 Table 8.

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:

- GSK3511294/placebo
  - If despite best efforts it is not possible to administer the dose of GSK3511294/placebo as defined in the protocol (see Section 6 Study Intervention and Concomitant Therapy), a maximum dose interval of 28 weeks may be used.
  - In-clinic visits are required for administration of GSK3511294/placebo (Week 0 and Week 26).
- Mepolizumab/placebo or benralizumab/placebo may be administered during home visits by a home healthcare professional.
- 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:

- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 16 Exit Visit).
- 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 utilised 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 Table 8.

- White boxes represent activities/assessments that are to be done during visits to the clinical study centre (pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 9, Exit Visit 16, and WS Visit if applicable).
- Grey boxes represent activities/assessments during study visits (Visits 3-8, Visits 10-15, and the FU Visit) that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion of the investigator, based on safety and tolerability).
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.
- Spirometry will not be conducted during home visits.

Table 8 Schedule of Activities (SoA) Indicating Assessments that may be Conducted Outside of a Clinical Study Site

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)															Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																				
Informed consent [a]	X	(X)																		Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [b]	X	(X)																		Conduct at Visit 1 if not completed at Visit 0; See footnote b.
Demography and childbearing status	X	(X)																		Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Screening Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																		
Medical history		X																		Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																		
Parasite screening		X																		Only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months. Use local laboratories for the parasitic test.
eDiary registration and training		X																		Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																	Assess prior to randomisation.

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)															Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Efficacy Assessments																				
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry (pre-bronchodilator FEV_1)			X			X				X				X			X	X		FEV_1=Forced expiratory volume in 1 second. Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (See Section 8.2.3).
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
ACQ-5		(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5; (ACQ-5 may be conducted at Screening if needed to meet inclusion criterion 3).
HRQoL: PRO and Health Outcomes Assessments																				
SGRQ			X	X		X				X							X	X		SGRQ=St. George's Respiratory Questionnaire
CCI [redacted]																				

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)															Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Safety Assessments																				
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		In addition to entry criteria related to confirming either mepolizumab or benralizumab for at least 12 months prior to entry, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X															X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X		X			X		X		X		X		X	X	X		
12-lead ECG		X	X							X							X	X		The 12-lead ECG central over-read values should be used at all visits with the exception of Visit 2 (randomisation) and Visit 9. At Visit 2 and Visit 9, the 12-lead ECG machine values should be used Note: ECGs at Visit 2 and Visit 9 must be performed and assessed pre-dose
AE/SAE Assessment	X [e]	X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote e.
Laboratory Assessments [f]																				
Haematology with differential [d]		X [d]	X	X	X	X		X		X	X			X		X	X	X	X	For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnote d.
Clinical Chemistry		X	X	X	X	X		X		X	X			X			X	X		Include liver chemistry.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**															**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Pregnancy Test (WOCBP only)		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; Pregnancy test must be performed prior to administration of any dose of study intervention. See Section 8.3.5 for additional information.
Urinalysis		X	(X)														X	X		Conduct at Visit 2 if not completed at Visit 1; Note: dipstick, send for analysis if abnormality is identified by dipstick.
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																	ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X			X				X				X			X	X		
Immunogenicity sample			X	X		X				X				X			X	X		
Genetics sample [b]			←==========							The genetics sample can be collected at Visit 2 or any visit after							==========→			See footnote b.
Study intervention [f]																				
Administer GSK3511294 or matching placebo			X							X										Conduct for all participants; GSK3511294/placebo will only be administered in the clinic. Monitor participant for at least 2h after administration (see Section 6.5).

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**															**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2 R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**Exit V16**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit
Study Week	**-10 to -1**	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-70 to -7	-56 to -7	1	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Administer mepolizumab or matching placebo			X	X	X	X	X	X	X		X	X	X	X	X	X				Conduct for participants who were receiving mepolizumab prior to randomisation.
Administer benralizumab or matching placebo			X		X		X		X			X		X		X				Conduct for participants who were receiving benralizumab prior to randomisation.
eCRF/worksheets/other																				
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				IRT=interactive response technology The initial IRT registration can be performed either at V0 or V1 but is preferred to be completed at V1. IRT visit registration is only needed for IP dispensation after V2. Benralizumab patients – not required to register dispensing visit at V3, V5, V7, V10, V12, V14 NOTE: Ensure that at least 7 days have passed from Visit 1 (Screening) before proceeding with Randomization
eDiary close out																	X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	eCRF=electronic Case Report Form

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Informed Consent for optional genetics research must be obtained before collecting a sample.

c. 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 GSK3511294/placebo, i.e., at Week 26 if the second dose of GSK3511294/placebo was not received, or at Week 52 if the second dose of GSK3511294/placebo was received. A follow-up visit should also be conducted 4 weeks after the WS visit for AE/SAE assessments and pregnancy testing.
d. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken pre-dose on dosing days.
e. SAEs must be collected from signing of Informed Consent if considered related to study procedures.
f. Any scheduled assessments or sample draws should be performed prior to administration of study intervention.

10.12. Appendix 12: Country-specific requirements

No country-specific requirements exist.

10.13. Appendix 13: Abbreviations and Trademarks

ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADE	Adverse device events
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
AxMP	Auxiliary Medicinal Product
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CS	Corticosteroid
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid or disodium edetate
EGPA	Eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FSH	Follicle stimulating hormone

FTIH	First Time in Humans
FVC	Forced vital capacity
g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
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
HFA	Hydrofluoroalkane product
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
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 corticosteroids
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IFU	Instruction for use
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	kilogram
L	Litre
LA	Long-acting
LABA	Long-acting β-agonist
LAM	Lactational amenorrhea method
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody

MAR	Missing at random
MART	Maintenance and reliever therapy
mcg (µg)	Microgram
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OCS	Oral corticosteroid
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
RBC	Red blood cell
RNA	Ribonucleic acid
SABA	Short-acting β-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of assessments
SoC	Standard of care
SOC	System organ class
SRM	Study Reference Manual
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
UACR	Urinary albumin-creatinine ratio

UK	United Kingdom
ULN	Upper Limit of Normal
w/v	Weight/volume
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
µL	Microlitre

DEFINITION OF TERMS

Term	Definition
Adverse drug reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
Auxiliary medicinal product (AxMP)	Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.
a. Authorized AxMP	Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. 1. Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.
b. Unauthorized AxMP	Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 1. Safety reporting for unauthorised auxiliary medicinal products will follow the same processes and procedures as SUSAR safety reporting

Co-administered (concomitant) product	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
NUCALA

Trademarks not owned by the GSK group of companies
CINQAERO
CINQAIR
DUPIXENT
FASENRA
MedDRA
SAS
TEZSPIRE
XOLAIR

10.14. Appendix 14: Protocol Amendment History

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

10.14.1. Protocol Amendment 1

Amendment 1: 01 December 2020

Overall Rationale for the Amendment:

This protocol amendment was created to correct the formulation of the placebo matching mepolizumab, from 0.9% (w/v) sodium chloride solution to the same liquid formulation as that used for mepolizumab without the active drug substance. The main changes are (1) correction of the placebo formulation; (2) clarification that the ACQ-5 assessment may be conducted at Screening if needed to meet inclusion criterion 3; (3) clarification of some endpoints and summary measures; (4) correction of the analysis populations; (5) addition of gamma glutamyl transferase to the table of laboratory test parameters. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Updated the ACQ-5 assessment to clarify that a Screening assessment may be conducted if necessary, to meet inclusion criterion 3. Updated the SoA table to include the completion of the eCRF at the FU visit.	Clarification.
Section 3.2. Secondary Estimands	Added text to clarify the endpoints and summary measures.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 6.1. Study Interventions Administered	Corrected the dose formulation for the placebo to match mepolizumab: from 0.9% (w/v) sodium chloride solution to the same liquid formulation used in mepolizumab.	Correction of placebo dose formulation.
Section 8.1.2. Critical Assessments performed at Screening (Visit 1)	Added a statement that the ACQ-5 assessment may be performed at Screening if needed to meet inclusion criterion 3.	Alignment with Section 1.3.
Section 8.2.5. Asthma Control Questionnaire-5 (ACQ-5)	Added clarification that after the Screening visit, ACQ-5 responses will be collected electronically.	Alignment with Section 1.3.
Section 9.3. Analysis Sets	Removed the Safety population from the table of defined populations and adjusted the description of the Modified Intent-to-Treat population to indicate that it will be used for safety endpoints.	Corrected the analysis populations.
Section 9.4.2. Secondary Endpoints (Main Estimand)	Added text to clarify the endpoints and summary measures (see change in Section 3.2).	Alignment with Section 3.2.
Section 10.2. Clinical Laboratory Tests	Added gamma glutamyl transferase to the table of protocol-required clinical laboratory test parameters.	Added to align with clinical laboratory worksheet.
Section 10.11. Recommended Measures Related to COVID-19 Pandemic	Updated the ACQ-5 assessment to clarify that a Screening assessment may be conducted if necessary, to meet inclusion criterion 3 (see change in Section 1.3). Updated the SoA table to include the completion of the eCRF at the FU visit.	Alignment with Section 1.3.
All sections	Other minor, grammatical or typographical corrections to improve readability.	

10.14.2. Protocol Amendment 2

Amendment 2: 09 August 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:

Amendment 02 is a global amendment to include an interim analysis in order to provide safety data in an interim Clinical Study Report (CSR) to inform the risk-benefit assessment of GSK3511294 (depemokimab) in asthma as the study will still be ongoing at the time of regulatory submission. This amendment also includes an update to the estimand strategy for the intercurrent event of taking prohibited medication CCI [redacted]. Furthermore, the amendment will include country-specific changes, and adding in a note for exclusion of adolescents in Germany, UK, Norway and Austria. Also, the amendment will provide clarity on the ECG process, clarity on the restart of previous anti IL-5 treatment following study completion, and updates to the GINA ICS doses, modification to the smoking history exclusion criterion and update to the use of maintenance and reliever therapy (MART).

Section # and Name	Description of Change	Brief Rationale
Title Page and Sponsor Signature	Updated to include depemokimab in parentheses in the title and brief title after the compound number. Also added in other study intervention information. Updated sponsor signatory	All changes made for clarification
Section 1.1 Synopsis	Updated to include depemokimab in parentheses in the title and brief title after the compound number.	Changes made to be consistent with the title page
Section 1.3. Schedule of Activities	Added text to clarify that 12-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 9 where 12-lead ECG machine read values should be used. Also added a note to indicate that ECGs at Visit 2 and Visit 9 should be done pre-dose. Added note text to the pregnancy testing to indicate that the pregnancy test must be done prior to administration of study intervention.	All changes made for clarification.

Section # and Name	Description of Change	Brief Rationale
	Updated the visit schedule to indicate when to register visits in IRT for participants who were on benralizumab as their prior therapy, And added in clarification in the notes on when to register the visits in IRT. Also added a note to clarify that at least 7 days have passed from Visit 1 (screening) before proceeding with randomization.	
Section 2.3.1 Risk Assessment (QTc prolongation)	Removed text related to postbaseline QTcF value of potential clinical importance from first time in human (FTIH) study (205722) Updated text related to ECG parameters including corrected QT interval using Fridericia's formula (QTcF) for depemokimab treatment groups in the FTIH study (205722) Updated wordings related to analysis of the relationship between depemokimab plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study Also amended wording in bullet point 3 in the mitigation strategy for QTc prolongation.	Modified text related to ECG parameters in the FTIH study (205722) for better clarity. No new safety information. Modified text to clarify participants exclusion based on cardiac condition
Section 3.1. Primary Estimands	Amended text to clarify treatment policy strategy to be used for intercurrent event of prohibited medication use and change in maintenance therapy.	Modification based on FDA feedback
Section 3.2. Secondary Estimands	Amended text to clarify treatment policy strategy to be used for intercurrent event of prohibited medication use and change in maintenance therapy.	Modification based on FDA feedback
Section 4.1 Study Design	Clarification added to text in final paragraph around remote visits to indicate that remote visits may occur if the participant is unable to attend the clinic.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 4.2, Scientific Rationale for Study Design	Amended text in the blood eosinophil and follow-up period paragraph – added clarity on when to re-start previous anti-IL5/IL 5 treatment following completion	Clarification
Section 5.1 Inclusion Criteria	**Criterion 1**: Added note to clarify that, in Germany, UK, and Norway only adult participants (≥18 years) are to be included in this clinical trial. Also added a note to clarify that in Austria, participants aged ≥16 years are to be included. **Criteria 2 and 4:** Amended GINA reference to latest guidelines. **Criterion 6:** Added in the following note: Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.	Clarification for criteria 1, 2 and 4. Criterion 6 added after feedback from Portuguese regulatory authority
Section 5.2 Exclusion Criteria (Prior/Concomitant therapy)	Added Tezepelumab (Tezspire) to exclusion criterion 10 Text added to exclusion criterion no. 11 (other mAbs not used for the treatment of asthma**)** to clarify that Authorized monoclonal antibodies (mAbs) treatments for COVID-19 are permitted	Updated in current guidelines Allowance of treatments for COVID-19 is not expected to impact the overall interpretability of the data generated from this study or lead to any safety concern with concomitant use of IMP

Section # and Name	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria (Diagnostic Assessment)	Text added to exclusion criterion no.13 (ECG Assessment) to clarify that the 12-lead ECG central over-read QTcF value is to be used	Clarification
Section 5.2 Exclusion Criteria **(Other Exclusions)**	Amended smoking history criterion no.14: changed former smokers with a smoking history of >/=10 pack years to >/=20 pack years. Also,text added to indicate that pipes and/or cigars, and/or electronic cigarettes/vaping use cannot be used to calculate pack-year history and all are exclusionary Amended exclusion criterion 16 to include excipients.	Amended smoking history criteria for former smokers to facilitate recruitment. Added in text on pipes/cigars/ electronic cigarettes for clarification Exclusion criterion 16 amended for clarification
Section 5.3.2. Randomisation Exclusion Criteria	Text added to randomisation exclusion criterion no. 3 to clarify that the 12-lead ECG machine read QTcF value is to be used at Visit 2 to determine eligibility for randomisation.	Clarification
Section 6.9.1 Permitted Medications and Non-Drug Therapies	Updated text to include that MART can be used as rescue treatment. Text added to clarify that participants can be treated for SARS-CoV-2 infection using authorized COVID-19 treatments (including mAbs) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted.	Allowance of MART added based on GINA 2023 guidelines Allowance of treatments for COVID-19 is not expected to impact the overall interpretability of the data generated from this study or lead to any safety concern with concomitant use of IMP
Section 6.9.2 Prohibited Medications and Non-Drug Therapies	Updated to include Tezepelumab (Tezspire) in list of prohibited medications.	Clarification and updates to be line with current guidelines

Section # and Name	Description of Change	Brief Rationale
	Updated text on other monoclonal antibodies to indicate that COVID-19 monoclonal antibody treatments are permitted. Added clarification notes on the use of hydrocortisone and short courses of oral steroids.	
Section 6.9.3 Rescue Medicine	Revised text to include that participants may use their MART.	Updated in line with GINA 2023 guidelines
Section 7.1.2 QTc Stopping Criteria	The following text is added: The QTcF value from the 12-lead ECG central over-read at randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study. At Visit 9, the 12-lead ECG machine-read values should be used and assessed against QTc Stopping Criteria, before administration of the study intervention. The 12-lead ECG central over-read values should be used at the remaining visits.	Clarification
Section 7.2 Participant Discontinuation/Withdrawal from Study	Added in text to indicate that all data and samples collected up to and including date of withdrawal of/last contact/follow-up will be included in the study analyses. Also added in text to indicate that the primary reason for discontinuation/withdrawal is to be documented in the eCRF and participants who are withdrawn because of an AE/SAE are to be distinguished from those withdrawn due to other reasons.	Updated for clarity
Section 8.1.1 Pre-screening visit (Visit 0)	Added the following information: Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF. Collection of sex, race and ethnicity data (if permitted	Added to provide rationale for

Section # and Name	Description of Change	Brief Rationale
	based on country legislation) 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. Updated wording on when to register visits in IRT	collecting race and ethnicity data Clarification
Section 8.2 Efficacy Assessments	Added in that the planned timepoints for efficacy assessments are provided in the SoA.	Added for clarity
Section 8.2.3 Pulmonary Function Testing/Spirometry	Added in MART.	Consistency
Section 8.3.3 Electrocardiograms (ECGs)	Added clarification in bullet point 3 in this section as follows: 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 **screened/randomised**/discontinued from the study intervention (but not from the study). Refer to Section 5.2 for exclusion criteria related to ECG assessment and Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.	Clarification.
Section 8.3.5 Pregnancy Testing	• Added in text to indicate WOCBP must perform the pregnancy test before the administration of any dose of study intervention. Also that pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.	Added for clarification.

Section # and Name	Description of Change	Brief Rationale
Section 8.4.4 Regulatory Reporting Requirements for SAEs	• Added the following text: For SAEs, the investigator must always provide an assessment of causality at the time of the initial report.	Added for clarification
Section 9.3. Analysis Sets	Added in Screened population and adjusted the description of the Enrolled and Full Analysis Set population	Corrected the analysis populations.
Sections 9.4.1.1 and 9.4.2.1 Main Estimand	Updated the intercurrent event text around the use of prohibited medication and using treatment policy strategy. Also removed the following text from the analysis methods: 'baseline maintenance OCS therapy (OCS vs no-OCS) Updated text within the 'Handling of missing data and intercurrent events leading to exclusion of data' sub section. Removed prohibited medication text.	Updated after feedback received from the FDA
Sections 9.4.1.2 and 9.4.2.2. Supplementary Estimands	Added in clarification around the intercurrent events	Clarification and alignment with earlier sections
Section 9.5 Interim Analysis	Added text to indicate that an interim analysis will be done on safety data	Added to indicate that an interim analysis will be conducted to provide safety data in an interim CSR to inform on the risk-benefit assessment of GSK3511294 as the study will still be ongoing at the time of regulatory submission
Section 10.1.4 Data Protection	Added in bullet points 2, 5 and 6 to provide more information on data protection	Updated wording to be consistent with new protocol instructions

Section # and Name	Description of Change	Brief Rationale
Section 10.1.5 Committee Structures	Added in the following wording 'An SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information'	Updated to provide clarity on SRT in line with new protocol instructions.
Section 10.1.6 Dissemination of Clinical Study Data	Added in text around study data being posted to Clintrials.gov and/or GSK Clinical Study Register, and national or regional clinical study registers	Updated wording to be consistent with new protocol instructions
Section 10.1.8 Source Documents	Updated to include wording on documents being shared with third parties	Updated wording to be consistent with new protocol instructions
Section 10.1.9 Study and Site Start and Closure	Updated study termination criteria to include that study could be stopped for safety reasons. Updated reason for site termination criteria to add that site could be terminated if total number of participants included earlier than expected	Clarity added after feedback from Portuguese regulatory authority. Updated wording to be consistent with the new protocol instructions
Section 10.10 - Appendix 10: Low, Medium and High Daily Doses of Inhaled Corticosteroids	Footnote added to clarify the GINA guideline updates.	Update as per GINA guidelines
Section 10.11 – Appendix 11: Recommended Measures Related to COVID-19 Pandemix	Updated Table 8 – Schedule of Assessments (SOA) to be in line with the changes in the SOA in Section 1.3	Consistency change
Section 11: References	Added in a reference and updated GINA reference	N/A
All sections	Other minor, grammatical, or typographical corrections to improve readability. As these were minor, they have not been summarised.	

10.14.3. Protocol Amendment 3

Amendment 3: 07 Dec 2023

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

Overall Rationale for the Amendment:

Amendment 03 is a global amendment to add in a table of definitions to provide clear definitions of an investigational product and comparator based on changes made in the protocol template.

Section # and Name	Description of Change	Brief Rationale
Section 6 .1 Study Intervention(s) Administered	Tables 2, 3, 4 and 5 updated to include rows defining designation of the product (added in two rows to show 'use' and whether it's IMP or non-IMP	Clarification
Section 6.9.3 Rescue Medication	Added in auxiliary medication	Clarification
Section 10.13. Appendix 13: Abbreviations and Trademarks	Added in a table of definitions Updated abbreviations list	Clarification
Section 11 References	Added in reference to the Summary of Product Characteristic (SmPC) for mepolizumab and benralizumab	Clarification

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