TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 206713/Amendment 02

Compound Number or Name: GSK3511294

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 (depemokimab) in participants with severe asthma with an eosinophilic phenotype

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

Sponsor Signatory:

David Lipson

Vice President and Disease Area Lead, Respiratory

Manufacturer: GlaxoSmithKline

Regulatory Agency Identifying Number(s):

IND: 146742

EudraCT: 2020-003632-25

Approval Date: 08 Apr 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 02	08 Apr 2022	TMF-14449557
Amendment 01	*17-AUG-2021*	TMF-13331263
Original Protocol	*01-Oct-2020*	TMF-2125331 (2020N439965_00)

Amendment 02: 08 Apr 2022

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 details about CCI [redacted] and the use of blinded interim data to complete a psychometric analysis of the Asthma Daily/Nightly Symptom Diary (ADSD/ANSD) and CCI [redacted]. Additional changes include repeated spirometry assessment and/or additional lab test if randomisation criteria are not met during screening, change in the ratio of medium/high ICS dose, allowance/permittance of authorized COVID-19 treatments, Global Initiative for Asthma (GINA) inhaled corticosteroid (ICS) doses update, and QT prolongation clarifications. Added note for exclusion of adolescents in Germany, United Kingdom (UK), Russia. Text added related to special procedure for the urinalysis in China sites.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Added new footnote "h" spirometry retest allowed during the run in period if a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria Added text to clarify that pregnancy text should be done at screening Visit 1 and Exit Visit/Withdraw from study visit Updated text in footnote "e" the Screening Visit laboratory assessment can be repeated during the run in period if a patient does not meet the blood	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population Clarification To add flexibility in screening tests; current information suggests this change is expected to result in improved screening

Section # and Name	Description of Change	Brief Rationale
	eosinophil count eligibility criteria at the Screening Visit test result Added text to clarify that, electrocardiogram (ECG) must be performed and assessed pre-dose 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 10 where 12-lead ECG machine read values should be used	while maintaining the integrity of the patient population Clarification Clarification
Section 1.3 Schedule of Activities SoA (Urinalysis) 10.2 Appendix 2: Clinical Laboratory Tests Section 10.11 Appendix 11: Recommended measures Related to COVID-19 Pandemic (Table 6)	Text added to clarify that for China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2.	Country specific procedure
Section 2.3.1 Risk Assessment (QTc prolongation)	Removed text related to post-baseline 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	Modified text related to ECG parameters in the FTIH study (205722) for better clarity. No new safety information.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 6.4.1 Treatment Assignment	Changed the ratio of medium/high ICS dose from 25% medium ICS dose and 75% high ICS dose to aiming up to 50% approximately of participants on medium ICS dose	To better reflect dosing in clinical practice while maintaining the integrity of the patient population
Section 5.1 Inclusion Criteria	Added note to clarify that, in UK, Russia and Germany only adult participants (≥18 years) are to be included in this clinical trial	Clarification
Section 5.2 Exclusion Criteria (Prior/Concomitant therapy)	Text added in exclusion criteria no. 12 to clarify that Authorized monoclonal antibodies (mAbs) treatments for COVID-19 are permitted	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 5.2 Exclusion Criteria (Diagnostic Assesments)	Text added in exclusion criteria no.15 to clarify that the 12-lead ECG central over-read QTcF value is to be used	Clarification
Section 5.3.2 Randomisation Exclusion Criteria	Text added in randomisation exclusion criteria no. 3 to clarify that the 12-lead ECG machine read QTcF value is to be used at Visit 2. The central over-read of the Screening Visit 1 12-lead ECG should be used to review ECG findings at Visit 2.	Clarification
CCI [redacted]		
Section 6.9.1 Permitted Medications and Non-Drug Therapies	"Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted **as maintenance** provided that they have been taken regularly in the 3 months prior to screening (Visit 1)".	Clarification Repeated text removed

Section # and Name	Description of Change	Brief Rationale
	Removed repeated wordings about vaccination against SARS-CoV-2 infection using authorized COVID-19 vaccines 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 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 7.1.2 QTc Stopping Criteria	Text added to clarify that 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 Text added to clarify that after randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used	Clarification Clarification
Section 8.1.2 Critical Assessment performed at Screening (Visit 1)	Added new text to clarify that if the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator Added text for spirometry to clarify that if a patient fails the protocol-specified reversibility criterion or FEV1 inclusion criteria, spirometry restest is allowed during the run-in period	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population

Section # and Name	Description of Change	Brief Rationale
Section 8.3.3 Electrocardiograms (ECGs)	Updated text related to additional ECGs to be performed if an ECG demonstrates a prolonged QTcF interval	Revised wording for clarification
Section 9.2.1 Sample Size Assumptions	Added text regarding the possibility that greater than 375 participants will be randomised in the study due to local country requests or requirements	Clarification
Section 9.2.3 Sample Size Re-estimation or Adjustment	Text related to the data to be used for clinical study report has been deleted.	All data (pre and post- target enrolment) would be used for clinical study report
Section 9.3 Analysis Sets	Updated text related to screened, enrolled, randomised, full analysis set, and safety population	Revised description of Analysis sets
Section 9.4.5 Safety Analyses	Safety population used for Safety analyses instead of mITT	To provide clarification that all safety analyses will be performed on the Safety Population
Section 9.6 CCI [redacted]	CCI [redacted] Added text to describe that blinded interim data will be used to complete a psychometric analysis of the ADSD/ANSD and CCI [redacted]	CCI [redacted] As part of the validation of the ADSD/ANSD and CCI [redacted] a blinded, data cut off will be used to complete a psychometric analysis of the measures
10.7.4 Recording and Follow-up of AE and/or SAE and Device Deficiencies (Assessment of Intensity)	Text deleted “other measures to evaluate AEs and SAEs may be utilised”.	Clarification
Appendix 10 Medium and High Daily Doses of Inhaled Corticosteroids	Footnote added to clarify GINA 2021 guidelines updates	Update as per GINA 2021 guidelines
Section 11 References	Added and updated the reference	Updated the references
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 (depemokimab) 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 the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy in participants with uncontrolled severe asthma with an eosinophilic phenotype.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of 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 study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design to assess the efficacy and safety of GSK3511294 in participants with severe uncontrolled asthma with an eosinophilic phenotype despite standard of care (SoC) treatment with medium to high dose inhaled corticosteroid (ICS) plus at least one additional controller. All participants will receive study intervention as an adjunct therapy while remaining on their existing asthma therapy throughout the study.

Brief Summary:

The purpose of this study is to assess the efficacy and safety of GSK3511294 as an adjunctive therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. During the 52-week treatment period, participants will receive two doses (at Week 0 and Week 26) of add-on study intervention (GSK3511294 100 mg or matching placebo) by SC injection, while remaining on their existing maintenance asthma therapy (that excludes biologics) throughout the study. Assessments will include the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety.

Number of Participants:

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

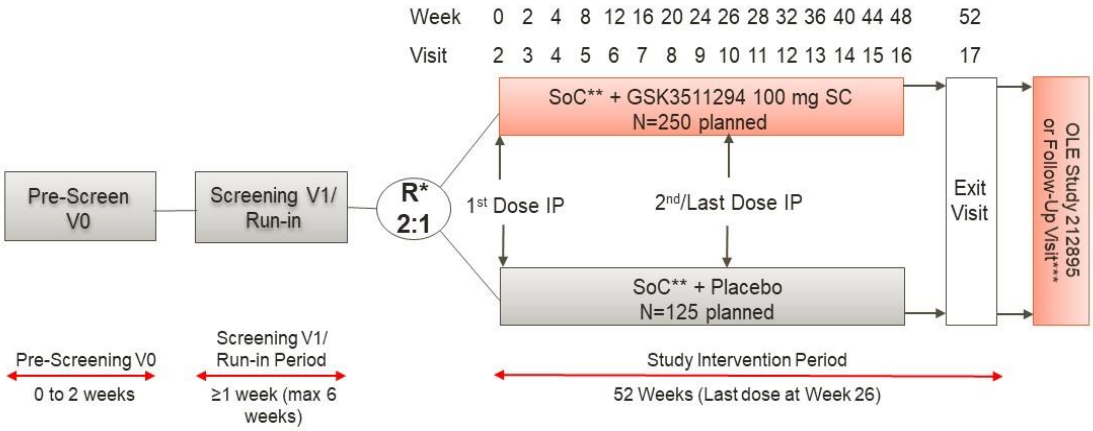
Intervention Groups and Duration:

The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) 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 3, Visit 10, Visit 11 Exit Visit 17, and WS Visit (if applicable).

Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks. Participants who do not enter the OLE study will have a follow-up visit/call at Week 56.

Independent Data Monitoring Committee: Yes

1.2. Schema



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	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 [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collection	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
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; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		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).
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

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted]																					
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
CCI [redacted]																					
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
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[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted] CCI																					
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure 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 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		

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.
AE/SAE Assessment	X [g]	X [g]	X	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 g.
Laboratory Assessments																					
CCI [redacted]																					
Total IgE			X																		
CCI [redacted]																					
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/ Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

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[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
CCI [redacted]																					
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted]																					
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
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. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
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 study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
f. CCI [redacted]

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

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, 2020]. Three antagonists of IL-5 (mepolizumab and reslizumab) or its receptor (IL-5R) (benralizumab) are approved for severe asthma with an eosinophilic phenotype, as an add-on treatment administered every 4 to 8 weeks.

GSK3511294 (depemokimab) is being developed as a LA SC injectable anti-IL-5 therapy and is anticipated 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 the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy to participants with uncontrolled severe asthma with an eosinophilic phenotype.

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 (Nucala), reslizumab (Cinqair/Cinqaero), and 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, 2020].

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. [redacted]. 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).

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

A detailed description of the chemistry, pharmacology, and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GlaxoSmithKline 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 [GlaxoSmithKline Document Number 2016N295843_03 or later]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3511294		
• Allergic reactions including anaphylaxis.	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity 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 post-injection (both at randomisation and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.
• Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded 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). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• 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 profiles and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants. Neutralising antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.8).
• 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	• 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK3511294 and one (8%) participant who received placebo.	
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), 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. • 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	• 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 15, Section 5.2). • Participants with a pre-existing clinically significant cardiac medical condition 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. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	bound of the CI is below zero) [GSK Document Number: 2020N457410_00].	
• 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 (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.	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (criterion 19, 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 prior to first dose and until 30 weeks after the last administered dose as described in Section 10.4.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. Mepolizumab 100 mg SC (every 4 weeks) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. The safety profile of mepolizumab is favourable.

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 others in its class 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

Taking into account the measures being implemented to minimise risk to participants in this study, the potential risks of participating in this study are justified by the anticipated benefits that may be afforded to participants with severe uncontrolled asthma with an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the 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 placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
CCI [redacted]	

Objectives	Endpoints
CCI	

Objectives	Endpoints
CCI [redacted]	
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma 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
CCI [redacted] CCI [redacted]	

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of 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 uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + 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: CCI [redacted]
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted]

- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): CCI [redacted]

Summary measure: Ratio of the rates of clinically significant exacerbations between GSK3511294 + SoC and placebo + SoC

For further details, see (Section 9.4

3.2. Secondary Estimands

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

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoints:

- Change from baseline in SGRQ at Week 52
- Change from baseline in ACQ-5 at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: CCI [redacted]
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted]
- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): CCI [redacted]

Summary measures:

- Difference in mean change from baseline in SGRQ at Week 52
- Difference in mean change from baseline in ACQ-5 at Week 52
- Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52
- Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit

between GSK3511294 + SoC and placebo + SoC.

For further details, see (Section 9.4)

4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design. The study will recruit adults and adolescents (≥12 years) with a confirmed diagnosis of severe asthma with an eosinophilic phenotype and who are on a regimen of medium to high dose ICS (≥440 mcg fluticasone propionate [FP] hydrofluoroalkane product [HFA] daily, or clinically comparable [GINA, 2020; see Appendix 10]) plus at least one additional controller medication, with evidence of bronchodilator reversibility or airway hyperresponsiveness as measured by methacholine/histamine challenge. Eligible participants must have uncontrolled asthma with a history of repeat exacerbations (≥2 exacerbations in the previous 12 months) while on their existing maintenance asthma therapy that excludes any biologics. Participants will be required to have a blood eosinophil count of ≥150 cells/µL at screening or ≥300 cells/µL documented in the 12 months prior to screening. Participants who have received any anti-IL-5/5R mAb therapy within the last 12 months will be excluded from this study.

Participants will attend a Pre-screen Visit (Visit 0) to sign consent and a Screening Visit (Visit 1; may be done on the same day as Visit 0) for eligibility assessments (see Section 8.1). At the conclusion of the run-in period (Visit 2), participants who meet the pre-defined criteria (see Section 5.1 and Section 5.3) will be randomised in a 2:1 ratio to receive either GSK3511294 100 mg or placebo, administered SC (at Week 0 and Week 26) in the clinic via a pre-filled safety syringe (PFS) as an adjunct therapy. Randomisation will be stratified based on baseline ICS dose (aiming to up to 50% approximately of participants on medium ICS dose; see Appendix 10). Participants will remain on their existing stable maintenance asthma therapy throughout the study (See Section 6.9 for details on concomitant medications). 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]) measured over the 52-week treatment period. Additional efficacy assessments will include lung function (pre- and post-bronchodilator FEV_1), asthma control (ACQ-5), HRQoL measured with SGRQ, CCI [redacted] CCI [redacted] CCI [redacted] daytime and night-time asthma symptoms (ADSD/ANSD), CCI [redacted] (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 100 mg SC following repeat dosing. CCI [redacted]

After randomisation, all participants will be encouraged to remain in the study and complete all scheduled visits, regardless of whether they receive the second dose of study intervention at Week 26. Participants who experience any of the study intervention

discontinuation conditions (listed in Section 7.1) will not receive another dose of 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 3, Visit 10, Visit 11 Exit Visit 17, and WS Visit (if applicable). Participants who are unable to attend their scheduled clinic visits due to COVID-19 restrictions or other unexpected events may complete some visits at home (see Appendix 11). Note: study intervention will only be administered in the clinic (at Week 0 and Week 26 visits).

4.1.1. Study Phases, Duration and Treatment Arms

At pre-screening, participants will be requested to participate in the study for a maximum of 60 weeks (Visit 0 to the Exit Visit, inclusive) or 64 weeks if not continuing into the OLE Study 212895 (Visit 0 to the Follow-up Visit, inclusive).

During the study, participants will remain on their existing maintenance asthma therapy whilst completing all phases of the study described in Table 1.

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	1-6 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 6 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. 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. 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).

Phase	Phase Title	Duration	Description
3	Study Intervention (Visit 2-Visit 17)	52 weeks	Participants who meet the randomisation criteria will enter the 52-week treatment period and will be randomised to receive either add-on **GSK3511294 (100 mg) or matching placebo in a 2:1 ratio.** During the treatment phase, a total of 2 doses of study medication will be administered SC via PFS: at Week 0 (Visit 2) and Week 26 (Visit 10).[a] Study visits will occur at Week 0, Week 2, Week 4 and every 4 weeks thereafter with an additional study visit at Week 26 for the administration of the second dose of study intervention. The study intervention period will conclude with the Exit Visit at Week 52 (Visit 17).
Only participants who choose not to enter the OLE study will complete the phase below:			
4	Follow-up	4 weeks	Participants will complete a Follow-up visit/call 4 weeks after the Exit Visit; this visit/call will capture AE/SAE assessments and a urine pregnancy test result. At the end of the Follow-up visit/call, participants will be prescribed appropriate alternative asthma therapy at the physician's discretion, if required.

a. 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. Treatment after the End of Study

Participants who receive both doses of double-blind treatment and complete the Week 52 Exit Visit will be eligible to participate in the OLE study 212895. See Section 6.7 for details.

Participants who are not entering the OLE study 212895 will enter a 4-week follow-up period and complete the study with a Follow-up visit/call at Week 56. After study completion, appropriate alternative asthma therapy may be prescribed at the physician's discretion.

4.1.3. 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: This study is designed to evaluate the efficacy and safety of GSK3511294 100 mg SC as an adjunct therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. Participants should have uncontrolled asthma, as evidenced by repeat exacerbations, despite treatment with optimised background therapy consisting of maintenance ICS treatment and at least one additional controller. Participants are also required to have the requisite elevated blood eosinophil count (see randomisation criterion 1, Section 5.3) that is indicative of asthma with an eosinophilic phenotype. This population has been shown to benefit from add-on anti-IL-5 therapies such as mepolizumab [Pavord, 2012, Ortega, 2014; Chupp, 2017] and is therefore anticipated to benefit from GSK3511294.

Blood eosinophil count screening: A Screening blood eosinophil count threshold of ≥150 cells/µL at Screening Visit 1 or ≥300 cells/µL in the previous 12 months has been selected as a criterion to identify participants likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous trials with mepolizumab.

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 direct benefit of GSK3511294 to a population with severe uncontrolled asthma with an eosinophilic phenotype. In the current 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 reslizumab [Castro, 2015].

Placebo-control design: An established randomised, double-blind and parallel-group study design will allow for a robust determination of participant response to GSK3511294 as an adjunct therapy to their maintenance asthma therapy. As such, the comparator arm in this study will be placebo plus continued maintenance asthma treatment. A 2:1 randomisation will be used in order to limit the number of participants randomised to placebo treatment and to provide more safety information on GSK3511294. All participants will continue to receive their optimised and stable maintenance asthma therapy throughout the entire duration of the study regardless of intervention arm assignment. The stable maintenance asthma therapy (per the inclusion criteria) will consist of medium to high dose ICS (≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]) with at least one additional controller medication e.g., long-acting beta-2-agonist (LABA), with or without maintenance oral corticosteroids (OCS). Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

Study Duration: A 52-week treatment period should allow sufficient time to assess whether GSK3511294 100 mg SC, administered as two repeat doses 26 weeks apart (at Week 0 [randomisation] and at Week 26), can reduce the annualised rate of clinically significant exacerbations to a similar extent to that observed with other anti-IL-5 mAbs. The study will also provide 12-month safety data with repeat dosing.

Run-in Period: The one-week (maximum 6 weeks) 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.

Open-label extension study: Following study completion, all eligible participants will have the option to participate in the OLE study to provide additional safety data (see Section 6.7).

Data collection after discontinuation from study intervention: The protocol objective is to collect data over the full study period, whether participants continue on study intervention or in the case of premature discontinuation from study intervention. However, the decision to continue in the study after premature discontinuation from study intervention remains the prerogative of the participant. Participants who agree to continue in the study after premature discontinuation from 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 52-week participation and follow up contact 4 weeks later, 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 for the participant's schedule

4.3. Justification for Dose

The dose rationale for this study is supported by the FTIH Study 205722 [GlaxoSmithKline Document Number 2019N411063_00] that investigated single SC doses of GSK3511294 ranging from 2 mg to 300 mg. CCI [redacted]

CCI

[redacted]

CCI

[redacted]

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 visit at Week 52, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

AGE

1. **Age:** Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent.

CCI [redacted]

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS

2. **Asthma:** Participants must 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, 2020] **AND**

   a) **Eosinophilic phenotype:** Have, or with high likelihood of having, asthma with an eosinophilic phenotype as per Randomisation Criteria 1 and 2 (see Section 5.3)

   AND

   b) **Exacerbation history:** Have previously confirmed history of ≥2 exacerbations requiring treatment with systemic CS (IM, IV, or oral), in the 12 months prior to Visit 1, despite the use of medium to high-dose ICS (see criterion 4). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater.

3. **Airflow obstruction:** Persistent airflow obstruction as indicated by:

   a) For participants ≥18 years of age at Visit 1, a pre-bronchodilator FEV_1 <80% predicted (NHANES III) recorded at Visit 1

   b) For participants 12-17 years of age at Visit 1:

   - A pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1

     OR

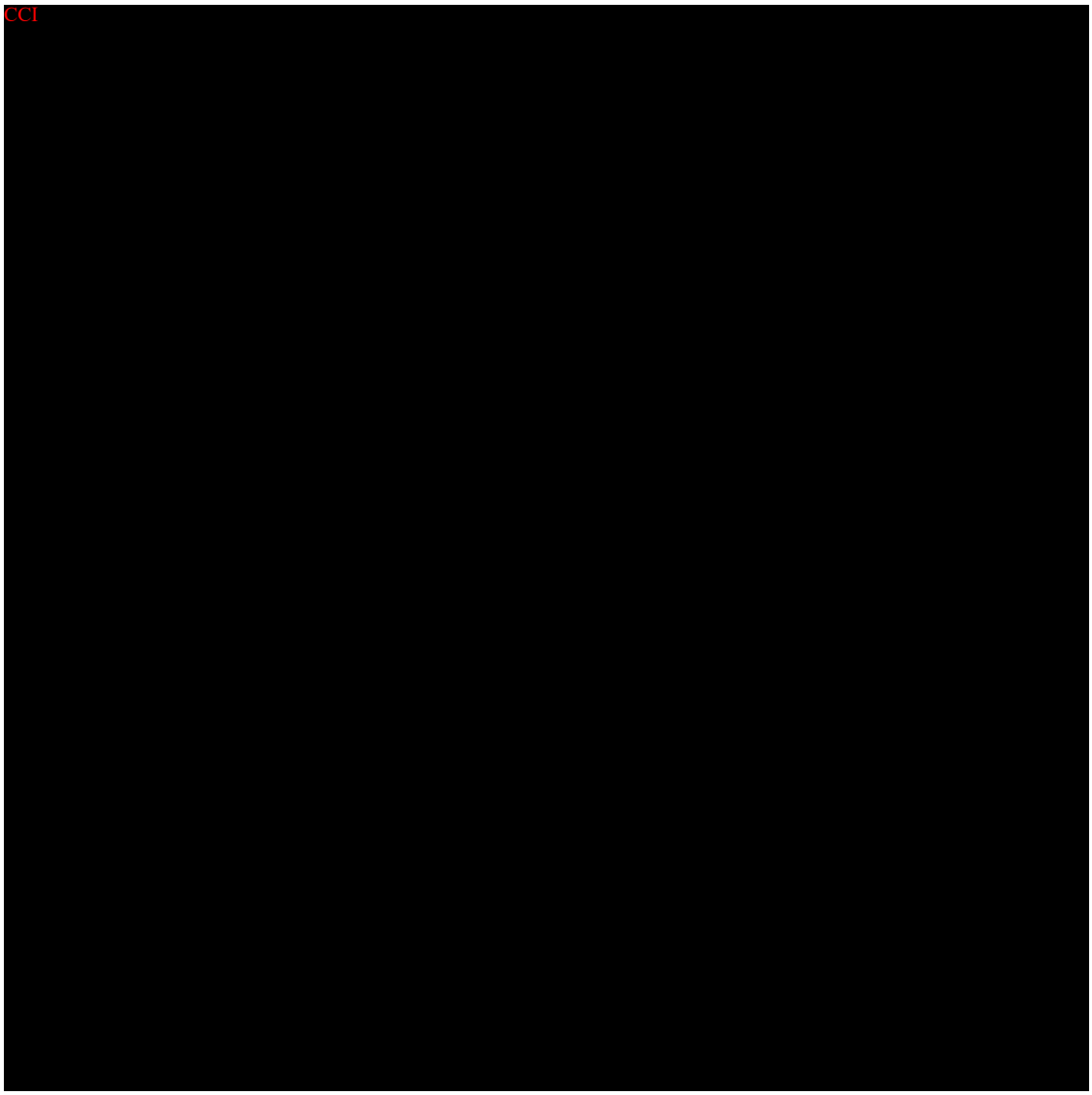
   - FEV_1:Forced Vital Capacity (FVC) ratio <0.8 recorded at Visit 1

ASTHMA MAINTENANCE THERAPY

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 FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]. Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.
5. **Additional Controller Medication:** Current treatment with at least one additional controller medication, besides ICS, for at least 3 months [e.g., LABA, long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline].

SEX

CCI



SEX	
	CCI [redacted]
INFORMED CONSENT	
7	CCI [redacted]

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.
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.

MEDICAL CONDITIONS

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 must be 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. **Monoclonal antibodies targeting IL-5/5R:** Participants who have received mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), or benralizumab (Fasenra) within 12 months prior to Visit 1 or who have a previous documented failure with anti-IL-5/5R therapy.
11. **Other mAbs in the treatment of asthma**: Participants who have received omalizumab (Xolair) or dupilumab (Dupixent) within 130 days prior to Visit 1.
12. **Other mAbs not used for the treatment of asthma:** Participants who have received any mAb within 5 half-lives of Visit 1. Authorized treatments for COVID-19 are permitted.
13. **Investigational Medications:** Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. **Previous participation:** Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.

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

OTHER EXCLUSIONS
16. **Smoking history:** Current smokers or former smokers with a smoking history of ≥10 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. 17. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1. 18. **Hypersensitivity:** Participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1 or any mAb or biologic. 19. **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. 20. **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 randomisation inclusion/exclusion criteria below in order to be randomised to study intervention.

5.3.1. Randomisation Inclusion Criteria

RANDOMISATION INCLUSION CRITERIA
1. **Blood eosinophil count:** a) An elevated peripheral blood eosinophil count of ≥300 cells/µL demonstrated in the past 12 months prior to Visit 1 that is related to asthma **OR** b) An elevated peripheral blood eosinophil count of ≥150 cells/µL at Screening Visit 1 that is related to asthma. 2. **Asthma:** Evidence of airway reversibility or responsiveness as documented by either: a) Airway reversibility (FEV_1≥12% and 200 ml) demonstrated at Visit 1 or Visit 2 using the Maximum Post Bronchodilator Procedure **OR**

RANDOMISATION INCLUSION CRITERIA
b) Airway reversibility ($FEV_1 \geq 12\%$ and 200ml) documented in the 24 months prior to Visit 2 (randomisation visit) **OR** c) Airway hyperresponsiveness (methacholine: PC_{20} of <8 mg/mL, histamine: PD_{20} of <7.8 µmol, mannitol: decrease in FEV_1 as per the labelled product instructions) documented in the 24 months prior to Visit 2 (randomisation visit) 3. CCI [redacted]

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:
   a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
   b) Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
   c) 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:** QTcF ≥450msec, or QTcF ≥480 msec for participants with Bundle Branch Block, in the 12-lead ECG machine read at randomisation Visit 2 are excluded. Participants are excluded if an abnormal ECG finding from central over-read of the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.
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).
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 6 weeks) until the investigator considers the participant to have returned to their baseline asthma status for at least 7 days.

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 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.

Study intervention will only be administered in the clinic; hence Visit 2 (Week 0) and Visit 10 (Week 26) are required to be in-clinic visits.

6.1. Study Intervention Administered

GSK3511294 is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. GSK3511294 liquid drug product will be supplied by GSK in a Type I glass syringe [redacted]. 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 [redacted] sterile liquid formulation. [redacted]

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

An overview of study intervention is provided in Table 2.

Table 2 Overview of Study Intervention

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	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

ARM Name	GSK3511294 100 mg	Placebo
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, IMP=Investigational Medicinal Product, N/A=not applicable

6.1.1. Medical Devices

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

- A pre-filled syringe contained within a safety syringe. CCI [redacted].
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) CCI [redacted]
- CCI [redacted]

The Instruction for use (IFU) of the injection device will be provided. CCI [redacted]

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

6.4.1. Treatment Assignment

- Eligible participants will be centrally randomised using an IRT system.
- CCI [redacted] 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.
- Randomisation will be stratified according to the participant's baseline ICS dose (aiming to up to 50% approximately of participants on medium ICS dose; see Appendix 10).
- At Visit 2 (Week 0), those participants who meet the randomisation criteria will be randomised in a 2:1 ratio to receive one of the following study treatments in addition to their stable maintenance asthma treatment:
    - GSK3511294 100 mg SC
    - Placebo SC
- Study intervention will be administered in the clinic at Visit 2 (Week 0) and Visit 10 (Week 26) as per the SoA (Section 1.3).

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.

- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. CCI [redacted].
- If a participant's intervention code is unblinded by the investigator or treating physician, that participant will continue with all study visits but will not receive the second dose of study intervention at Week 26. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF (see Section 7.1).
- CCI [redacted].
- 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.

CCI [redacted]

6.5. Study Intervention Compliance

Both doses of GSK3511294 or 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.

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

6.6. 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 treatment.

At the end of the study, participants will be eligible to screen to enter the OLE Study 212895 and have continued access to open-label GSK3511294 if he/she:

- has received both doses of study intervention (at Week 0 and Week 26), AND
- completed the scheduled Exit Visit at Week 52, AND
- did not meet any of the study intervention discontinuation conditions (Section 7.1) during the study.

For participants who enrol into the 12-month OLE study, the Day 1 visit of the OLE study can occur on the same day as the Exit Visit of the current study. Specific details on the OLE study will be documented separately.

Participants who do not enter the OLE study will complete a follow-up visit/call and be prescribed alternative asthma therapy if needed and as determined by the study investigator.

6.8. Treatment of Overdose

The dose of GSK3511294 that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 (refer to the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]), single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

CCI [redacted] (see Section 6.1).
In the event of an 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.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.9. Concomitant Therapy

At pre-screening and/or screening, information on the participant's baseline maintenance asthma therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, 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 (any 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 maintenance asthma treatment consisting of ICS plus at least one other controller, e.g. LABA, LAMA, with or without maintenance OCS (see inclusion criteria 4 and 5, Section 5.1). 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 as maintenance 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.

Albuterol/salbutamol is permitted throughout the study but should be withheld in the 6-hour period prior to spirometry assessments, if possible. Study-provided albuterol/salbutamol should not be recorded in the eCRF, only in the 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 authorized 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 authorized 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]	130 days
Mepolizumab [Nucala], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra]	12 months
Other monoclonal antibodies	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)
Methotrexate, 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 throughout the study. Albuterol/salbutamol will be sourced for all centres. Use of low dose ICS-formoterol as rescue medication is not allowed during the study.

Participants will be dispensed an MDI at Screening Visit 1 to be used primarily to treat asthma symptoms on an as needed basis and also during the reversibility assessments (see Section 8.2.3.1). The MDI should be replaced as needed.

Although the use of rescue medications is allowable (at any time during the study), the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the spirometry assessments. Rescue medication usage will be recorded in the eDiary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- 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 another 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).

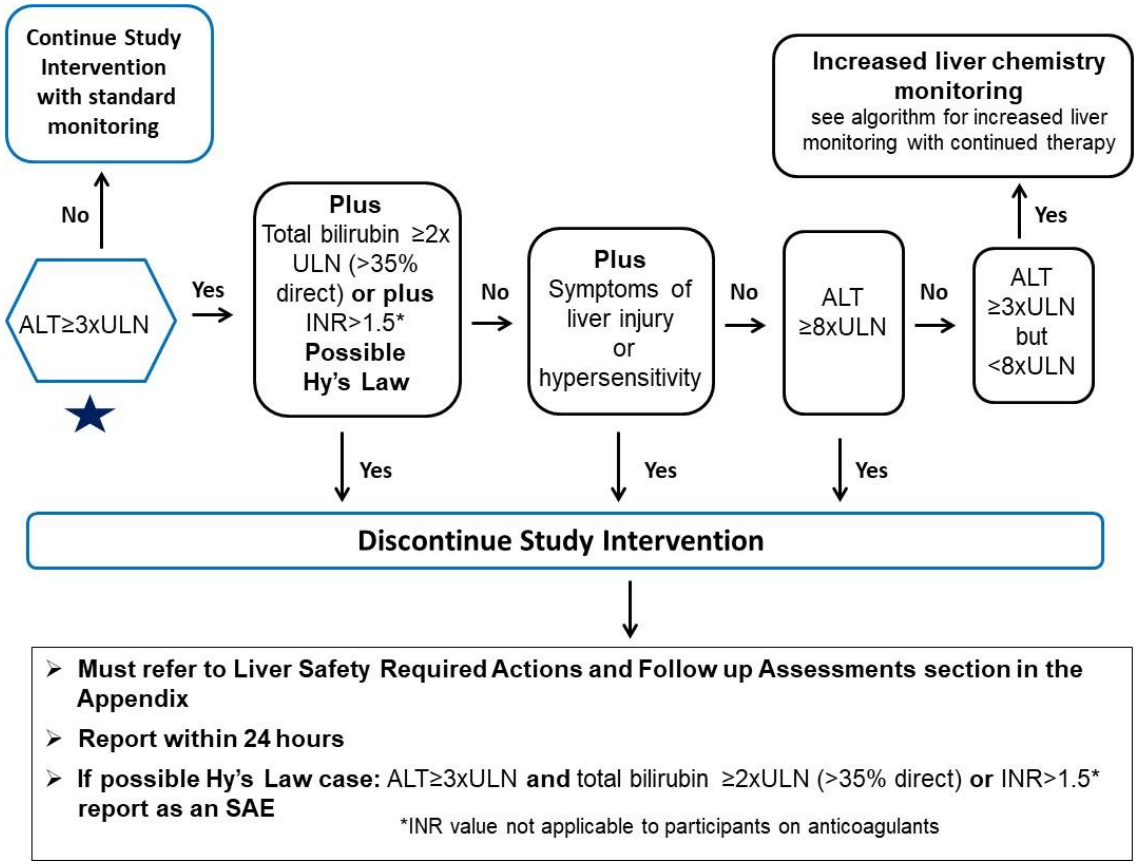
7.1.1. Liver Chemistry Stopping Criteria

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 one 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.

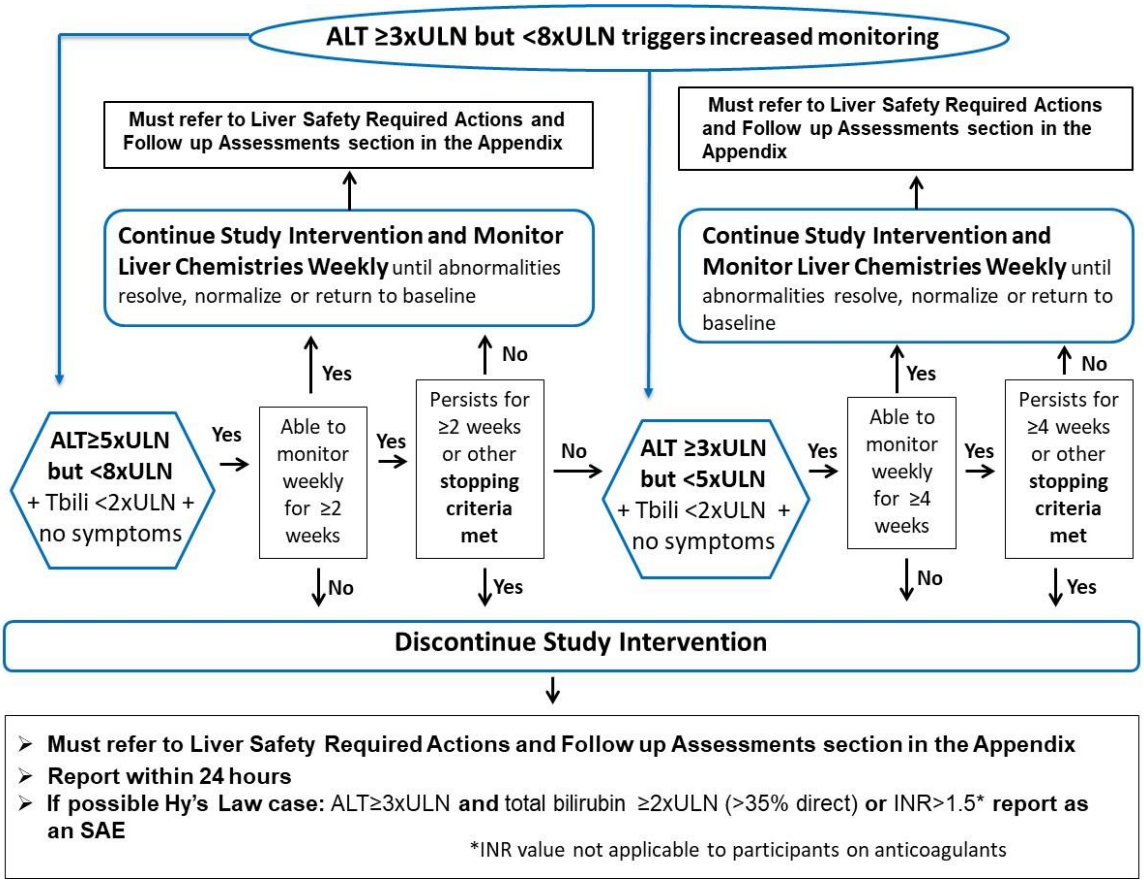
Liver Chemistry Stopping Criteria Algorithm



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 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. After randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used.

7.1.3. Temporary Discontinuation

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

If a participant becomes infected (parasitic infection) during the study intervention period before receiving the second dose of study intervention and does not respond to anti-helminth treatment, 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, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
  - a Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy 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.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. A final attempt will be made to contact the participant for a safety follow-up 30 weeks after the last administered dose of study intervention.

Discontinuation of specific sites or 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 III Hypersensitivity (Immune Complex Disease /Vasculitis)

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not 6-month, nonclinical toxicology studies, events potentially representing type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the Medical Monitor is encouraged. Treatment for the event will be given as medically required. CCI [redacted]

CCI [redacted]

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.

CCI [redacted]

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), participants who are not entering the OLE study 212895 should make every effort to complete the Week 56 follow-up visit/call on the scheduled day. The visit may be completed within 7 days of the scheduled time-point.
- 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.
- CCI [redacted]
- 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 information including gender, ethnic origin, race, and year of birth (can be conducted 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 of 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 from Pre-screening Visit 0 to the Exit Visit (or if applicable, the WS Visit or the Follow-up Visit) should be completed in the relevant eCRF form. Visit 1, 2, 10 and WS visit must be registered in the IRT.

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)

The following critical assessments will be conducted at Screening Visit 1:

- Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Review 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.
- 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
  - Historical blood eosinophil count - participants without a documented blood eosinophil count ≥300 cells/µL in the 12 months prior to Screening Visit 1 must show a blood eosinophil count ≥150 cells/µL, based on the sample collected at Visit 1 (see randomisation criterion 1, Section 5.3.1). If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
- Spirometry including bronchodilator responsiveness testing using the Maximum Bronchodilator Procedure (see Section 8.2.3). If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

- 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
- CCI [redacted]
- eDiary registration and training
- CCI [redacted] (see Section 8.9)
- Complete ADSD/ANSD (to be completed daily at home; see Section 8.2.10)

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, including, if applicable, verification that the asthma-related peripheral blood eosinophil count is ≥150 cells/μL, based on the sample collected at Visit 1
- Review of concomitant medications
- Spirometry (if airway reversibility was not demonstrated at Visit 1, the Maximum Bronchodilator Procedure may be repeated at Visit 2) (see Section 8.2.3)
- SGRQ (see Section 8.2.4)
- ACQ-5 (see Section 8.2.5)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Safety assessments including:
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)

- AE/SAE assessment

- CCI [redacted]
  - CCI [redacted]

- Provide and review CCI [redacted] (see Section 8.9)

The following items will be completed at home:

- CCI [redacted]
- Complete ADSD/ANSD daily (see Section 8.2.10)

8.2. Efficacy Assessments

8.2.1. Efficacy Endpoints

Efficacy endpoints and estimands are provided 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.

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 Exit Visit or Follow-up Visit if applicable.

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 screening (Visit 1), 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) for ≥6 hours and LAMAs/LABAs for ≥12 hours prior to the clinic visit, if possible.

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

8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method

Pre-bronchodilator measurements will be taken at the clinic visits specified in the SoA (Section 1.3): at screening, randomisation, Week 26 Visit, and Exit Visit (or EW Visit). In addition, post-bronchodilator values will be recorded following reversibility testing using the Maximum Post-Bronchodilator Method. Participants' reversibility will be assessed at Visit 1 (Screening). For participants unable to achieve ≥12% reversibility and 200 mL change at Visit 1, reversibility can be repeated at Visit 2 to confirm eligibility for the study (see randomisation criterion 2, Section 5.3.1). The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the Pulmonary Physiology Subcommittee [Tepper, 2012]. Additional details on the reversibility testing procedures using the Maximum Post-Bronchodilator Method can be found in the spirometry section of the SRM.

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

The SGRQ is a well-established instrument, comprising 50 items designed to measure Quality of Life in participants with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered as per guidance from the measure developers and completed 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 five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze) over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. This will be completed electronically according to the SoA (Section 1.3).

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.2.9. CCI [redacted]

CCI [redacted]

The evaluations will be completed electronically at the visits specified in the SoA (Section 1.3).

8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective [Gater, 2016].

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant:

- ADSD is to be completed before going to bed and refers to asthma symptoms during the day.
- ANSD is to be completed upon waking and refers to asthma symptoms during the previous night.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

The ADSD/ANSD questionnaire should only be administered to participants for whom an appropriate translation is available. Further details are contained in the SRM.

CCI

CCI

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

- 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 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 participant should be screened/ randomised/ discontinued from the study intervention (but not from the study). Refer to Section 5.2 and Section 5.3.2 for exclusion/randomisation 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 II rhythm strip. There will be electronic capture and storage of the data by a validated method.
- Paper ECG traces are required to be maintained at the site with other source documents.

8.3.4. 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 Exit Visit (or Follow-up visit/call if applicable) should be repeated until the values return to normal or baseline or are

no longer considered significantly abnormal by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the Sponsor notified.

- 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).
- CCI [redacted]

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/call (if applicable) as per the SoA (Section 1.3).
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last administered dose of study intervention:
    - Participants who enter the OLE study will have a urine pregnancy test prior to receiving the first dose of open-label GSK3511294.
    - Participants who do not enter the OLE study should have a urine pregnancy test at the Follow-up Visit/call (Week 56). A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
    - Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the WS Visit (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 adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3. Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

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

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 Exit Visit or follow-up visit/call (if applicable) 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 Exit Visit or the follow-up visit/call (if applicable) 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.
- 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 and until 30 weeks after the last administered dose of study intervention.
- 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 III 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

- Blood samples will be collected for measurement of plasma concentrations of GSK3511294 as specified in the SoA (Section 1.3).
- The actual date and time (24-hour clock time) of each sample will be recorded. Samples obtained at Visit 2 (Week 0) and Visit 10 (Week 26) should be drawn prior to dosing.
- Collection, processing, storage and shipping procedures are provided in the central laboratory manual.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Genetics and Pharmacogenomics

China only: Genetic blood samples will not be collected from participants in China.

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. Additional country specific requirements are specified in the SRM.

CCI

CCI

CCI

CCI

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

9.2. Sample Size Determination

Approximately CCI participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of CCI participants in a CCI ratio to GSK3511294 CCI and matching placebo CCI

9.2.1. Sample Size Assumptions

A sample size of CCI participants CCI GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

There is a possibility that greater than CCI participants will be randomised in the study due to local country requests or requirements, for example, the local competent authority specifying a minimum number to be enrolled.

9.2.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a CCI reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of CCI randomised participants (CCI to GSK3511294, CCI to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of CCI for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that CCI of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a CCI reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

9.2.1.2. Secondary Endpoints

Table 3 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 3 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
CCI			

9.2.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 4 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 4 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate
CCI	CCI

9.2.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

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. 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.
Randomised	All participants who were randomly assigned to study intervention in the study.
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation. This population will serve as the primary population for analyses of efficacy endpoints.
Safety	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations, in which case the participant will be analysed according to the actual intervention they received. This population will serve as the primary population for analyses of safety endpoints.

Further populations to be used for other assessments will be defined in the statistical analysis plan (SAP).

9.4. Statistical Analysis

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.

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

9.4.1. General Considerations

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC.

9.4.2. Primary Endpoint

9.4.2.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype 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 and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: CCI [redacted] b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted] c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): CCI [redacted]
Summary measure	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The primary analysis of the annualised rate of clinically significant exacerbations will use a negative binomial model. Covariates included will be baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), region, number of exacerbations in the year prior to the study, baseline % predicted FEV_1 and treatment group with $\log_e$(time in study in years) as an offset variable. The rate ratio and 95% confidence interval (CI) will be provided for the comparison between GSK3511294 + SoC and placebo + 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) CCI [redacted]

	CCI [redacted] **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing data for (b) above. CCI [redacted]

9.4.3. Secondary Endpoints

9.4.3.1. Main Estimands

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Secondary Endpoints	• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: CCI [redacted] b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted] c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): CCI [redacted]
Summary measure	Difference in means between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The analysis will be performed using a repeated measures mixed model. Covariates included will be baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), number of exacerbations in the year prior to the study, baseline % predicted FEV_1,treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. The difference in means and 95% CI will be provided for the comparison between GSK3511294 + SoC and placebo + 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) CCI [redacted] b) [redacted] **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. CCI [redacted]

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be evaluated using the same strategy as that described for the primary endpoint (see Section 9.4.2).

9.4.4. Other Endpoints

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

9.4.5. Safety Analyses

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. 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. Multiple Testing Strategy

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

CCI

[redacted]

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 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/assent 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.
- The participant must be informed that his/her personal study-related data will be used by GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An 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. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their 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 clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- GSK or a designee is responsible for the data management of this study including quality checking of the data.
- GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, GSK will generally support publication of 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.

CCI [redacted]

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

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

For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2. Urine pregnancy test must still be performed at the site.

Table 5 Protocol-Required Safety Laboratory Tests

CCI [redacted]

NOTES:

CCI [redacted]

2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international 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 untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient 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.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalised ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

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

Assessment of Causality

- 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. • 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):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   a) A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   b) Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female participants:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of 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

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
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 ovulationc
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • 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

China only: No genetic samples will be collected from participants in China.

- 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 clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on 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)
MONITORING:
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:</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.
• Fractionate bilirubin, if total bilirubin≥2xULN</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• 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.	• 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 leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form

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

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK as an SAE**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the 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.

References

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

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.

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:
   a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.9. CCI [redacted]

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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.

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
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.

Reproduced with permission from Global Initiative for Asthma [GINA, 2020]).

- The medium to high dose for Japanese adolescent subjects 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 2021:
- 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 6.

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

Study Intervention:

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Intervention and Concomitant Therapy), a maximum dose interval of 28 weeks may be used.
- In-clinic visits are required for administration of the study intervention (Week 0 and Week 26).
- In some cases, trial participants who no longer have access to study intervention or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- The medical problems and healthcare utilisation worksheet may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of the paper worksheet are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If 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 17 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 6.

- 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 3, Visit 10, Visit 11 Exit Visit 17, and WS Visit if applicable).
- Grey boxes represent activities/assessments during study visits (Visits 4-9, Visits 12-16, 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).
- The FU Visit may be conducted as a remote/home visit or as a phone call.
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.

Table 6 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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	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 [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collections	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			

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[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
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; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		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).
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

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted]																					
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
CCI [redacted]																					
Complete ADSD/ANSD		←========= daily =========→									X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
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[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted]																					
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure 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 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		

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.
AE/SAE Assessment	X [g]	X [g]	X	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 g.
Laboratory Assessments																					
CCI [redacted]																					
Total IgE			X																		
CCI [redacted]																					
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/ Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI																					

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[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted]																					
Genetics sample			←==========								The genetics sample can be collected at Visit 2 or any visit after							==========→			See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

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**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
CCI [redacted]																					
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
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. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
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 study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
f. CCI [redacted].

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

10.12. Appendix 12: Country-specific requirements

CCI

[redacted]

10.13. Appendix 13: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
ADE	Adverse device events
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
Anti-HBc	Hepatitis B core antibody
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
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
eCRF	Electronic case report form
ECG	Electrocardiogram
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid or disodium edetate
EGPA	Eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FAS	Full Analysis Set
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
CCI	[redacted]
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 corticosteroid
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

mcg (µg)	Microgram
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
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
PC_{20}	Provocative concentration causing a 20% fall in FEV_1
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD_{20}	Provocative dose that decreases FEV_1 by 20%
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
CCI [redacted]	
CCI [redacted]	
PRO	Patient-reported outcomes
CCI [redacted]	
QTcF	QTc corrected by Fridericia's formula
QTL	Quality tolerance limits
R&D	Research and Development
RNA	Ribonucleic acid
RBC	Red blood cell
SABA	Short-acting β-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SDAC	Statistical data analysis centre
CCI [redacted]	
SGRQ	St. George's Respiratory Questionnaire
CCI [redacted]	

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
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
w/v	Weight/volume
µL	Microlitre

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
CINQAERO
CINQAIR
DUPIXENT
FASENRA
MedDRA
SAS
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.

10.14.1. Amendment 1: 17-Aug-2021

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 01 is a global amendment to include modifications based on regulatory suggestion and additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Section # and Name	Description of Change	Brief Rationale
Title page, Section 1.1 Synopsis and Section 2.1 Study Rationale	Addition of name “depemokimab”	To update the protocol with the recently approved generic name of GSK3511294
Section 1.3 Schedule of Activities and Table 6 of Appendix 11	Term “Demography and childbearing status” modified to “Demography data collection” Added text “Collection of exacerbations at Visit 1 is historical data” CCI [redacted]	Minor modification for more clarity
	Text “-56 to -7” modified to “-56 to -42”, “Week -8 to –1” modified to “Week -8 to -6”	Clarification
	Inclusion of an ECG at week 2 and week 28	Revision to address request of health authority
	Only screening, randomization, dispensing and withdrawal visits need interactive response technology (IRT), hence corrections	Visits which require IRT registration were clarified

Section # and Name	Description of Change	Brief Rationale
	made accordingly	
	Added CCI [redacted] at week 48 Added a CCI [redacted] visit at week 48	Modification with respect to the planned open label extension study
Section 1.1 Synopsis, Section 4.1 Overall design and Appendix 11	Added Visits 3 and 11 as in-person clinic visits.	Due to the inclusion of an ECG at week 2 and week 28 these visits can not be conducted remotely or virtually.
Section 4.1.1 Study Phases, Duration and Treatment Arms (Table 1)	Term “Clinic” modified to “Study”	Clarification
Section 5.1 Inclusion Criteria	Added text in inclusion criteria related to pregnancy	Clarification
Section 5.2 Exclusion Criteria	Exclusion of participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1	Updated wording for more clarity for study intervention and its excipients
Section 5.3.1 Randomization Inclusion Criteria	Airway reversibility or Airway hyperresponsiveness documented in the 24 months prior to Visit 2 instead of previous 12 months	To provide flexibility for enrolling participants that have demonstrated airway reversibility/hyperresponsiveness
Section 5.3.2 Randomization Exclusion Criteria	Revised QTc criteria	Revised wording for clarification
Section 6.9.1 Permitted Medications and Non-Drug Therapies	Text added for permission to receive COVID-19 Vaccine	Clarification considering the COVID-19 pandemic situation
Section 6.9.2 Prohibited Medications and Non-Drug Therapies	Removed “troleandomycin” from prohibited medication	As per the program level updated troleandomycin is no longer a prohibited medication
Section 6.9.3. Rescue Medicine	Low dose ICS/LABA is not permitted as rescue medication. Rescue medication usage will be recorded in the eDiary.	Revised wording for providing more clarity
Section 8.1.1 Pre-screening Visit (Visit 0)	Only screening (Visit 1), randomization (Visit 2), dispensing (Visit 10) and withdrawal visits need IRT, hence corrections made accordingly	Visits which require IRT registration were clarified
Section 8.2.2 Asthma	Text deleted “Additional details on	Text removed to align with the

Section # and Name	Description of Change	Brief Rationale
Exacerbations	the process for determination of clinically significant exacerbations can be found in the SAP".	Statistical Analysis Plan
8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method	Current "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the **Pulmonary Physiology Subcommittee** " Previously "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the and not by *Asthma Clinical Research Network"* Current "Details of reversibility procedure mentioned in **SRM**" Previously "Details of reversibility procedure mentioned in in *third party vendor manual*"	Clarification
Section 8.2.4. St. George's Respiratory Questionnaire (SGRQ)	The SGRQ will contain 50 items instead of previous 51.	Clarification
CCI [redacted] Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	CCI [redacted]	Clarification
Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Updated the information regarding use of ADSD and ANSD	Correction of the timeframe for completing CCI [redacted]
Section 8.3.2 Vital Signs	Text "Oral or skin Temperature" modified to "Temperature"	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.6 Genetics and Pharmacogenomics, CCI	CCI	
Section 9.3 Analysis sets	mITT description updated, Safety Population deleted	Revised description of mITT population to provide clarification that mITT population will be used as primary population for some other endpoints apart from efficacy.
	Clarification of analysis populations which will be defined in SAP.	Clarification
Appendix 2 Clinical Laboratory Tests	Added CCI to the table of protocol-required clinical laboratory test parameters.	Added to align with clinical laboratory worksheet.
Section 10.3.2 Definition of SAE	Modified definition of SAE	Revised as per the latest definition of SAE.
Section 10.3.5 Reporting of SAE to GSK	Removed the requirement of SAE reporting in eCRF within 72 hours	Removal of additional step of eCRF check.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

11. REFERENCES

Bagnasco D, Caminati M, Menzella F, Milanese M, Rolla G, Lombardi C, et al. One year of mepolizumab: Efficacy and safety in real-life in Italy. Pulm Pharmacol Ther. 2019;58:101836.

Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189–97.

Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2115-27.

Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med. 2019;7(1):46-59.

Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10):1125-32.

Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3(5):355-66.

Cella D, Lai JS, Jensen SE, Christodoulou C, Junghaenel DU, Reeve BB, et al. PROMIS fatigue item bank had clinical validity across diverse chronic conditions. J Clin Epidemiol. 2016;73:128-34.

Christodoulou C, Junghaenel DU, DeWalt DA, Rothrock N, Stone AA. Cognitive interviewing in the evaluation of fatigue items: results from the patient-reported outcomes measurement information system (PROMIS). Qual Life Res. 2008;17(10):1239-46.

Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.

Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet. 2017;5(5):390-400.

FDA Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. https://www.fda.gov/media/71372/download. October 2005

FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128-41.

Gater A, Nelsen L, Fleming S, Lundy JJ, Bonner N, Hall R et al. Assessing asthma symptoms in adolescents and adults: qualitative research supporting development of the Asthma Daily Symptom Diary. Value Health 2016;19(4):440-50.

GlaxoSmithKline Document Number 2016N295843_03 (report date 10-AUG-2020) or later; GSK3511294 Investigator's Brochure (IB).

GlaxoSmithKline Document Number 2019N411063_00 A randomised double-blind (sponsor open), placebo controlled, single ascending dose, First Time in Human study in participants with mild to moderate asthma to assess safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of GSK3511294 administered subcutaneously. Report date 21-APR-2020.

GlaxoSmithKline Document Number 2019N418119_00 A Bayesian non-linear mixed effects dose-time exposure-response analysis of GSK3511294 effect on blood eosinophils to select Phase III dose using quantitative decision-making criteria. Report date 21-NOV-2019.

GlaxoSmithKline Document Number 2020N457410_00. Initial investigation of GSK3511294 effect on QTcF in study 205722. Report Date 13-JAN-2021.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2020. Available from: http://www.ginasthma.org/.

Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360(10):973-84.

Harrison T, Canonica GW, Chupp G, Lee J, Schleich F, Welte T, et al. Real-world mepolizumab in the prospective severe asthma REALITI-A study – initial analysis. Eur Respir J. 2020; in press (https://doi.org/10.1183/13993003.00151-2020).

Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447-54.

Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure for chronic airflow limitation - the St George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-7.

Juniper EF, Svensson K, Mőrk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Resp Med. 2005;99(5):553-8.

Khatri, S; Moore, W, Gibson, PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol. 2019;143(5):1742-51.

Khurana S, Brusselle GG, Bel EH, FitzGerald JM, Masoli M, Korn S, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX Study. Clin Ther. 2019;41(10):2041-2056.e5.

Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, Phase IIIb study. Clin Ther. 2016;38(9):2058-2070.e1.

Marshall S, Madabushi R, Manolis E, Krudys K, Staab A, Dykstra K, et al. Model-informed drug discovery and development: current industry good practice and regulatory expectations and future perspectives. CPT Pharmacometrics Syst Pharmacol. 2019;8(2):87-96.

Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005;26(1):153-61.

Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. J Allergy Clin Immunol Pract. 2017;5(6):1572-81.e3.

National Institutes of Health. National Heart, Lung, and Blood Institute (NHLBI). Guidelines for the Diagnosis and Management of Asthma (EPR-3). Aug 2007. Available at https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma

Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198-207.

PASS 2020 Sample Size Software, NCSS.com. Tests for the Ratio of Two Negative Binomial Rates. Ch 438:1-17. Available at https://www.ncss.com/wp-content/themes/ncss/pdf/Procedures/PASS/Tests_for_the_Ratio_of_Two_Negative_Binomial_Rates.pdf

Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380:651-9.

Pertzov B, Unterman A, Shtraichman O, Shitenberg D, Rosengarten D, Kramer MR. Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma. J Asthma 2019. DOI:10.1080/02770903.2019.1658208.

Pollanen P, Cooper TG. Vascular permeability to effectors of the immune system in the male rat reproductive tract at puberty. J Reprod Immunol. 1995;28(2):85-109.

Pollanen P, Setchell BP. Microvascular permeability to IgG in the rat testis at puberty. Int J Androl. 1989;12(3):206-18.

Roger JH, Bratton DJ, Mayer B, Abellan JJ, Keene ON. Treatment policy estimands for recurrent event data using data collected after cessation of randomised treatment. Pharmaceutical statistics. 2019;18(1):85-95.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson Jr NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391-7.

Schleich F, Graff S, Nekoee H, Moermans C, Henket M, Sanchez C, et al. Real-world experience with mepolizumab: Does it deliver what it has promised? Clin Exp Allergy. 2020;50(6):687-95.

Setchell BP, Waites GMB. The blood-testis barrier. In: Hamilton DW, Greep RO, editor. The Handbook of Physiology, Section 7, Vol. V. Male Reproductive System. Washington, DC:American Physiological Society, 1975:143-72.

Setchell BP. Physiologie de la barrière sang-testicule. Andrologie. 2001;11:15-20.

Sohn W, Lee E, Kankam MK, Egbuna O, Moffat G, Bussiere J, et al. An open-label study in healthy men to evaluate the risk of seminal fluid transmission of denosumab to pregnant partners. British Journal of Clinical Pharmacology. 2016;81(2):362-9.

Tepper RS, Wise RS, Covar R, Irvin CG, Kercsmar CM, Kraft M et al. Asthma outcomes: pulmonary physiology. J Allergy Clin Immunol. 2012 Mar;129(3 Suppl): S65-87.

Wang Y, Zhu H, Madabushi R, Liu Q, Huang SM, Zineh I. Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations. Clin Pharmol Ther. 2019;105(4):899-911.