CLINICAL STUDY PROTOCOL

Primary study intervention(s)	Depemokimab
Other study intervention(s)	NA
Study identifier	223529
Abbreviated title	Depemokimab Asthma Imaging and Bronchoscopy Sub-Study
EU CT number	2024-519976-19
Approval date	04 Feb 2025
Title	The IMAGINE study: A phase 3b open label, single arm study to assess the effect of depemokimab on airway structure and function in asthma with Type 2 inflammation characterized by an eosinophilic phenotype utilizing quantitative high-resolution CT and bronchoscopic airway sampling in a sub-study
Compound number/Name	GSK3511294 (Depemokimab)
Brief title	A phase 3b study of depemokimab on airway structure and function in patients with type 2 asthma utilizing quantitative high-resolution CT and a bronchoscopic airway sampling sub study
Sponsor	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Sponsor signatory	Peter Howarth Senior Global Medical Director, Global Medical Affairs, Respiratory Specialty Care.

Medical monitor name and contact information can be found in the local study contact information document.

Based on TMF-14732712 Protocol v4.0.

Protocol Investigator Agreement

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

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Investigator name	
Signature	
Date of signature **(DD Month YYYY)**	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ-5	Astha Control Questionnaire-5
ADA	Anti-Drug antibody
ADE	Adverse device effect
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI	Artificial intelligence
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
Ax	Area of reactance
BD	Bronchodilator
BEC	Baseline Eosinophill Count
BVX	Blood vessel distribution
CA	Competent authority
CFD	Computational fluid dynamics
CLC	Charcot Leyden crystals
CONSORT	Consolidated standards of reporting trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-2019
CP	Conditional power
CS	Corticosteroid
CSR	Clinical study report
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic case report form
ED	Early discontinuation
EDTA	Ethylenediaminetetraacetic acid
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EoS	End-of-study
FAAN	Food Allergy and Anaphylaxis Network
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced Expiration Volume in 1 second
FRC	Functional Residual Capacity
Fres	Frequency response
FTiH	First-time in human
FU	Follow-up
FVC	Forced vital capacity
GCP	Good clinical practices
GINA	Global Initiative for Asthma
GLI	Global Lung Initiative

Abbreviation	Definition
GSK	GlaxoSmithKline
HIV	Human immunodeficiency viruses
HRCT	High Resolution Computed Tomography
HRQoL	Health-Related Quality of Life
IB	Investigator's brochure
ICE	Intercurrent events
ICF	Informed consent form
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IFU	Instruction for use
IgG	Immunoglobulin G
IgE	Immunoglobulin E
IL-5	Interleukin-5
ILC-2	Innate lymphoid cells
IMP	Investigational medicinal product
IRB	Institutional review board
IRT	Interactive response technology
IV	Intravenous
LABA	Long-acting Beta 2 agonists
LAMA	Long-acting muscarinic antagonists
LAR	Legally acceptable representative
LSLV	Last subject last visit
LTRA	Leukotriene receptor antagonist
mAb	monoclonal Antibody
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed Model Repeated Measures
MSDS	Material safety data sheet
NHLBI	National Heart Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
OCS	Oral corticosteroid
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PRO	Patient reported Outcomes
qHRCT	Quantitative High Resolution Computed Tomography
QTc	QT interval corrected
QTcF	Corrected QT interval using the Fridericia formula
QTL	Quality tolerance limit
R5-R20	Resistance at 5Hz- Resistance at 20Hz
RNA	Ribonucleic acid

Abbreviation	Definition
RV/TLC	Residual volume/total lung capacity
SABA	Short acting Beta 2 agonists
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SCS	Systemic corticosteroid
SC	subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of activities
SRT	Safety Review Team
SSRE	Sample size re-estimation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TLC	total lung capacity
Th2	T helper 2
ToC	Table of contents
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Term	Definition
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard of care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (e.g., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.

Term	Definition
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
LAR	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Medicinal products used to assess endpoints	A product given to the participant in a clinical trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Non-IMP	Any products used in a clinical trial (other than the investigational product being tested) which are stipulated to be used to evaluate the efficacy and safety of the investigational drug in the protocol including comparators, co-administration drugs, rescue drugs and premedication drugs. • Non-IMPs products can be approved in Japan or other countries or can be products that are not approved.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.
Remote visit	A visit conducted in the place other than the study site.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.

Term	Definition
Study completion date	The date on which the last participant in a clinical study has completed all periods of the study including visit at Week 61, regardless of whether the second dose of study intervention (at Week 26) was received (that is, the last participant's last visit or LSLV).
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.
Telemedicine (TM)	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A phase 3b, open label, single arm study to assess the effect of depemokimab on airway structure and function in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype utilizing quantitative high-resolution computed tomography (HRCT) and bronchoscopic airway sampling in a sub-study: the IMAGINE study.

Brief title: A phase 3b study of depemokimab on airway structure and function in asthmatic patients with Type 2 inflammation utilizing quantitative high-resolution CT and a bronchoscopic airway sampling sub-study.

Rationale:

Asthma is characterized by chronic airway inflammation leading to airway obstruction and variable and recurring symptoms, resulting in unpredictable exacerbations. Treatment with biologics have demonstrated benefits in patients with asthma, predominantly by reducing exacerbations and oral corticosteroid (OCS) use. However, underutilization and delay in initiation of treatment with a biologic in eligible patients as well as treatment with suboptimal OCS bursts remain common in clinical practice. This could lead to inconsistent suppression of chronic inflammation contributing to risk of exacerbations and accelerated disease progression.

Timely identification and initiation of therapy that provides sustained suppression of inflammation provides an opportunity for patients to achieve long-term goals.

While approved biologic therapies for the treatment of asthmatic patients have been shown to decrease exacerbations, reduce the requirement for systemic steroids, and enhance patient outcomes, a lack of adherence to the indicated dosing schedules (SC or IV administration every 2 to 8 weeks) can impact these endpoints. In general, biologics with shorter dosing intervals have worse adherence and there is a need for treatments that have a favorable benefit/risk profile with a prolonged dosing interval in this patient population.

Depemokimab is the first ultra-long-acting biologic engineered to demonstrate enhanced interleukin-5 (IL-5) binding affinity, high potency and an extended half-life, enabling sustained inhibition of type 2 inflammation and dosing every 6 months in patients with asthma. Primary results from SWIFT-1 and SWIFT-2 studies showed clinically meaningful reductions in exacerbations following treatment with depemokimab (administered every 26 Weeks) in adults and adolescents with asthma with type 2 inflammation characterized by an eosinophilic phenotype. There is a need to further assess the effects of depemokimab on lung structure and function beyond forced expiratory volume in 1 second (FEV_1) data from Phase 3 studies i.e., improvements in mucus plugging, airway dynamics, remodeling and correlation with clinical and

physiological outcomes, including measures of small airway function which are poorly reflected by FEV_1 spirometric measures.

Therefore, this mechanistic study will investigate the effect of sustained IL-5 inhibition by depemokimab on lung structure and function, including mucus plugs and airway remodeling, assessed by quantitative HRCT (qHRCT) in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype. The relationships between airway dynamic measurements and asthma control and disease-specific Health-Related Quality of Life (HRQoL) using patient-reported outcomes (PROs) (ACQ-5 and SGRQ) will also be explored, aiming to identify a link between PROs with functional aspects at baseline, as well as the impact of treatment on these important PROs. Additionally, to further evaluate the impact of treatment, clinical remission status will also be assessed.

A sub-group of participants will undergo bronchoscopic airway sampling prior to the initiation of treatment with depemokimab and at 39 weeks after the commencement of treatment to obtain airway samples to evaluate the tissue cellular and structural impact of depemokimab therapy and to relate these findings to qHRCT measurements.

Refer to Section 2.1 for detailed rational of the study.

Objectives, endpoints, and estimands:

The primary and key secondary objectives, endpoints and estimands are provided below. Refer to the Section 3 for full list of objectives, endpoints, and estimands.

Objective	Endpoint and Estimand
Primary	
To describe the change from baseline (Week 0) in **total mucus plug volume** measured at total lung capacity (TLC) at **Week 26** following treatment with depemokimab.	**Population:** Asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype on medium to high dose inhaled corticosteroids (ICS) plus another asthma controller. **Endpoint:** Change from baseline in total mucus plug volume measured at TLC at Week 26. **Summary Measure:** Mean change from baseline in total mucus plug volume measured at TLC at Week 26. **Treatment Condition:** Depemokimab 100 mg. **Intercurrent Event and Handling strategies** • Treatment switch to any alternative biologic prior to Week 26: **Hypothetical** strategy, i.e., had the intercurrent event (of switching to an alternate biologic) not occurred. • Modification to inhaled asthma medication: **Treatment Policy** strategy, i.e., all participants shall be analyzed irrespective of any modification to inhaled asthma medication; • Addition of maintenance OCS use by participants who do not have a baseline maintenance OCS (mOCS): **Hypothetical strategy** i.e., had the intercurrent event (of using an additional maintenance OCS) not occurred.

Objective	Endpoint and Estimand
Key Secondary	
1. To describe the change from baseline (Week 0) in **airway wall thickness** measured at TLC **at Week 52** following treatment with depemokimab.	**Population:** Asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype on medium to high dose ICS plus another asthma controller. **Treatment Condition:** Depemokimab 100 mg **Endpoint:** Change from baseline in airway wall thickness measured at TLC at Week 52. **Summary Measure:** Mean change from baseline in airway wall thickness measured at TLC at Week 52. **Intercurrent Event and Handling strategies:** • Treatment switch to any alternative biologic: **Hypothetical strategy**, i.e., had the intercurrent event not occurred. • Treatment discontinuation after first dose: **Hypothetical strategy**, i.e., had the intercurrent event (of treatment discontinuation) not occurred. • Modification to inhaled asthma medication: **Treatment Policy** strategy, i.e., all participants shall be analysed irrespective of any modification to inhaled asthma medication; • Addition of maintenance OCS use by participants who do not have a baseline maintenance OCS (mOCS): **Hypothetical** strategy i.e., had the intercurrent event (of using an additional maintenance OCS) not occurred.

ICS= Inhaled corticosteroids; OCS= oral corticosteroid; TLC= Total lung capacity.

Overall design:

This is a Phase 3b, single-arm, open label interventional multicenter study of depemokimab in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype utilizing quantitative HRCT (qHRCT) methods to assess lung structure and function based on detailed 3D models of the airways with direct comparison of images taken at baseline (Week 0), between Week 24 to Week 26 and between Week 50 to Week 52, along with a nested bronchoscopic direct airway sampling sub-study. A total sample size for this study is planned to be approximately 103 participants.

The study will consist of three periods which includes screening period, study intervention period and follow up period. The screening Visit will occur within 4 weeks prior to the administration of study intervention (can be extended up to maximum of 8 weeks if participant experiences a clinically significant asthma exacerbation during the screening period). Participants who meet all the eligibility criteria at screening Visit will sign the informed consent for participation into the study prior to the initiation of any study related assessments. In addition, a subset of approximately 24 participants from the main study who meet the eligibility criteria and consent to participate will be enrolled in the bronchoscopy sub-study.

All participants who continue to meet study inclusion criteria will receive the first dose of depemokimab 100 mg SC at Week 0 and second dose at Week 26. The maximum time participants will spend in each study period is summarized below:

- Screening period– up to 4 weeks (or up to maximum of 8 weeks if participant experiences a clinically significant asthma exacerbation during the screening period).
- Treatment period – 52 weeks
- Safety follow-up period- 9 weeks (63 days post EoS or ED visit).

A participant is considered to have completed the study if the participant has completed all periods of the study including Week 61 Visit, regardless of whether the second dose of study intervention (at Week 26) was received.

In the event that a participant discontinues the study, the participant should be encouraged to complete an Early Discontinuation (ED) visit 26 weeks after last dose of study intervention and a safety follow-up visit 35 weeks after the last dose of study intervention.

For each participant enrolled, the duration will be approximately 65 Weeks which includes screening period (up to 4 weeks prior to the administration of study intervention or up to 8 weeks maximum if participant experiences a clinically significant asthma exacerbation during the screening period), 52 weeks (Visit 1 to Visit 6) of study intervention period and 9 weeks of follow up period.

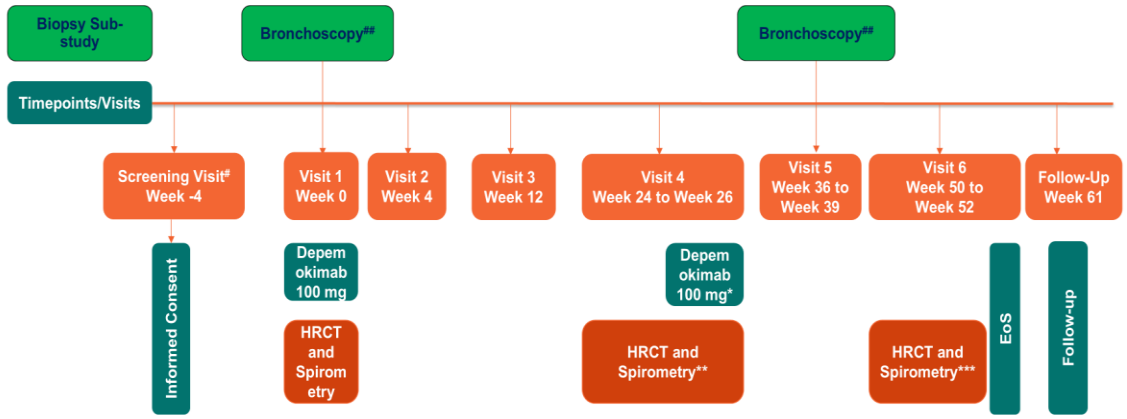
Even if the main study is discontinued due to futility, the sub-study participants will continue with bronchoscopy sub-study assessments. In this case all the enrolled main study participants (including participants in interim analysis) will be required to complete an ED and follow up visits. Refer to Section 4.1 for detailed description on study design.

Number of participants:

A total of 103 participants will be enrolled upfront. The sample size justification is described in the Statistical Considerations in Section 9.5. In addition, a subset of approximately 24 participants from the main study who meet the eligibility criteria and provide consent to participate will be enrolled in the bronchoscopy sub-study.

1.2. Schema

Figure 1 Study design overview



EoS= End of Study; HRCT= High-resolution CT; PRO= Patient reported outcome

* Depemokimab second dose administration must be performed at Week 26.

**Study assessments including HRCT and spirometry must be performed within a 14 days timeframe (from Week 24 to Week 26) prior to study intervention administration at Week 26. Spirometry should be done after HRCT scan procedure.

***Study assessments including HRCT and spirometry must be performed within a 14 days window (from Week 50 to Week 52). Spirometry should be done after HRCT scan procedure.

#Screening will be extended up to maximum of 8 weeks if participant experiences a clinically significant exacerbation during the screening period.

Bronchoscopy must be performed at Visit 1 (Week 0) after HRCT and lung function assessments as well as at Visit 5 (Week 36 to Week 39). Please refer to the Section 8.2 for order of assessments.

Note: Assessments of AEs/SAEs will be performed throughout the study period (from signing of the informed consent until Week 61).

1.3. Schedule of activities

All assessments planned for participants in Study 223529 are shown in the time and events tables as follows:

- Table 1: Screening, On Treatment, End of Treatment, and Follow- Up- Assessments for Main imaging study and bronchoscopy sub-study.
- Table 2: Schedule of Activities for participants in the bronchoscopy sub-study and main study to be followed in the event that a main imaging study is discontinued due to futility after Week 26.

Table 1: Screening, On Treatment, End of Treatment and Follow Up Assessments for Main study and bronchoscopy sub-study

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	V0	V1	V2	V3	V4	V5	V6 EoS	ED*	FU	
Study Week (W)	W-4 (±1 day)	W0 (±7 days)	W4 (±7 days)	W12 (±7 days)	W24 to W26 (±7 days)***	W36 to W39 (±7 days)****	W50 to W52 (±7 days) ***	W26 or W52 (±7 days)***	W61 (±7 days)	
General Eligibility Assessments										
Informed consent[1]	•									

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
Inclusion and exclusion criteria	●	●[3]								Recheck clinical status before first dose of study medication; See footnote 3.
Demography Data collection and childbearing status	●	●[11]								
Height measurement	●									
Historical blood eosinophil count	●									
Medical history (includes substance usage [and family history of premature CV disease])	●									
Current medical conditions	●									
Smoking status (non-smoker/ex-smoker/	●									

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
current smoker)[5]										
Parasite screening	●									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.
Laboratory Assessments										
Haematology with differential counts	●	●[3]	●		●[3, 6]		●[9]	●		Refer to Section 10.2 (Appendix 2) for additional information on clinical laboratory tests.
Total IgE		●[3]								

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
Serum pregnancy test (WOCBP only)	○						○ [4, 9]	○ [4]		
FSH and estradiol (For WONCBP to confirm post-menopausal status)	●									These tests will only be performed in the absence of 12 months amenorrhea to confirm post-menopausal status
Urine pregnancy test		○ [3,4]	○	○	○ [3, 4, 6]	○ [8]			○	
Urinalysis	●	● [3]			● [3, 6]		● [9]	●		
Blood chemistry (include liver chemistries)	●	● [3]	●	●	● [3, 6]	● [8]	● [9]	●		
Safety Assessments										
Physical examination including weight measurement	●						●	●		Only weight will be documented in the eCRF
Vital signs	●	● [3]			● [3, 6]		● [9]	●		

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
12-lead ECG	●	●[3]			●[3, 6]		●[9]	●		
AE/SAE Assessments	●[2]	●[3]	●	●	●[3, 6]	●[8]	●[9]	●	●	

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
Concomitant medication Assessment	●	●[3, 4]	●	●	●[3, 6]	●[8]	●[9]	●		Ensure maintenance asthma medications from the 12 months prior to Screening Visit, all medications within the 3 months prior to Screening Visit and all current medications are reviewed. Additionally, ensure any biologic treatment history for asthma is reviewed and captured.

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
PRO and Health Outcomes Assessments										
ACQ-5	●	●[3]	●	●	●[3, 6]	●	●[9]	●		
SGRQ		●[3]			●[3, 6]		●[9]	●		
Efficacy Assessments										
Review for asthma exacerbation	●	●[3, 4]	●	●	●[3, 4, 6]	●[8]	●[4, 9]	●		
HRCT scan (at TLC and FRC)		●[3]			●[3, 6]		●[9]	●[10]		
Spirometry (pre-BD)#	●	●[3]	●	●	●[3, 6]	●	●[9]	●		
Spirometry (post- BD)#		●[3]			●[3, 6]	●[12]	●[9]	●		Reversibility test will only be performed at Visit 1.
Pre-BD Oscillometry (R5-R20, AX, Fres)		●[3]	●	●	●[3, 6]	●	●[9]			

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
Post-BD Oscillometry (R5-R20, AX, Fres)		●[3]			●[3, 6]	●[12]	●[9]			
Whole body plethysmography (RV/TLC ratio)[13]		●[3]			●[3, 6]		●[9]			
Biomarker Assessments										
Fractional exhaled nitric oxide (FeNO)	●	●[3]			●[3, 6]	●	●[9]			
Serum Biomarkers		●[3]			●[3, 6]	●	●[9]			
Nasal brushing for RNA		●[3]			●[3, 6]	●	●[9]			
Study intervention										
Administration of study intervention[7]		●			●					
Bronchoscopy sub-study										
Biopsy eligibility met	●									
Bronchoscopy**		●[3]				●				

Procedure	Screening	Intervention period [weeks]							Follow-up (63 days post EoS or ED visit)	Notes
Visit/Cycle	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W-4 (±1 day)**	**W0 (±7 days)**	**W4 (±7 days)**	**W12 (±7 days)**	**W24 to W26 (±7 days)*** **	**W36 to W39 (±7 days)**** **	**W50 to W52 (±7 days) *** **	**W26 or W52 (±7 days)*** **	**W61 (±7 days)**	
Bronchial biopsies		●				●				
Bronchial brushings for RNA		●[3]				●				
eCRF/worksheets/other										
Register Visit in the IRT system	○	○			○			○		

ACQ-5 = Asthma Control Questionnaire-5; AE= Adverse event; AX = area of reactance; BD= bronchodilator; CA = Competent authority; CV = Cardiovascular; ECG = Electrocardiogram; ED = Early discontinuation; EoS = End of Study; FeNO = Fractional exhaled nitric oxide; FRC = Functional Residual Capacity; Fres= frequency response; FU = Follow-up; FEV_1 =Forced expiratory volume in 1 second; HRCT = High-resolution computed tomography; ICF = Informed consent form; IEC = Independent Ethics Committee; IgE = Immunoglobulin E; IRT =interactive response technology; PD = Pharmacodynamics; PK = Pharmacokinetics; R5-R20 = Resistance at 5Hz-resistance at 20Hz; RNA = ribonucleic acid; RV/TLC = residual volume/total lung capacity; SAE = Serious adverse event; SGRQ = St. George's Respiratory Questionnaire; TLC = Total Lung Capacity; V = visit; W= Week; WOCBP = Women of childbearing potential; WONCBP = Women of non-child bearing potential.

● Is used to indicate a study procedure that requires databasing (either in eCRF, device, laboratory, or another third-party vendor).

○ Is used to indicate a study procedure that does not require databasing (in source only).

* If a participant discontinued from the study early, then the early discontinuation (ED) 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 35 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.

**Bronchoscopy and biopsies must be performed after HRCT and lung function assessments at Visit 1. Please refer to Section 8.2 for order of efficacy assessments.

***If a participant experiences an asthma exacerbation requiring SCS prior to HRCT scan, a visit window of 4 weeks will be provided for the scan, allowing the participant to recover, stop exacerbation treatment, and the investigator considers that the participant has returned to their baseline asthma status for at least one week, however the depemokimab dosing should take place within the specified 2 week window and not to be delayed.

****if participants in bronchoscopy sub-study experiences an asthma exacerbation requiring SCS prior to bronchoscopy, a visit window of 4 weeks will be provided, allowing the participant to recover such that there is a period of at least 4 weeks between the end of exacerbation treatment and the bronchoscopy procedure.

Spirometry should be done after HRCT scan procedure. Please refer to Section 8.2 for order of efficacy assessments

1. Informed Consent must be obtained prior to initiating any study related assessments. Screening visit can occur any time within 4 weeks prior to the administration of study intervention provided appropriate washout period requirements for prohibited medications and bronchodilator use have been met. Short acting Beta 2 agonists (SABAs) such as albuterol/salbutamol should be withheld for at least 6 hours. Long-acting Beta 2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), fixed dose combinations of ICS/LABA or ICS/LABA/LAMA should be withheld for ≥12 hours prior to screening spirometry assessments. For participants who do not meet the wash-out period requirements, a separate screening visit should be scheduled to accommodate bronchodilator washout periods.
2. AEs and SAEs must be collected from signing of Informed Consent if considered related to study procedures.
3. Study procedures including pregnancy test and ECG assessments must be performed at Week 0 and Week 26 prior to the administration of study intervention. The results of the pregnancy test and ECG must be reviewed prior to the administration of study intervention. Refer to section 7.1.2 on QTc stopping criteria.
4. Study procedure including pregnancy test must be performed prior to HRCT. The results of pregnancy test must be obtained prior to the HRCT scan.
5. For participants who are ex-smokers and current smokers, number of pack years will be collected.
6. Study assessments including HRCT must be performed within a 14 days' window (from Week 24 to Week 26) prior to study intervention administration at Week 26, except in the case of exacerbations (please refer to footnote ***). All the laboratory assessments should be performed on the same day.
7. Study intervention administration must be performed at Week 0 and Week 26. Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-dose (both at week 0 and at Week 26).
8. For participants who are not a part of bronchoscopy sub-study, the study procedure should be completed within a 21 days' window (from Week 36 to Week 39). All the laboratory assessments should be performed on the same day.
9. Study assessments including HRCT must be performed within a 14 days' window (from Week 50 to Week 52). All the laboratory assessments should be performed on the same day.
10. HRCT scan at the ED visit will be performed based on the participant's consent and the Principal Investigator's (PI's) clinical judgement with appropriate consultation with the Medical Monitor (MM), if required.
11. Study procedure must be performed at Visit 1 if not completed at Visit 0.
12. The post-BD spirometry and post-BD oscillometry assessments at Visit 5 will only be performed for participants in bronchoscopy sub-study.
13. The aim is to perform this assessment for all study participants but based on site feasibility will set a minimum target of 50% of total study participants.

Table 2. Schedule of Activities for participants in the bronchoscopy sub-study and main imaging study to be followed in the event that a main imaging study is discontinued due to futility after Week 26

Even if the main study is discontinued due to futility, participants will continue with bronchoscopy sub-study with the following SoA after Week 26. In this case, all the participants in the main study (including participants in interim analysis) must complete an ED visit and follow-up visit.

Procedure	Intervention period [weeks]			Follow-up (63 days post EoS/ED visit))	Notes
Visit/Cycle	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W39 (±7 days) ******	**W50 to W52**	**W26 or W52 (±7 days)*****	**W61 (±7 days)**	
Laboratory Assessments					
Haematology with differential counts	●	●[1]	●		Refer to Section 10.2 (Appendix 2) for additional information on clinical laboratory tests.
Serum pregnancy test (WOCBP only)		○[1]	○		
Urine pregnancy test	○			○	
Urinalysis		●[1]	●		
Blood chemistry (include liver chemistries)	●	●[1]	●		
Safety Assessments					
Physical examination including weight measurement		●[1]	●		Only weight will be documented in the eCRF
Vital signs		●[1]	●		
12-lead ECG		●[1]	●		
AE/SAE Assessments	●	●[1]	●	●	

Procedure	Intervention period [weeks]			Follow-up (63 days post EoS/ED visit))	Notes
Visit/Cycle	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W39 (±7 days) ******	**W50 to W52**	**W26 or W52 (±7 days)*****	**W61 (±7 days)**	
Concomitant medication Assessment	●	●[1]	●		Ensure maintenance asthma medications from the 12 months prior to Screening Visit, all medications within the 3 months prior to Screening Visit and all current medications are reviewed. Additionally, ensure any biologic treatment history for asthma is reviewed and captured.
PRO and Health Outcomes Assessments					
ACQ-5	●	●[1]	●		
SGRQ		●[1]	●		
Efficacy Assessments					
Review for asthma exacerbation	●	●[1]	●		
Spirometry pre-BD)	●	●[1]	●		
Spirometry (post-BD)	●	●[1]	●		
Pre and Post BD Oscillometry (R5-R20, AX, Fres)	●	●[1]			
Whole body plethysmography (RV/TLC ratio)[2]	●	●[1]			
Biomarker Assessments					
Fractional exhaled nitric oxide (FeNO)	●	●[1]			
Serum Biomarker	●	●[1]			

Procedure	Intervention period [weeks]			Follow-up (63 days post EoS/ED visit))	Notes
Visit/Cycle	**V5**	**V6 EoS**	**ED***	**FU**	
Study Week (W)	**W39 (±7 days) ******	**W50 to W52**	**W26 or W52 (±7 days)*****	**W61 (±7 days)**	
Bronchoscopy	●				
Bronchial biopsies	●				
Nasal brushing for RNA	●				
Bronchial brushing for RNA	●				
eCRF/worksheets/other					
Register Visit in the IRT system			○		

ACQ-5= Asthma Control Questionnaire-5; AE = Adverse event; AX= area of reactance; BD= bronchodilator; ECG = Electrocardiogram; ED= Early Discontinuation; EoS= End of Study; FeNO= Fractional exhaled nitric oxide; Fres= frequency response; FU= Follow-up; RNA= ribonucleic acid; R5-R20= Resistance at 5Hz-resistance at 20Hz; RV/TLC= residual volume/total lung capacity; SAE= Serious adverse event; SGRQ- St George's Respiratory Questionnaire V = visit; W= Week; WOCBP = Women of childbearing potential

● Is used to indicate a study procedure that requires databasing (either in eCRF, device, laboratory, or another third-party vendor).

○ Is used to indicate a study procedure that does not require databasing (in source only).

* If the main imaging study is discontinued due to futility, the main study participants must complete an ED Visit which should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 or at Week 52 if the first or second dose of study intervention was received, respectively. A follow-up visit/call should also be conducted 35 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.

**** if participants in bronchoscopy sub-study experience an asthma exacerbation requiring SCS prior to bronchoscopy, a visit window of 4 weeks will be provided, allowing the participant to recover, such that there is a period of at least 4 weeks between the end of exacerbation treatment and the bronchoscopy procedure.

1. Study assessments must be performed within a 14 days' window (from Week 50 to Week 52).
2. The aim is to perform this assessment for all study participants but based on site feasibility will set a minimum target of 50% of total study participants.

2. INTRODUCTION

2.1. Study rationale

Asthma is characterized by chronic airway inflammation leading to airway obstruction and variable and recurring symptoms, resulting in unpredictable exacerbations. Treatment with biologics have demonstrated benefits in patients with asthma, predominantly by reducing exacerbations and oral corticosteroid (OCS) use. However, underutilization and delay in initiation of treatment with a biologic in eligible patients as well as treatment with suboptimal OCS bursts remain common in clinical practice. This could lead to inconsistent suppression of chronic inflammation contributing to a higher risk of exacerbations and accelerated disease progression. Timely identification and initiation of

therapy that provides sustained suppression of inflammation provides an opportunity for patients to achieve long-term goals.

Anti- interleukin-5 (Anti-IL-5) therapies have an established efficacy and long-term safety profile in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype [GINA, 2024]. Three biologics targeting IL-5 or its receptor (mepolizumab, reslizumab and benralizumab) are approved for the treatment of asthma with elevated blood eosinophil count, administered as an add-on treatment once every 4 to 8 weeks. All 3 biologics, by utilizing blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce exacerbations in asthma patients with type 2 inflammation characterized by increased eosinophils [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014 ; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017]. While these therapies have been shown to decrease exacerbations, reduce the requirement for systemic steroids, and enhance patient outcomes [GINA, 2024], a lack of adherence to the indicated dosing schedules (SC or IV administration every 2 to 8 weeks) can impact these endpoints [Cristancho, 2024]. In general, biologics with shorter dosing intervals have worse adherence [Ledford, 2023; Gelhorn, 2019] and there is a need for treatments that have a favorable benefit/risk profile with a prolonged dosing interval in these patient populations.

Depemokimab is the first ultra-long-acting biologic engineered to have enhanced binding affinity, high potency and an extended half-life, enabling sustained inhibition of type 2 inflammation and dosing every 6 months in patients with asthma. Primary results from SWIFT-1 and SWIFT-2 trials showed clinically meaningful reductions in exacerbations following treatment with depemokimab (administered every 26 Weeks) in adults and adolescents with asthma with type 2 inflammation characterized by an eosiniphilic phenotype [Jackson, 2024].

There is a need to evaluate the effect of depemokimab on lung structure and function beyond forced expiratory volume in 1 second (FEV_1) data from Phase 3 studies i.e., improvements in mucus plugging, airway dynamics, remodeling and correlation with clinical and physiological outcomes, including measures of small airway function that are poorly reflected by conventional FEV_1 spirometric measures. These findings would demonstrate the impact of depemokimab on endpoints related to airway remodeling and disease modification. It will also enhance knowledge on the role of inhibition of IL-5 on modifying disease biology in a bronchoscopy sub-study, to understand the biological impact and relationship to clinical and imaging outcomes.

Therefore, this mechanistic study will investigate the effect of sustained IL-5 inhibition by depemokimab on lung structure and function, including mucus plugging and airway remodeling, in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype as assessed by quantitative high-resolution computed tomography (qHRCT). The relationships between airway dynamic measurements and disease-specific patient-reported outcomes (PROs) will also be explored, aiming to identify a link between PROs with functional aspects at baseline, as well as the impact of treatment on these important PROs. Additionally, to further evaluate the impact of treatment, clinical remission status will also be assessed.

A sub-group of participants will undergo bronchoscopic airway sampling prior to the initiation of treatment with depemokimab and at 39 weeks after the commencement of treatment to obtain airway samples to evaluate the tissue cellular and structural impact of depemokimab therapy and to relate these findings to those obtained from the qHRCT assessment.

2.2. Background

2.2.1. Asthma with type 2 inflammation characterized by an eosinophilic phenotype

Asthma is a chronic heterogeneous lung disease characterized by inflammation, airway hyperresponsiveness and variable airflow obstruction. Symptoms varies over time and in intensity and can include wheezing, shortness of breath, chest tightness, and cough. Despite optimal guideline-directed treatment, and irrespective of underlying disease severity, patients with asthma experience exacerbations caused by an accentuation of existing inflammatory processes and a loss of disease control [Castillo, 2017]. Exacerbations are particularly disabling, usually necessitating treatment with systemic corticosteroids (SCS). Short-term OCS bursts, which are administered in up to 93% of patients with severe or difficult-to-treat asthma, have been associated with increased risk for infections and hyperglycemia [Bleecker, 2020; Bourdin, 2020]. Longer term complications resulting from multiple OCS courses (or chronic OCS use) include metabolic syndrome (weight gain, type 2 diabetes, and hypertension), osteoporosis and fractures, and ocular abnormalities including cataracts [Sarnes, 2011; Bourdin, 2020]. Repeat exacerbations have been associated with lung function decline [Ortega, 2018] and can lead to hospitalization and potentially death [Sado, 2023]. Exacerbations are also responsible for significant asthma-related health care expenditures, lost education/work, and can impact economic productivity [Fuhlbrigge, 2012; Burnette, 2023; Yang, 2023]. Type 2 inflammation is the underlying pathology for more than 80% of patients with asthma [Heaney, 2021], and is driven by T helper 2 (Th2) cells and Group 2 innate lymphoid cells (ILC2), which both produce IL-5 [Maspero, 2022]. Eosinophilic inflammation, reflective of IL-5 driven disease, is a recognized risk factor for severe disease exacerbations, airway remodeling and lung function decline in asthma [Pelaia, 2019; Green, 2002; Siddiqui, 2023].

The IL-5 is a core cytokine in type 2 inflammation. It is critical to the inflammatory actions of eosinophils, a key biomarker of type 2 inflammation in asthma. New evidence suggests that dysregulated IL-5 has multidirectional effects on a broad range of structural and immune cells, leading to immune imbalance, epithelial barrier dysfunction, mucus plugging, and airway remodeling.

Asthma guidelines recommend add-on targeted therapy for asthma patients who have evidence of type 2 inflammation and frequent exacerbations and/or poor symptom control, despite treatment with optimized inhaled corticosteroids (ICS) and long-acting beta 2-agonists (ICS-LABA) [GINA, 2024]. The guidelines also state that higher blood eosinophils are predictive of good response to IL-5 inhibition [Ortega, 2016], and also recommend that dosing frequency and patient preference are taken into account when considering treatments, as these factors can affect adherence [GINA, 2024].

2.2.2. Effect and clinical benefit of Depemokimab

Depemokimab is a humanized, ultra long-acting, monoclonal antibody (mAb) that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for asthma management. The sustained effects of depemokimab resulted in significant reductions in exacerbations by 58% and 48% across SWIFT 1 and SWIFT 2 studies, respectively, compared with placebo. In a pooled analysis, depemokimab reduced the annualized rate of exacerbations leading to hospitalization and/or emergency department visits by 72% compared with placebo.

Depemokimab was well-tolerated with an overall incidence and severity of treatment emergent adverse events (TEAEs) that were similar to patients receiving placebo [Jackson, 2024].

2.2.3. High Resolution Computed Tomography (HRCT)

In this study, non-contrast HRCT will be performed to measure changes in airway structure and dynamics using qHRCT. These qHRCT scans provide detailed visualization and evaluation of the lungs and airway structures, allowing for an in-depth description of baseline lung health and disease severity and a better understanding of post-treatment effects. Leveraging artificial intelligence (AI) based segmentation, classical computer vision methods, and computational fluid dynamics (CFD) relatively novel quantitative imaging-based metrics that measure biological responses to therapeutic interventions can be derived. By assessing changes close to the site of action of the intervention, the method is more sensitive (larger effect size) compared with standard lung function tests [De Backer, 2012]. Several clinical trials in patients with asthma [De Backer, 2008; Vos, 2013; De Backer, 2015] showed significant correlations between the change in FEV_1, other pulmonary function test parameters or asthma control, and the change in both image-based volume and/or airway resistance following bronchodilation or resolution of exacerbation [De Backer, 2011; Vos, 2016; De Backer, 2018; Van Geffen, 2018].

2.2.4. Bronchoscopy sub-study

Bronchoscopic airway sampling, with approaches such as endobronchial biopsy with or without bronchial brushing, is the gold standard to directly evaluate the underlying pathophysiology in severe asthma [Wilson, 2016; Kuo, 2017] as well as to understand the impact of therapy on airway pathology, particularly tissue airway remodeling [Domvri, 2024; Diver, 2021]. Whilst airway CT imaging can inform about airway wall thickness, it cannot define the components that contribute to the change in structure and how these

components are modified by therapy. This is dependent upon direct airway sampling. Immunohistochemical assessment on airway biopsies is commonly used to evaluate both cellular and structural components [Wilson, 2016; Domvri, 2024; Diver, 2021] but this approach does not inform about cell activation. Cell activation is standardly assessed through transcriptomic analysis, such as bulk RNA sequencing [Kuo, 2017], although unless undertaken on a relatively pure cell population, such as epithelial brushings or at the single cell level, does not permit understanding of the cell specificity of the gene changes and by implication the impact of therapy on distinct cell populations. As such preferred approaches are now either single cell sequencing to link the transcriptomic profile to specific cell populations and/or tissue spatial transcriptomics, that allows not only assessment of distinct cell populations and their activation status but also the geographic localization and co-localization of cell populations within the tissue architecture [Cao, 2024; Megas, 2024; Duhan, 2024]. In the bronchoscopy sub-study, proximal airway tissue biopsies will be taken for both spatial transcriptomic and immunohistochemical analysis, along with both proximal and distal airway brushings for transcriptomic analysis to inform about change in epithelial cell activation and cellular infiltration at these airway sites.

2.3. Benefit-risk assessment

Summaries of findings from nonclinical studies and completed studies conducted with depemokimab as well as more detailed information about the known and expected benefits and risks and reasonably expected AEs of depemokimab may be found in the Investigator's Brochure (IB) [GSK Document Number RPS-CLIN-132006].

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 Depemokimab		
Allergic reactions including anaphylaxis	• Allergic reactions, with the most severe form being anaphylaxis (see Section 10.10; Appendix 10), are potential risks associated with mAbs. • No AEs, considered by the investigator to represent systemic type I hypersensitivity reactions, were reported in the placebo controlled-asthma studies (206713; 213744). There were no events of anaphylaxis. • Systemic reactions, including type I hypersensitivity (allergic) reactions, reported in the completed studies with depemokimab are summarized in the investigator's Brochure (IB) (Section "Safety in Clinical studies"). Further information is summarized in Section 6 of the IB titled 'Summary of Data and Guidance for the Investigator' [GSK Document Number RPS-CLIN-132006].	• Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at week 0 and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose (see Section 7.1). • Use of dedicated eCRF pages to collect information on systemic reactions. • Use of criteria of Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Section 10.10; Appendix 10). • Daily monitoring of serious adverse events (SAEs) by Medical Monitor; regular systematic review of AEs/SAE data from ongoing studies by a GSK safety review team.

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs, considered by the investigator to represent type III hypersensitivity (immune complex disease/ vasculitis), were reported in the placebo controlled-asthma studies (206713, 213744). • Further information is summarized in the IB (section titled “Safety in Clinical studies”) and in Section 6, ‘Summary of Data and Guidance for the Investigator’ [GSK Document Number RPS-CLIN-132006].	• 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 5.2.1). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.4). • 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). • Use of dedicated eCRF page to collect information on type III hypersensitivity (immune complex disease/ vasculitis). • Daily monitoring of SAEs will be done by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies will be performed by a GSK safety review team.
Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • Local injection site reactions reported in the completed studies with depemokimab are summarized in the IB (Section “Safety in Clinical studies”). Further information is summarized in Section 6 of the IB titled ‘Summary of Data and Guidance for the Investigator’ [GSK Document Number RPS-CLIN-132006].	• Use of dedicated eCRF page to collect information on local injection site reactions. • Daily monitoring of SAEs by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team.

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Risk of depemokimab affecting an unborn baby	• Reproductive studies have not been conducted with depemokimab; however, in the 6-month repeat dose study in monkey, 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 preclinical 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 depemokimab 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 will be excluded (EXC# 17, Section 5.2.4). 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 at least 35 weeks after the last administration of depemokimab.
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).
Exposure of subjects to ionizing radiation from chest high-resolution Computed tomography (HRCT) scans	• Scans will be performed at three study visits: baseline (Visit 1), Between Week 24 to Week 26 (Visit 4) and Between Week 50 to Week 52 (Visit 6). The HRCT scan at the ED visit will be performed based on the participant's consent and the Principal Investigator's (PI's) clinical judgement with appropriate consultation with the Medical Monitor (MM), if required.	• Low radiation scanning protocols tailored to the specific scanner available at participating sites will be provided to reduce participant's exposure to ionizing radiation. • The minimum number of HRCT procedures will be performed to achieve study objectives (with approximately 24 weeks spacing between procedures). • The average estimated radiation exposure received by participants in this study for 6 HRCT scans at 2.2 mSv (based on the scanner brands and models in Table 12 (Appendix 9)

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
	• Each participant will undergo 6 scans (2 scans per visit, 3 visits) which will result in an average exposure of 2.2*6 = 13.2 mSv over a time period of 52 weeks, equivalent to approximately 4.3 years of background radiation (the average annual global background radiation dose is approximately 3.1 mSv). The additional risk of developing a fatal malignancy is estimated to be: • 18-year-old female: 1:378 or 0.26%; • 18-year-old male: 1:621 or 0.16%; • 50-year-old female: 1:1121 or 0.09%; • 50-year-old male: 1:1498 or 0.07% [Radiation risk calculator]. • The radiation related risks are exclusively stochastic effects and are effects that occur by chance specifically as it relates to a fatal malignancy. The doses estimated in this protocol of ~13.2 mSV are well below the threshold for deterministic effects, which generally starts at above 2000 mSV [ICRP, 2007; UNSCEAR, 2010].	is approximately 3.6 times lower than 6 standard chest CT scans which would expose a person to 48 mSv of radiation (8 mSv per scan). • The first HRCT scan must be performed at visit 1. The participant should have completed their screening visit and all screening lab results, should be assessed by the PI before a HRCT scan is conducted. • The second CT scan should be performed at Visit 4 and the third HRCT scan should be performed at Visit 6. The HRCT must be performed within a 14 days' window i.e from Week 24 to Week 26 for Visit 4 and from Week 50 to Week 52 for Visit 6. • If a participant is permanently discontinued from the study intervention, and the second dose of study intervention was not received, third HRCT scan will not be performed. • HRCT scan at the ED visit will be performed based on the participant's consent and the PI's clinical judgement with appropriate consultation with the MM, if required. • Participants will be informed of the risks associated with the CT procedure before entering the study. • Participants who have occupational ionizing-radiation exposure exceeding 10 mSV over 3 years or have been exposed to elevated ionizing radiation from research imaging studies are excluded (EXC# 19, Section 5.2.4). • WOCBP will be required to have a negative highly sensitive urine pregnancy test within the 24 hours before each HRCT scan to avoid accidental exposure of pregnant subjects. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. • Please refer to Section 8.3.5 for Pregnancy testing requirements (WOCBP only).
Exposure of foetus to ionizing radiation from chest HRCT scans	• As the study procedure is a chest HRCT scan, the abdomen is out of the field of view and in the event of an undetected pregnancy the fetal	• The participant will be excluded from participation in the study, if the serum pregnancy result at screening is positive.

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
	radiation dose will be limited to scatter and hence very small. Nevertheless, steps are required to avoid accidental exposure of pregnant participants.	• WOCBP will be required to have a negative highly sensitive urine pregnancy test within the 24 hours before each HRCT scan. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. If the pregnancy test is positive, the participant will be excluded from HRCT procedure.
Potential risk for injury with Bronchoscopy and airway sampling	*Flexible bronchoscopy under local anesthesia* Risks associated with local anesthesia utilized during the procedure include allergic reactions, toxicity, dizziness, unpleasant taste and cough. Risks associated with the bronchoscopy procedure include coughing, bronchospasm, laryngospasm with additional risks of bleeding and infection associated with the biopsy procedure. *Rigid bronchoscopy under general anesthesia* Unlikely to be used but depends on local practice. Additional risks with this procedure are those linked to the general anesthesia such as nausea, vomiting, itching, dizziness, headaches and shivering with rarely allergic reactions. *General bronchoscopy risks* Bronchoscopy may lead to an acute deterioration in asthma.	• Inclusion criteria for the bronchoscopy sub-study will only include participants who have no known increased risk for bleeding, are not currently undergoing anticoagulant and antiplatelet therapy, have not used acetylsalicylic acid within 2 weeks prior to the planned procedure, have normal screening platelet count (INC #12), and have no specific contraindication to bronchoscopy with endobronchial biopsy in the opinion of the investigator (INC #13). Those with known history of allergic reactions to local or general anesthetic agents (depending upon context) will be excluded. • Procedures to be performed by skilled and experienced clinician with careful monitoring and adequate anaesthesia to prevent discomfort and other risks. Participants will be given bronchodilator therapy before bronchoscopy to prevent bronchoconstriction and will be monitored post-bronchoscopy to ensure that their lung function, if it has fallen, has recovered before discharge and receive additional bronchodilator therapy if needed. There will be standardised post-bronchoscopy care which also involves contact the following day to ensure that the participant is stable

2.3.2. Benefit assessment

Depemokimab is the first ultra-long-acting biologic therapy with enhanced binding affinity for IL-5 that enables effective 6-month dosing intervals. Results from the Phase 3a, SWIFT 1 and SWIFT 2 studies showed that depemokimab, administered every 6 months for 52 weeks, was associated with significant reductions in the annual rate of exacerbations. A 58% reduction (rate ratio: 0.42; 95% CI: 0.30, 0.59; P<0.001) in the annualized rate of clinically significant exacerbations over 52 weeks for depemokimab versus placebo was seen in SWIFT 1 study and a 48% reduction (rate ratio 0.52; 95% CI: 0.36, 0.73; P<0.001) in SWIFT 2 study. Depemokimab reduced the percentage of participants who experienced at least 1 clinically significant exacerbation compared to placebo (32% versus 46% in SWIFT-1; 32% versus 48% in SWIFT-2); or reported multiple exacerbations (13% versus 29% in SWIFT-1; 12% versus 31% in SWIFT-2). In both studies, depemokimab also reduced the rate of clinically significant exacerbations requiring hospitalization and/or emergency department visits (i.e., the most clinically significant exacerbations). In a pooled analyses across SWIFT 1 and SWIFT 2, there was a nominally significant reduction of 72% in the annualized rate of clinically significant exacerbations requiring hospitalization and/or emergency department visit for depemokimab compared with placebo over 52 weeks. Additionally, in the SWIFT studies, a rapid and sustained reduction of blood eosinophil count was observed, demonstrating sustained inhibition of inflammatory response over the duration of treatment and dosing interval [Jackson, 2024]. As such, depemokimab offers the convenience of an improved dosing schedule, with the possibility to improve adherence to biologic therapy which could potentially result in improved clinical outcomes in asthma patients.

In this study, qHRCT will be performed to measure changes in airway structure and dynamics using qHRCT. To minimize radiation exposure, low-dose radiation scanning protocols will be provided to the participating sites. The low-dose radiation protocols will be tailored to the study-allocated HRCT scanner and will be evaluated by conducting a phantom scan prior to site activation.

The bronchoscopy sub-study will obtain lower airway bronchial brushings and endobronchial biopsies to directly inform about the impact of therapeutic intervention on airway inflammation, epithelial activation and tissue structure, all relevant to the understanding of the impact of therapy on airway remodeling. This will add to the imaging main study which indirectly informs on the airway wall thickness but cannot delineate the components that contribute to the wall dimensions. The bronchoscopy sampling will be undertaken in a sub-population, as it is an invasive procedure, but without this it would not be possible to understand either the biology that was affected and how this relates to the imaging end-point outputs. Furthermore, the bronchoscopic analysis will allow understanding of the structural components within the airway wall, such as airway smooth muscle area/collagen deposition/extracellular matrix composition, that were modified by treatment.

Based on mechanism of action, the efficacy and safety profile, depemokimab is expected to be an effective treatment with an acceptable safety profile in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype.

In addition, throughout the study, each participant will benefit from extensive monitoring of their disease activity and safety including physical examinations, vital signs, laboratory tests, pulmonary function testing and HRCT scans.

2.3.3. Overall benefit-risk conclusion

Taking into account the measures being implemented to minimize 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 asthma with type 2 inflammation characterized by an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the efficacy, and safety of depemokimab is justified in this study with a positive benefit:risk ratio.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

The following tables give the estimand framework for the primary, secondary and the biopsy sub-study objectives.

Table 3 Objectives, endpoints, and estimand

Objective	Endpoint and Estimand
Primary	
To describe the change from baseline (Week 0) in **total mucus plug volume** measured at total lung capacity (TLC) at **Week 26** following treatment with depemokimab.	**Population:** Asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype on medium to high dose inhaled corticosteroids (ICS) plus another asthma controller. **Endpoint:** Change from baseline in total mucus plug volume measured at TLC at Week 26. **Summary Measure:** Mean change from baseline in total mucus plug volume measured at TLC at Week 26. **Treatment Condition:** Depemokimab 100 mg. **Intercurrent Event and Handling strategies** • Treatment switch to any alternative biologic prior to Week 26: **Hypothetical** strategy, i.e., had the intercurrent event (of switching to an alternate biologic) not occurred. • Modification to inhaled asthma medication: **Treatment Policy** strategy, i.e., all participants shall be analysed irrespective of any modification to inhaled asthma medication; • Addition of maintenance OCS use by participants who do not have a baseline maintenance OCS (mOCS): Hypothetical strategy i.e., had the intercurrent event (of using an additional maintenance OCS) not occurred.

Objective	Endpoint and Estimand
Key Secondary	
1. To describe the change from baseline (Week 0) in **airway wall thickness** measured at TLC **at Week 52** following treatment with depemokimab.	**Population:** Asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype on medium to high dose ICS plus another asthma controller. **Treatment Condition:** Depemokimab 100 mg **Endpoint:** Change from baseline in airway wall thickness measured at TLC at Week 52. **Summary Measure:** Mean change from baseline in airway wall thickness measured at TLC at Week 52. **Intercurrent Event and Handling strategies:** • Treatment switch to any alternative biologic: **Hypothetical strategy**, i.e., had the intercurrent event not occurred. • Treatment discontinuation after first dose: **Hypothetical strategy**, i.e., had the intercurrent event (of treatment discontinuation) not occurred. • Modification to inhaled asthma medication: **Treatment Policy** strategy, i.e., all participants shall be analysed irrespective of any modification to inhaled asthma medication; • Addition of maintenance OCS use by participants who do not have a baseline maintenance OCS (mOCS): **Hypothetical** strategy i.e., had the intercurrent event (of using an additional maintenance OCS) not occurred.
Other Secondary	
2. To describe the change from baseline (Week 0) **in airway wall thickness** measured at TLC at **Week 26** following treatment with depemokimab.	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint:** Change from baseline in airway wall thickness measured at TLC at Week 26. **Summary Measure:** Mean change from baseline in airway wall thickness measured at TLC at Week 26. **Intercurrent Event and Handling strategies:** Same as primary estimand.
3. To describe the change from baseline (Week 0) in total **mucus plug volume** measured at TLC at **Week 52** following treatment with depemokimab.	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint:** Change from baseline in total mucus plug volume measured at TLC at Week 52. **Summary Measure:** Mean change from baseline in total mucus plug volume measured at TLC at Week 52. **Intercurrent Event and Handling strategies:** Same as key secondary estimand.
4. To describe the change from baseline (Week 0) in **mucus segment score** measured at TLC at **Week 26** following treatment with depemokimab,	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint:** Change from baseline in the **mucus segment score** at TLC at **Week 26** **Summary Measure:** Mean change from baseline at Week 26 for **mucus segment score** **Intercurrent Event and Handling strategies**: Same as primary estimand.
5. To describe the change from baseline (Week 0) in **mucus segment score** at TLC at	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint:** Change from baseline in **mucus segment score** at **TLC at Week 52**

Objective	Endpoint and Estimand
Week 52 following treatment with depemokimab	**Summary Measure:** Mean change from baseline at Week 52 for **mucus segment score.** **Intercurrent Event and Handling strategies**: Same as key secondary estimand.
6. To describe the change from baseline (Week 0) at **Week 26** in **conventional lung function** measurement	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint:** Change from baseline in **pre- and post-BD FEV_1** at **Week 26** **Summary Measure:** Mean change from baseline in pre- and post-BD FEV_1 at Week 26 **Intercurrent Event and Handling strategies**: Same as primary estimand.
7. To describe the change from baseline (Week 0) at **Week 52** in **conventional lung function** measurement.	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint:** Change from baseline in **pre- and post-BD FEV_1** at **Week 52** **Summary Measure:** Mean change from baseline in pre- and post-BD FEV_1 at Week 52. **Intercurrent Event and Handling strategies**: Same as key secondary estimand.
8. To evaluate the **safety and tolerability** of depemokimab100 mg (SC)	**Population:** Same as primary estimand. **Treatment Condition:** Same as primary estimand. **Endpoint(s):** • Incidence of AEs/SAEs **Summary Measure:** Frequency and proportion of AE and SAE following exposure to Depemokimab. **Intercurrent Event and Handling strategies**: **Participant Discontinuation**: Participants shall be followed for the entire duration of the study (including the follow up period) irrespective of treatment discontinuation. **Treatment Switch**: Participants who switch to another biologic shall be followed for the entire duration of the study (including the follow up period).
Supplementary (Primary Estimand)	
To describe the change from baseline (Week 0) in **total mucus plug volume** measured at total lung capacity (TLC) at **Week 26** following treatment with depemokimab.	**Population:** Asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype on medium to high dose ICS plus another asthma controller. **Endpoint:** Change from baseline in total mucus plug volume measured at total lung capacity (TLC) at Week 26. **Summary Measure:** Mean change from baseline in total mucus plug volume at total lung capacity (TLC) at Week 26. **Treatment Condition:** Depemokimab 100 mg. **Intercurrent Event and Handling strategies:** • Treatment switch to any other biologic. • Modification to inhaled asthma medication. • Addition of maintenance OCS use by participants who do not have a baseline maintenance OCS (mOCS). • Participants experiencing any of the above intercurrent events shall be excluded from the analysis.

Similar to the Supplementary (Primary Estimand) there shall also be a Supplementary estimands for all the secondary endpoints, where Participants who experience any of the intercurrent events shall be analyzed in the same manner as the Supplementary (Primary) Estimand. The supplementary analysis shall be further described in the statistical analysis plan (SAP).

Tertiary/Exploratory	
Objectives	**Endpoints**
1. To describe the change from baseline in airway structure and function at **Week 26** and **Week 52** following treatment with depemokimab, as measured by qHRCT endpoints.	Change from baseline in the following qHRCT endpoints measured at **Week 26** and **Week 52:** • Air trapping at FRC • Specific airway volume at TLC and FRC • Airway wall percentage at TLC
2. To describe the change from baseline (Week 0) on **lung functions** measurements at **Week 26** and **Week 52.**	Change from baseline at **Week 26** and **Week 52** in following lung function endpoints: • Pre- and post-BD FVC • RV/ TLC ratio • Pre- and Post- BD oscillometry (R5-R20, AX, Fres)
3. To describe the change from Baseline (Week 0) at **Week 4, 12,26, 39** and **Week 52** for **patient reported outcomes (PRO)**	Change from baseline in PRO at **Week 4, 12, 26, 39** and **Week 52** as measured by **ACQ-5** score.
4. To describe the change from Baseline (Week 0) at **Week 26** and **Week 52** for **patient reported outcomes (PRO)**	Change from baseline in PRO at **Week 26** and **Week 52** as measured by **SGRQ score.**
5. To describe the change from baseline (Week 0) on additional imaging endpoints at Week 26 and Week 52 following treatment with depemokimab.	Change from baseline at **Week 26** and **Week 52** in following qHRCT endpoints: • Lobar volume at TLC and FRC • Blood vessel distribution (BVX) at TLC • Ventilation/perfusion ratio • Ventilation mapping • Airway radius at TLC • Total mucus plug count at TLC
6. To describe the change from baseline at **Weeks 4, 12 and 39** for conventional lung function measurements **(pre-BD)**	Lung capacity endpoints at baseline, Weeks 4, 12, and 39 • Pre-BD FEV_1 • Pre-BD oscillometry (R5-R20, AX, Fres)
7. To describe the **correlation** between airway structure and function as measured by qHRCT and conventional lung function measurements, cross-sectionally at baseline, Week 26 and Week 52.	qHRCT endpoints at baseline, Week 26 and Week 52 • Airway wall thickness at TLC • Mucus plug metrics at TLC (volume, count, and score) • Air trapping at FRC Lung capacity endpoints at baseline, Week 26 and Week 52: • Post-BD FEV_1 • Post BD FVC • RV/TLC ratio • Post-BD oscillometry (R5-R20, AX, Fres)

Tertiary/Exploratory	
Objectives	**Endpoints**
8. To describe the **correlation** between changes from baseline (Week 0) in airway structure and function as measured by qHRCT at Week 26 and change from baseline in conventional lung function measurements at Week 52.	Change from baseline at Week 26 of qHRCT endpoints: • Airway Wall Thickness at TLC • Mucus plug metrics at TLC (volume, count, and score) • Air trapping at FRC Change from baseline at Week 52 of following lung capacity endpoints: • Post-BD FEV_1 • Post-BD FVC • RV/TLC ratio • Post-BD oscillometry (R5-R20, AX, Fres)
9. To describe the relationship between changes from baseline (Week 0) in airway structure and function at Week 26 and Week 52, as measured by qHRCT endpoints, and PRO between Week 0, Week 26 and Week 52.	• Change from baseline in the qHRCT endpoints at Week 26 and Week 52. • Patients reported outcomes at baseline, Week 26 and Week 52 as measured by ACQ-5 and SGRQ total score.
10. To describe clinical Remission Status at Week 52 using the 3- and 4-point definitions, respectively.	Clinical Remission Status at Week 52 defined as: 4-point definition: • Maintenance and systemic /oral corticosteroid free; and • Exacerbation free over 52 weeks; and • Asthma Control Questionnaire-5 (ACQ-5) score ≤1.5 at Week 52; and • change from baseline in FEV_1 ≥0 ml at Week 52. 3-point definition: • maintenance and systemic/ oral corticosteroid free; and • Exacerbation free over 52 weeks; and • Asthma Control Questionnaire-5 (ACQ-5) score ≤ 1.5 at Week 52.
11. To describe the relationship between airway structure and function and clinical remission status at Week 52.	• Change from baseline in qHRCT endpoints at Week 52. • Clinical remission status at Week 52 utilizing 3- and 4-point definitions
12. To describe the change from baseline (Week 0) in aerosol deposition at Week 26 and Week 52 following treatment with depemokimab, as measured by qHRCT.	Change from baseline at Week 26 and Week 52 of qHRCT aerosol deposition (micrograms).
13. To describe the change from baseline in post-BD FEV_1 at Week 26 and Week 52 stratified by mucus segment score at baseline	Change from baseline in post-BD FEV_1 at Week 26 and Week 52 stratified by baseline mucus segment score.

Tertiary/Exploratory	
Objectives	**Endpoints**
(mucus segment score between 0 - 4 and mucus segment score of 5 and above).	
14. To characterize the spatial-temporal relationship of mucus plugs following treatment at Week 26 and Week 52	Change from baseline at Week 26 and Week 52 of mucus plug metrics (e.g. size and shape) located in different lung regions (e.g. lobar locations).
15. To evaluate the effect of depemokimab over time on exploratory biomarkers.	Change from baseline to Week 52 in biomarker levels.
16. To describe the change from baseline in FeNO levels at week 26, Week 39 and Week 52 in response to depemokimab.	Change from baseline to Week 52 in FeNO levels.
17. To describe the change from baseline in nasal brushing transcriptomics at week 26, Week 39 and Week 52 in response to depemokimab.	Change from baseline to week 52 in nasal transcriptomics.
18. To evaluate the additional safety of depemokimab100 mg (SC)	• Change from baseline in ECG values at Week 26 and Week 52. • Change from baseline in vital signs (pulse rate, systolic and diastolic blood pressure, body temperature) at Week 26 and Week 52. • Change from baseline in laboratory parameters (including hematological and clinical chemistry parameters) and hepatobiliary laboratory abnormalities at discrete timepoints during the 52-week period.
Airway bronchoscopy sub-study	
1. To explore the mechanisms of action of depemokimab over time.	Change from baseline to Week 39 in disease biomarkers from bronchial brushing and bronchial biopsies.
2. To describe the change from baseline in post bronchodilator FEV_1 and Oscillometry endpoints at Week 39.	Change from baseline in post-BD FEV_1 and post BD oscillometry endpoints at Week 39 (R5-R20, AX, Fres).

ACQ= Asthma Control Questionnaire; AE= adverse event; AX= area of reactance; BD= bronchodilator; BVX= Blood vessel distribution; FeNO= Fractional Exhaled Nitric Oxide; FEV_1= forced expiratory volume in 1 second; Fres= resonant frequency; FRC= Functional Residual Capacity; FVC= forced vital capacity; HRQoL= health related quality of life; ICS= Inhaled corticosteroids; NA= Not applicable; OCS= oral corticosteroid; qHRCT: quantitative HRCT; RV= residual volume; SABA= short-acting beta-agonist; SAE= serious adverse event; SGRQ= St George's Respiratory Questionnaire; TLC= Total lung capacity.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 3b, interventional multicenter study of depemokimab in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype utilizing qHRCT methods to assess lung structure and function based on detailed 3D models of the airways with direct comparison of images taken at baseline (Week 0), between Week 24 to Week 26 and between Week 50 to Week 52 (Figure 1), along with a nested bronchoscopic direct airway sampling sub-study. The study schematic is provided in Section 1.2.

The study will comprise a single-arm, open label study in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype who are uncontrolled on medium to high dose ICS plus at least one other controller. A total upfront sample size for this study is planned to be 103 participants. The total sample size of the trial may increase or remain the same depending on the interim values based on the sample size re-estimation (SSRE) procedure. However, the maximum sample size shall be restricted to 150. The study will consist of three periods which includes screening period, study intervention period and follow up period. The screening Visit will occur within 4 weeks prior to the administration of study intervention (can be extended up to maximum of 8 weeks if participant experiences a clinically significant exacerbation during the screening period). Participants who meet all the eligibility criteria at screening visit will sign the informed consent form (ICF) for participation into the study prior to the initiation of any study related assessments. Eligible participants from selected designated sites will be invited to participate in a bronchoscopy sub-study. Participants who meet eligibility criteria for bronchoscopy sub-study will sign the separate ICF for participation into bronchoscopy sub-study. During screening visit, the participant's compliance with study related procedures and wash out of prohibited medications (Table 5) will be assessed. Albuterol/salbutamol is permitted throughout the study but should be withheld for at least 6-hours and long-acting beta 2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), fixed dose combinations of ICS/LABA or ICS/LABA/LAMA for ≥12 hours prior to all spirometry and HRCT assessments, if possible. After screening period, all participants who continue to meet study inclusion criteria will receive the first dose of depemokimab 100 mg SC at Week 0 (Visit 1) and second dose at Week 26 (Visit 4) as outlined in the SoA (Section 1.3) and Table 1.

The maximum time participants will spend in each study period is summarized below:

- Screening period– up to 4 weeks (or up to 8 weeks if participant experiences a clinically significant exacerbation during the screening period).
- Treatment period – 52 weeks
- Safety follow-up period- 9 weeks (63 days post EoS or ED visit).

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

A participant is considered to have completed the study if the participant has completed all periods of the study including visit at Week 61, regardless of whether the second dose of study intervention (at Week 26) was received.

In the event that a participant discontinues the study, the participant should be encouraged to complete an ED visit 26 weeks after last dose of study intervention and a safety follow-up visit 35 weeks after the last dose of study intervention.

If a participant is permanently discontinued from study intervention after administration of first dose and before the second dose at Week 26, third HRCT scan (between Week 50 to Week 52) will not be performed.

If a participant switches to another biologic therapy after administration of study intervention, the subsequent HRCT scan at Week 26 (if switch happens prior to second dose at Week 26) or Week 52 (if switch happens post second dose at Week 26) will not be performed.

The HRCT scan at the ED visit will be performed based on the participant's consent and the Principal Investigator's (PI's) clinical judgement with appropriate consultation with the Medical Monitor (MM), if required.

For each participant enrolled, the duration will be approximately 65 Weeks which includes screening period (up to 4 weeks prior to the administration of study intervention), 52 weeks (Visit 1 to Visit 6) of study intervention period and 9 weeks of follow up period.

Even if the main study is discontinued due to futility, participants selected for the bronchoscopy sub-study will continue with bronchoscopy sub-study with separate SoA provided in Section 1.3 (Table 2). In this case all the enrolled main study participants (including participants in interim analysis) will be required to complete an ED and follow-up visits.

4.1.1. Screening period

Details about the study and procedures will be explained through the informed consent process. Informed consent should be taken on the day of the Screening Visit and must be completed prior to initiating any study-related procedures. A separate informed consent will be obtained for participation into the bronchoscopy sub-study. During screening visit, participant's compliance with the study related procedures and wash-out of prohibited medications (Table 5) will be assessed. Albuterol/salbutamol is permitted throughout the study but should be withheld for 6-hours and LABAs, long-acting muscarinic antagonists (LAMAs), fixed dose combinations of ICS/LABA or ICS/LABA/LAMA for ≥12 hours prior to all spirometry and HRCT assessments, if possible. Participant eligibility will be assessed, as outlined in the SoA (Section 1.3; Table 1). Data regarding past biologic use for the treatment of asthma, including participation in other clinical studies will be collected. Parasite screening will be performed in regions with high-risk or for participants who have visited a high-risk

region in the past 6 months. All screening procedures should be completed within 4 weeks (8 weeks for participants who have a clinically significant asthma exacerbation during the screening period) prior to administration of study intervention (Day 1) and must be performed as specified in the SoA (Section 1.3; Table 1)

Participants who will be part of bronchoscopy sub-study shall undergo bronchoscopic airway sampling prior to the initiation of treatment with depemokimab to obtain airway samples to evaluate the tissue cellular and structural impact of depemokimab therapy and to relate these findings to those obtained from the qHRCT assessments.

If a participant experiences an exacerbation within 4 weeks prior to screening, their screening visit should be rescheduled to a time when at least 4 weeks have lapsed from the time of stopping their exacerbation treatment.

4.1.2. Treatment period

Participants who continue to meet the eligibility criteria at screening period will enter the 52-week treatment period and will receive the first dose of depemokimab 100 mg SC at Week 0 (Visit 1) and second dose at Week 26 (Visit 4). Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-dose (both at week 0 and at Week 26).

Study visits will occur at Week 0, Week 4, Week 12, Week 24 to Week 26, Week 36 to Week 39 and Week 50 to Week 52. The study intervention period will conclude with the End of Study (EoS) Visit at Week 50 to Week 52 (Visit 6). Visits and assessments will be performed as described in the SoA (Section 1.3; Table 1). An interim analysis will be performed when 62 (which is 60% of enrolled sample size of 103) enrolled study participants complete Week 26 efficacy assessment. The primary efficacy assessments for main study will be performed at Week 26 and final (also called key secondary) efficacy assessment at Week 52.

Participants who will be part of the bronchoscopy sub-study will undergo bronchoscopic airway sampling at Week 39 to evaluate cellular and mechanistic effects in response to the treatment with depemokimab. Airway samples will be obtained to evaluate the tissue cellular and structural impact of depemokimab therapy and to relate these findings to those obtained from the qHRCT assessments.

4.1.3. Follow-up period

Participants will complete a Follow-up visit/call 9 weeks after the EoS/ED Visit; this visit/call will capture adverse event (AE)/serious adverse event (SAE) assessments and a urine pregnancy test result. If the participant is not able to complete EoS/ED visit, a follow-up visit should be performed 35 weeks after the last dose.

At the end of the Follow-up visit/call, participants will be prescribed appropriate alternative asthma therapy at the physician’s discretion, if required.

Follow-up- period assessments will be performed as described in the SoA (Section 1.3; Table 1)

4.2. Scientific rationale for study design

Population: This study is designed to evaluate the effect of sustained IL-5 inhibition by depemokimab on airway structure and function and mucus plugs in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype. The relationships between airway dynamic measurements and disease-specific PROs will also be explored, aiming to identify a link between PROs with functional aspects at baseline, as well as the impact of treatment on these important PROs. Additionally, to further evaluate the impact of treatment, clinical remission status will also be assessed

Participants must have asthma with type 2 inflammation indicated by an eosinophilic phenotype and with a history of 2 or more exacerbations in the prior year and on medium to high dose ICS plus another controller (see inclusion criterion #2, Section 5.1). Results from the Phase 3a, SWIFT 1 and SWIFT 2 studies showed that depemokimab, administered every 6 months for 52 weeks, was effective in this population [Jackson, 2024].

Blood eosinophil count screening: There is evidence to demonstrate that eosinophilia is linked to mucus plug formation in asthmatic patients, leading to airflow obstruction. Therefore, to evaluate the impact on mucus secretions, a screening blood eosinophil count threshold of ≥300 cells/µL or ≥300 cells/µL in the 3 months prior to the screening visit has been selected as a criterion to identify participants defined as having an eosinophilic phenotype and likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous studies with depemokimab and mepolizumab. A threshold entry blood eosinophil level of 300 cells/µL has been selected, which is higher than the randomized control trials entry criteria, to enrich for those with mucus plugging, as the presence of mucus plugs has been shown to be linked to the intensity of eosinophilic inflammation [Dunican, 2018; Tang, 2022]. As sputum eosinophils are not measured in this study but are reflected by FeNO measures, due to the positive correlation between these measures [Gao J, 2018], and FeNO thresholds of ≥21ppb have been found to better predict sputum eosinophilia than lower levels [Alvarez-Puebla, 2015], a threshold entry criteria of FeNO ≥25ppb has also been included. This is additional to the blood eosinophil threshold, to enrich for those patients with severe asthma likely to have mucus plugging evident on their CT scans.

Primary efficacy endpoint: A primary efficacy endpoint of change from baseline in total mucus plug volume measured at TLC at Week 26 has been selected as a robust and clinically relevant measure of the direct benefit of depemokimab in asthmatic patients with type 2 inflammation characterized by an eosinophilic phenotype.

Mucus plugging is common and often persistent in asthmatic patients with eosinophilic inflammation. Mucus plugs, which are visible in most patients with severe asthma on CT scans, may have a profound effect on pulmonary function and the development of exacerbations [Dunican, 2018; Dunican, 2021]. Since, eosinophils are the major source of the Charcot Leyden crystals (CLC) in mucus plugs, CLC along with other eosinophil products, such as eosinophil peroxidase, are considered responsible for the change in mucus properties underlying mucus plug formation, depletion of eosinophils should lead to a reduction in mucus plugging, resulting in improvement of airway patency and airflow distribution. Imaging of bronchial segments and scoring of mucus plugging is an emerging research tool in respiratory disease [Oguma, 2021]. In addition to the radiologist-derived mucus segment score, total volume (mL) and total number (counts) of fully occluded mucus plugs in the airway can be derived from HRCT images offering further insights to mucus burden in asthmatic patients [Huang, 2024].

Key secondary efficacy endpoint: A key secondary efficacy endpoint of change from baseline (Week 0) in airway wall thickness measured at TLC at Week 52 has been selected. The bronchial wall thickening resulting from inflammation and airway remodeling is a well-described feature in asthma. Previous studies have shown that anti-IL-5 related biologic therapy may impact the extracellular matrix in the reticular basement membrane and the airway smooth muscle mass in the airway wall [Flood-Page, 2003; Chachi, 2019], findings that were confirmed in clinical practice with mepolizumab 100 mg SC prescribed for severe asthma [Domvri, 2024].

Diagnostic Method: In this study, HRCT will be used as a diagnostic tool to detect changes in mucus plugging and airway wall thickness. Quantitative HRCT-derived measurement is an important non-invasive tool to detect changes in airway wall thickness that may reflect a reduction in airway remodeling. Earlier research has already demonstrated the responsiveness of airway wall thickness to therapeutic interventions using HRCT imaging in asthma [Hoshino and Ohtawa, 2012; Hoshino and Ohtawa, 2013; Tajiri, 2014; Tsubokawa, 2023]. In addition, correlations were found with reductions in sputum eosinophilia [Hoshino and Ohtawa, 2012], and pulmonary function [Hoshino and Ohtawa, 2012; Hoshino and Ohtawa, 2013]. The time course of evident resolution of mucus plugging is likely to be more rapid than the change in airway wall thickening, which requires reversal of established tissue remodeling. As such, GlaxoSmithKline (GSK) has designed the current study to assess the impact of depemokimab, on airway structure and function, using qHRCT at two different follow-up timepoints. Leveraging these two follow-up timepoints over the treatment course of depemokimab allows imaging to quantify the effectiveness of the first dose of depemokimab on mucus plugging reduction (Week 26 time-point, primary outcome), and the long-term effects that may contribute to disease modification through airway remodeling reversal (Week 52 time-point, key secondary outcome) with associated lung function improvements, particularly those relating to small airways disease that are not well reflected by standard spirometry.

Single Arm Study Design: Findings from a recently conducted Phase 4 imaging study involving dupilumab in similar asthmatic patients, with moderate-to-severe asthma characterized by type 2 inflammation with an eosinophilic phenotype, reported an increase in mucus score and no significant improvement in mucus volume at Week 24 for participants who were assigned to the placebo group. Conversely, there was significant improvement in mucus score and mucus volume for participants treated with dupilumab 300 mg as compared to placebo [Porsbjerg, 2024]. In another phase 2, exploratory, double-blind study involving tezepelumab in a comparable patient population with moderate-to-severe asthma with eosinophilic phenotype, no improvement in mucus plug score for participants randomized to the placebo group was reported, unlike the active treatment group [Nordenmark, 2023].

As previous clinical data from similar studies indicates that asthma patients in the placebo arm did not experience any meaningful improvements in the clinical outcomes being evaluated, subjecting participants in our study to ionizing radiation while randomized to the placebo group, without the potential for benefit of biologic treatment where it is warranted on account of inadequate disease control, would be unethical.

Also, as multiple biologics are approved and available as treatment for this patient population, randomizing suitable patients to a placebo group would not be ideal. Therefore, a single arm design was conceptualized for this study.

4.2.1. Participant input into design

- No participant engagement activity will be performed for this study.

4.3. Justification for dose

Based on a single-dose FTIH study in mild to moderate asthma patients with a blood eosinophil count ≥200 cells/µL, using model-informed drug development principles, GSK identified that the dose and dosing frequency of depemokimab that matches Phase 3 mepolizumab-like PD response (blood eosinophil count suppression) is 100 mg SC once every 26 weeks [Ortega, 2016; Chupp, 2017]. Since, depemokimab targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils as mepolizumab, via the same IL-5 neutralization, was expected to generate a comparable clinical efficacy and safety profile in the selected participant population. Therefore, the selected dosing regimen for the SWIFT studies of 100 mg SC once every 26 weeks was expected to result in a positive benefit-risk.

The pivotal Phase 3 SWIFT-1 and SWIFT-2 studies in asthma assessed depemokimab 100 mg SC once every 26 weeks administered over 52 weeks [Jackson, 2024]. In the depemokimab treatment groups, suppression of blood eosinophil counts was apparent from Week 2 (the first timepoint measured) and was maintained throughout the entire 52-week dosing interval tested. In these studies, the suppression of eosinophils in the depemokimab groups was accompanied by a statistically significant reductions in the annualized rate of clinically significant exacerbations. Thus, the phase 3 program of depemokimab confirmed 100 mg every 6 months as the appropriate dose for asthma.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including visit at Week 61, regardless of whether the second dose of study intervention (at Week 26) was received.

The EoS is defined as the date of the last participant last visit related to secondary endpoints (Week 52) regardless of whether the second dose of study intervention (at Week 26) was received. If EoS is not equal to last subject last visit (LSLV), it must be achieved no later than 8 months after LSLV.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment 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:

- Participants must be ≥18 years of age, at the time of signing the informed consent form (ICF). **INC #1**
- Documented physician diagnosis of asthma for ≥2 years as per the National Heart, Lung, and Blood Institute guidelines (NHLBI, 2020) or GINA guidelines [GINA, 2024] along with the following: **INC #2**
    - An eosinophilic phenotype as evidenced by a blood eosinophil count of ≥300 cells/μL at screening or a documented history of blood eosinophil count ≥300 cells/μL within 3 months prior to screening.
    - Exhaled nitric oxide (FeNO) measure of ≥25ppb recorded at screening.
    - Previously confirmed history of ≥ 2 exacerbations requiring treatment with systemic corticosteroid (SCS; IM, IV, or oral), in the 12 months prior to screening, despite the use of medium to high dose ICS.

Note: For participants receiving maintenance SCS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater.

- Uncontrolled asthma indicated by ACQ5 > 1.5 recorded at screening. **INC #3**
- Persistent airflow obstruction as indicated by pre-bronchodilator FEV_1 <80% predicted (GLI 2012) and recorded at screening. **INC #4**
- A well-documented requirement for regular treatment with medium or high dose ICS (in the 12 months prior to screening with or without maintenance OCS). **INC #5**

Note: The maintenance ICS dose after actuation must be≥250 mcg fluticasone propionate hydrofluoroalkane prescribed dose, or clinically comparable [GINA, 2024].

- Current treatment with at least one additional asthma controller medication, besides ICS, for at least 3 months [e.g., LABA, LAMA, leukotriene receptor antagonist (LTRA), or theophylline]. **INC #6**
- **Male or female.**

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- **Male Participants**: No additional requirements for male participants. **INC#7**
- **Female Participants:** A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 (Appendix 4: Contraception and barrier guidance)

    OR

  – Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 14 days prior to and during the study intervention period and for at least 35 weeks after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention. **INC#8**

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention (see Section 8.3.5 Pregnancy testing).
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
  - Additional requirements for pregnancy testing during and after the study intervention are located in Section 8.3.5.
  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

    Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.

- Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. **INC#9**

5.1.1. Inclusion criteria for the bronchoscopy substudy

Participants are eligible to be included in the bronchoscopy sub-study only if all of the following criteria apply (in addition to the inclusion criteria provided in section 5.1):

- Participants who sign Informed Consent for biopsy sub-study. **INC #10**
- Participants with post-bronchodilator $FEV_1 \geq 50\%$ predicted. **INC #11**
- Participants with no known increased risk for bleeding including: **INC #12**
  - No history of easy bleeding, bruising or known bleeding diathesis
  - No current anticoagulant and antiplatelet therapy
  - No acetylsalicylic acid use within 2 weeks of the planned procedure
  - Normal screening platelet count
- Participants with no specific contraindication to bronchoscopy with endobronchial biopsy in the opinion of the investigator. **INC #13**
- No history of allergic reaction to local anesthesia or general anesthetic agent, which ever relevant to the procedure being performed. **INC #14**

5.2. Exclusion criteria

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

5.2.1. Medical conditions

- 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 a history of lung cancer. Participants with current diagnoses of emphysema or chronic bronchitis (COPD other than asthma) are excluded. **EXC#1**
- 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. **EXC#2**
- Participants who developed an exacerbation within 4 weeks before screening. **EXC#3**

Note: participants may reschedule their screening visit such that the exacerbation is resolved and at least 4 weeks have lapsed after the last dose of any medication to treat the exacerbation.

- Participants with a known, pre-existing parasitic infestation within 6 months prior to screening unless treated and evidenced to have been resolved. **EXC#4**
- A known immunodeficiency (e.g. human immunodeficiency virus- HIV), other than that explained by the use of CSs taken as therapy for asthma. **EXC#5**

- A current malignancy or previous history of cancer in remission for less than 12 months prior to screening. **EXC#6**

Note: Participants who had localized carcinoma of the skin which was resected for cure will not be excluded.

- Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, psychiatric, renal, gastrointestinal, hepatic, hematologic or any other system abnormalities that are uncontrolled with standard treatment. **EXC#7**
- Participants with current diagnosis of vasculitis. **EXC#8**

Note: Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrollment.

5.2.2. Prior/Concomitant/Diagnostic therapy

- Participants who have received mepolizumab, reslizumab, or benralizumab within 12 months prior to screening or who have a previous documented failure with anti-IL-5/5R therapy. **EXC#9**
- Participants who have received omalizumab (Xolair), dupilumab (Dupixent) or tezepelumab (Tezspire) within 12 months prior to the screening. **EXC#10**
- Participants who have received any mAb within 5 half-lives of the drug prior to the screening. Authorized treatments for COVID-19 are permitted. **EXC#11**
- Participants who have received treatment with an investigational drug within the past 30 days or 5 terminal phase half-lives of the drug whichever is longer, prior to the first dose of study intervention (this also includes investigational formulations of marketed products). **EXC#12**

5.2.3. Prior/Concurrent clinical study experience

- Previously participated in any clinical study with biologic treatments for asthma (e.g., omalizumab, mepolizumab, dupilumab, reslizumab, benralizumab, other monoclonal antibodies (including Tezepelumab) or depemokimab and received study intervention (including placebo) within 12 months prior to the first dose of study intervention. **EXC#13**

5.2.4. Other exclusion criteria

- A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to the first dose of study intervention. **EXC#14**
- Current smokers or former smokers with a smoking history of ≥20 pack years (number of pack years = [number of cigarettes per day/20] x number of years smoked) and vapers. **EXC#15**

Note: A former smoker is defined as a participant who quit smoking at least 6 months prior to screening.

- Participants with allergy/intolerance to a mAb or biologic or any of the excipients of depemokimab presented in Table 4. **EXC#16**
- Participants who are pregnant or breastfeeding. **EXC#17**

Note: Participants should not be enrolled if they plan to become pregnant during the time of study participation.

- Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations. **EXC#18**
- Participants who:
  - have occupational ionizing-radiation exposure exceeding 10 mSV over 3 years as documented with a dosimeter.
  - have been exposed to elevated ionizing radiation from research imaging studies, for example:
    - Participation in a research study with a single positron emission tomography scan in the past 3 years.
    - Participation in a research study with 2 or more CT scans in the past 3 years in the following anatomical regions: chest, abdomen, cardiac, or spine. **EXC#19**

Note: Calculation of prior radiation exposure should exclude imaging done for clinical care. If documentation of prior radiation exposure is not available, verbal communication from the participant will be acceptable and will be documented in the source notes. Investigator judgement should be applied to determining risk of prior radiation exposure.

- Presence of metal objects that may interfere with chest CT quantification including presence of a cardiac pacemaker, defibrillator, metal prosthetic heart valve, metal projectile or metal weapon fragment (bullet, shrapnel, shotgun shot) or metal shoulder prosthesis. **EXC#20**
- Evidence of clinically significant abnormality in the hematological, biochemical or urinalysis screen at screening (Visit 0), as judged by the investigator. **EXC#21**

5.2.5. Liver safety exclusion criteria

- Alanine aminotransferase (ALT) >2xULN. **EXC#22**
- Total bilirubin >1.5xULN; For participants with Gilbert's syndrome can be included with total bilirubin >1.5xULN as long as direct bilirubin is ≤1.5xULN. **EXC#23**
- Cirrhosis or current unstable liver or biliary disease as per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice. **EXC#24**

Note: Stable non-cirrhotic chronic liver diseases (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B [in whom Hepatitis D has been excluded] or C) are acceptable if participant otherwise meets inclusion criteria.

5.2.6. Cardiac safety exclusion criteria

- 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, or in the 12-lead ECG machine read at Visit 1. **EXC#25**
- Participants are excluded if an abnormal ECG finding from central over-read of the 12-lead ECG conducted at Screening Visit is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator. **EXC#26**

5.2.7. Exclusion criteria for the bronchoscopy sub-study

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

- Participants who are currently on maintenance OCS at the time of screening. **EXC#27**

5.3. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the consolidated standards of reporting trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAE. If a participant experiences an exacerbation within 4 weeks prior to screening, the screening visit may be rescheduled to a later time when at least 4 weeks have lapsed since the discontinuation of any exacerbation treatment.

5.4. Criteria for temporarily delaying enrollment/administration of study intervention

Participants who experience a clinically significant asthma exacerbation between the screening visit (Visit 0) and study intervention visit (Visit 1) should receive treatment for their exacerbation; have their study intervention administration visit delayed and remain in the screening period (up to 8 weeks) so that Visit 1 takes place at least 4 weeks after the discontinuation of exacerbation treatment.

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

A participant who is not eligible to continue in the study at the end of the screening period, should be considered a screen failure but may be rescreened after consultation with the Medical Monitor (Section 5.3).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

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

An overview of study intervention is provided in Table 4.

Table 4 Study intervention(s) administered

Study intervention label	GSK3511294	
Study intervention name	Depemokimab	Albuterol/ Salbutamol
Intervention description	Depemokimab is a humanized IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Depemokimab liquid drug product will be supplied by GSK in a Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex-free rubber plunger). The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each Syringe enables SC delivery of 100 mg Depemokimab in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, EDTA, water for injection and polysorbate 80.	Albuterol/Salbutamol is a white crystalline powder intended for oral inhalation only.
Type	Biologic	Drug
Dose formulation	Sterile liquid formulation in single-use prefilled syringe	Metered dose inhaler
Unit dose strength	100 mg/mL; 1.0 mL (deliverable)	100 mcg/actuation (deliverable)
Dosage level	100 mg once every 26 weeks (Week 0 and Week 26)	As needed, 1-2 inhalations repeated every 4 to 6 hours, not to exceed 12 inhalations in 24 hours

Route of administration	SC injection	Oral inhalation only
Use	IMP	Rescue medication
Non-IMP	Not Applicable	Not Applicable
Authorized AxMP/Unauthorized AxMP	Not Applicable	Authorized AxMP
Sourcing	Provided centrally by the Sponsor	Sourced or reimbursed for all centers by the Sponsor partner as required per country requirement
Packaging and labeling	Study Intervention will be provided as a prefilled syringe in a safety syringe device. Each syringe will be labelled as required per country requirement.	Packaging and labelling will be as required per country requirement.

AxMP= Auxiliary medicinal product; IMP = Investigational medicinal product; Non-IMP = Non-investigational medicinal product. PFS= prefilled syringe; SC= Subcutaneous.

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. The devices used in the study are representative of the devices
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) are sourced from Becton Dickinson. The pre-filled syringe is filled with study intervention (Depemokimab) and assembled at GSK, Barnard Castle.
- The safety syringe device components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.
- The Instruction for use (IFU) of the injection device will be provided. The instructions were developed and optimized as a result of formative human factors studies for depemokimab.
- All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.4.10) and appropriately managed by GSK.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) 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 authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, the head of the medical institution (where applicable), or authorized site staff 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 interventions are provided in the pharmacy manual or other specified location.
- 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.
- If allowed by country regulation/ethics, study intervention (including rescue study medication and ancillary supplies related to IMP administration) can be shipped from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will provide operational details.
- Specific procedures and requirements related to site staff responsibility, oversight and processes related to DTP are provided in the Pharmacy Manual.

6.3. Assignment to study intervention

As this is a single arm, open-label study, the study treatment will be directly assigned to all participants.

6.4. Blinding, masking

As this is an open-label study, blinding and masking are not applicable.

6.5. Study intervention compliance

Doses of depemokimab 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 eCRF.

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 depemokimab, 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

No dose modifications of the study treatment are allowed during the study.

6.7. Continued access to study intervention after the end of the study

There are no plans to provide access to study intervention once the study is concluded.

6.8. Treatment of overdose

The dose of depemokimab that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 (refer to the current IB [GSK Document Number: RPS-CLIN-132006]), single SC doses of depemokimab up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS will enable the delivery of a single dose of study intervention (see Section 6.1). In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the 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 depemokimab.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 35 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. Prior and concomitant therapy

At 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 maintenance OCS and background asthma medications)

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 **INC #5** and **INC #6**, Section 5.1). It is recognized that in a year-long study, changes may need to be individualized if clinically crucial for a participant, particularly maintenance OCS reduction. The investigator is encouraged to discuss any cases with the Medical Monitor before initiating changes to a participant's maintenance asthma medication.

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

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

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

6.9.2. Prohibited Medications and Non-Drug Therapies

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

Table 5. Prohibited medications and Washout

Medication	Washout Time Prior to Screening Visit
Investigational non-biologic drugs	1 month or 5 half-lives whichever is longer
Omalizumab (Xolair), dupilumab (Dupixent), Mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), benralizumab (Fasenra), Other monoclonal antibodies (including Tezepelumab [Tespire])	12 months
Experimental anti-inflammatory drugs (non-biologicals)	3 months

6.9.3. Rescue medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication (auxiliary medication) throughout the study. Albuterol/salbutamol will be sourced or reimbursed by the Sponsor partner for all centers.

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

Participants on maintenance and reliever therapy (MART regimen) and use of low dose ICS-formoterol as rescue medication will not be allowed during the study.

Although the use of rescue medications (SABAs e.g., Albuterol or Salbutamol) 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 all spirometry and HRCT assessments. The date and time of dispensing rescue medication as well as the name and dosage regimen must be recorded in eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF as specified below:

Reasons
AE
Lack of efficacy
Lost to follow-up
Participant reached protocol-defined stopping criteria
Physician decision
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Sponsor terminated study intervention
Withdrawal by participant
Other
Death

AE = Adverse event.

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

- Liver event: Meets any of the protocol-defined liver event stopping criteria (Refer to the Section 7.1.1.
- Cardiac changes: Meets any of the protocol defined QTc stopping criteria (Refer to the Section 7.1.2.
- Pregnancy: Positive pregnancy test (Refer to Section 8.3.5 and Section 8.4.6 for details on pregnancy testing).
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (Refer to Section 10.10 [Appendix 10] for Anaphylaxis Criteria).
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (Refer to the Section 7.4).

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

- The investigator will make every effort to encourage the participant to remain in the study and to continue with all remaining study visits.
- The primary reason for premature 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. 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, ED Visit should be conducted according to the SoA (Section 1.3).

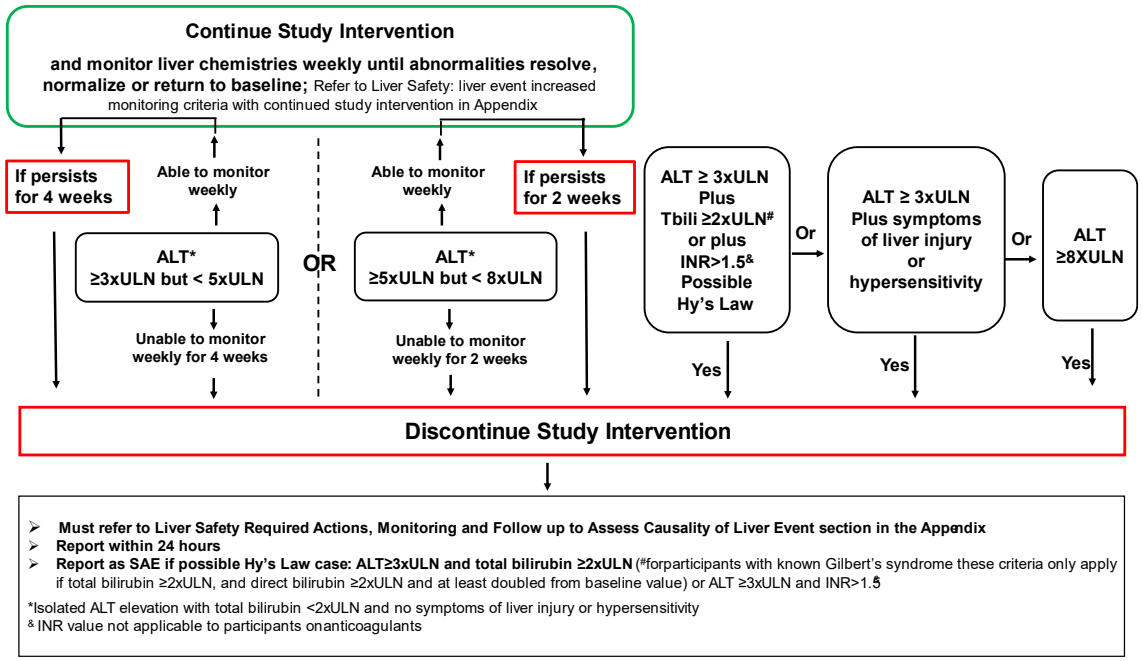
7.1.1. Liver event stopping criteria

Liver event stopping criteria with increased monitoring and required follow-up assessments have been designed to assure participant safety and evaluate liver event etiology.

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

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

Figure 2. Liver event study intervention stopping criteria and liver event increased monitoring with continued study intervention algorithm.



ALT = Alanine transaminase; INR = International normalized ratio; SAE = Serious adverse event; ULN = Upper limit of normal, Tbili = Total bilirubin.

Refer to Section 10.5.1 for required liver safety actions, monitoring and follow-up to assess causality of liver event.

Participants who do not meet protocol-specified liver event stopping criteria but met protocol-defined increased monitoring criteria (see algorithm above) may continue study intervention with increased (weekly) liver chemistry monitoring. Refer to Section 10.5.2 for required liver event increased monitoring criteria with continued study intervention.

7.1.2. QTc stopping criteria

- 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.
- If either of the criteria mentioned below are met, the participant(s) must be discontinued:
  - 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 from Visit 1 (on the day of study intervention administration) should be used as baseline QTcF value for any changes from baseline calculations during the study. At Visit 4 (Week 26), 12-lead ECG machine read values should be used and assessed against QTc Stopping Criteria, before administration of the study intervention. The 12-lead ECG central over-read values should be used at the remaining visits.

7.1.3. Temporary discontinuation

Not applicable

7.1.4. Rechallenge

Not applicable

7.1.4.1. Study intervention restart or rechallenge after liver event stopping criteria are met

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

7.2. Participant discontinuation/withdrawal from the clinical study

A participant may withdraw from the study at any time at the participant’s own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of withdrawing from the study, if possible, an ED visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. The HRCT scan at the ED visit will be performed based on the participant's consent and the PI’s clinical judgement with appropriate consultation with the MM, if required.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be available for the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- Participants who prematurely withdraw from the study should attend:
  - ED Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
  - Follow-up visit/call, 35 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.

The primary reason for participant withdrawal from the study will be documented in the eCRF based on the list below:

Reasons
AE
Lack of efficacy
Lost to follow-up
Participant reached protocol-defined stopping criteria
Physician decision
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Withdrawal by participant
Other
Death

AE = Adverse event.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status information of the participant within legal and ethical boundaries for all participants, including those who did not get study intervention. Public sources may be searched for vital status information. If the vital status of the participant is determined as deceased, this will be documented along with other relevant study information. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

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

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

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

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

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

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

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

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

Unscheduled PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [ANA], anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3; Table 1). Protocol waivers or exemptions are not allowed.
- 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. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of “screen failure.”
- Procedures conducted as part of the participant’s routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the timeframe defined in the SoA (Section 1.3; Table 1).

- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- The maximum amount of blood collected from each participant will not exceed the National Institutes of Health (NIH) limit of 550 mL in an 8-week period.
- Repeat or unscheduled samples may be taken based on the investigator's discretion for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the study participants, and to determine if the study participants are truly representative of the impacted population.

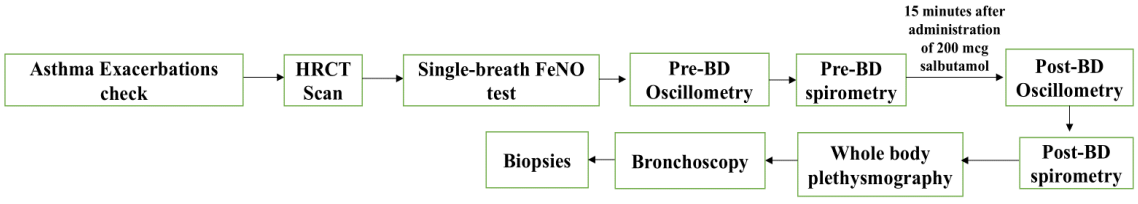
8.1.2. Medical history

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

8.2. Efficacy assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

Assessments are recommended to be conducted in the order as specified below:



Note: The above order of efficacy assessments will be followed at Visit 1, Visit 4, and Visit 6. At Visit 5, bronchoscopy and biopsies will be performed after lung function 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 hospitalization and/or Emergency Department visit[1].

[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 EoS Visit or Follow-up Visit if applicable.

8.2.3. Clinical Remission

Clinical remission status will be evaluated using both the 3- and 4-point definitions, as provided below:

4-point definition:

- Maintenance and systemic /oral corticosteroid free; and
- Exacerbation free over 52 weeks; and
- Asthma Control Questionnaire-5 (ACQ-5) score ≤1.5 at Week 52; and
- Change from baseline in FEV_1 ≥0 ml at Week 52.

3-point definition:

- Maintenance and systemic/ oral corticosteroid free; and
- Exacerbation free over 52 weeks; and
- Asthma Control Questionnaire-5 (ACQ-5) scores ≤ 1.5 at Week 52.

8.2.4. High-Resolution Computed Tomography (at TLC and FRC)

The HRCT is used as the imaging modality to serve as a base since HRCT is currently accepted as the gold standard to evaluate structural characteristics of the airways and lung parenchyma. Compared to chest radiography and magnetic resonance imaging, chest CT offers images with higher resolution and greater detail to distinguish between different tissues. Participants will undergo HRCT scans with respiratory gating to ensure the scans are taken optimally at the correct two different breathing levels: TLC and FRC. HRCT scans will be performed at three study visits: baseline (Visit 0), between Week 24 to Week 26 (Visit 4) and between Week 50 to Week 52 (Visit 6) in the order as specified in Section 8.2. The HRCT scan at the ED visit will be performed based on the participant's consent and the PI's clinical judgement with appropriate consultation with the MM, if required. If a participant experiences an asthma exacerbation requiring SCS prior to HRCT scan and subsequent depemokimab dosing, a visit window of 4 weeks will be provided, allowing the participant to recover and stop exacerbation treatment. The HRCT scan procedure should be performed in the order as specified in Section 8.2.

To minimize radiation exposure, low radiation scanning protocols will be provided to the participating sites. The low radiation protocols will be tailored to the study-allocated CT scanner and will be evaluated by conducting a phantom scan prior to site activation.

The software CT-expo will be used to give an estimation of the radiation dose. Based on a selection of CT scanner brands and models from four manufacturers, the estimated radiation exposure using the low radiation scanning protocols recommended for this study can be found in Table 12 (Appendix 9). Specific settings that were used in CT-expo are described in Table 13 (Appendix 9). More detailed information on HRCT and the metrics measured are provided in Appendix 8.

8.2.5. Pulmonary Function Testing/ Spirometry and Reversibility using the Maximum Pre- and Post-Bronchodilator Method

Spirometry lung function assessments, utilizing spirometers provided by the sponsor, 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 American Thoracic Society (ATS) guidelines [Miller, 2005]. Spirometry includes FEV_1, percent predicted FEV_1 and Forced Vital Capacity (FVC). Pre-BD spirometric assessments will be performed at the Screening Visit, Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6 or ED and at scheduled clinic visits as specified in the SoA (Section 1.3; Table 1). Post-BD spirometric assessments will be performed at Visit 1, Visit 4, Visit 5, Visit 6 or ED and at scheduled clinic visits as specified in the SoA (Section 1.3; Table 1) at least 15 minutes after administration of 200 mcg salbutamol.

Spirometry should be performed in the order as specified in Section 8.2. Participants should try to withhold short acting Beta2 agonists (SABAs) such as albuterol/salbutamol for 6 hours prior to all spirometry assessments, if possible. In addition, long-acting beta 2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), fixed dose combinations of ICS/LABA or ICS/LABA/LAMA should be withheld for ≥12 hours prior to all spirometry assessments, if possible. At each visit, spirometry should be

performed at the same time of day (+/- 1 hour) as the assessment performed at Visit 1 (the baseline assessment).

For participants who do not meet the wash-out period requirements at screening, as this is a study enrolment visit, a separate screening visit should be scheduled to accommodate BD washout periods.

Post-bronchodilator values will be recorded following reversibility testing using the Maximum Post-BD Method. Reversibility will be derived for Visit 1. The procedures involved in the Maximum Post-BD- Method are those generated by the Pulmonary Physiology Subcommittee [Tepper, 2012]. Additional details on the spirometry and reversibility procedures can be found in Section 10.11 (Appendix 11).

8.2.6. Whole Body Plethysmography (RV/TLC ratio)

Whole body plethysmography is performed to measure lung volumes, specifically Residual Volume (RV) and TLC. It provides valuable information about lung hyperinflation and gas trapping that reflect small airway dysfunction. Small airway physiology is inadequately evaluated by spirometry, which is predominantly influenced by larger airway physiology. The test involves using a body plethysmograph chamber to measure lung volumes based on changes in pressure.

Residual Volume (RV) is the amount of air remaining in the lungs after a full exhalation.

Total Lung Capacity (TLC) is the total volume of air the lungs can hold, which is the sum of RV, Inspiratory Capacity (IC), and Expiratory Reserve Volume (ERV).

The ratio of RV to TLC (RV/TLC) is then calculated to assess the extent of gas trapping after a standard full exhalation.

Whole body plethysmography assessments will be performed for all participants (but based on site feasibility will set a minimum target of 50% of total study participants) at study sites by the Investigator or qualified designee according to ATS/ERS guidelines [Wanger, 2005] according to SoA (Section 1.3; Table 1) to measure the RV and TLC.

Lung volumes (RV and TC) will be determined by body plethysmography. The assessments will be performed at Visit 1, Visit 4, and Visit 6. The test will be performed by qualified pulmonary function technicians with experience in performing this assessment. At least 3 FRC values that agree within 5% (i.e., the difference between the highest and lowest value divided by the mean is <0.05) should be obtained and the mean value reported.

Body plethysmography assessments should be performed in the order as specified in Section 8.2. Each site is expected to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by GSK.

Note: The test is typically done after other lung function tests and the participant should be in a relaxed state. The participant will need to enter a sealed airtight chamber for the assessment, which is safe and non-invasive.

8.2.7. Oscillometry (R5-R20, AX, Fres)

Oscillometry involves using a device that can measure airway impedance through the application of small pressure oscillations during normal breathing. These measurements help to assess the mechanical properties of the respiratory system. This procedure is non-invasive, does not require any forced respiratory manoeuvre, as undertaken during quiet tidal breathing, is simple to perform and can be undertaken quickly.

R5-R20 (Resistance at 5 Hz and 20 Hz):

- R5 and R20 are measures of airway resistance at different frequencies. The oscillometric device generates oscillations at specific frequencies (5 Hz and 20 Hz, typically).

R5 is the total airway resistance at 5 Hz, which reflects both large and small airway resistance. R20 is measured at 20 Hz and primarily reflects the resistance in the large airways (because higher frequencies are more sensitive to larger airway structures). The difference between R5 and R20 (R5 - R20) reflects the contribution of small airway resistance and can thus help to differentiate between large and small airway involvement in obstructive conditions.

AX (Reactance at a Frequency X):

AX refers to the airway reactance, which represents the elastic properties of the respiratory system, including both lung and the chest wall.

It is derived from the phase angle between pressure and flow during oscillatory testing. Reactance changes with frequency and provides information about the elastic properties of the airways and as such may be influenced by structural airway changes, such as airway remodelling.

Fres (Resonant Frequency):

Fres is the resonant frequency of the respiratory system, which is the frequency at which the reactance of the airways and the respiratory system changes sign (from negative to positive).

It reflects the point at which the elastic and inertial properties of the respiratory system balance each other. A higher Fres indicates a more compliant (less stiff) respiratory system, while a lower Fres suggests more stiff or obstructed airways.

Oscillometry assessments will be performed for all participants at study sites by the Investigator or qualified designee experience in performing this assessment according to SoA (Section 1.3; Table 1). All sites will be provided with standardized equipment for oscillometry measures (Tremflo® C100, Thorasys. Montreal, Canada).

R5-R20, AX, and Fres will be assessed by oscillometric device pre- and post-BD administration. Pre-BD assessments will be performed at Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, and Visit 6 and post-BD assessment at Visit 1, Visit 4, Visit 5, and Visit 6 in the order as specified in Section 8.2. Post-BD oscillometric assessments should be performed 15 minutes after administration of 200 mcg salbutamol.

8.2.8. Patient Reported Outcome (PRO) and Health Outcomes Assessments

Patient Reported outcome (PRO) will be assessed using ACQ-5 and SGRQ. Primarily, PROs will be collected during clinic visits using eCOA 'tablet' device and if allowed 'eCOA Web Backup' will be used as a backup option to collect PRO data.

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. The final score is a mean result of the five questions with a score >1.5 indicating uncontrolled asthma. This will be completed electronically according to the SoA (Section 1.3; Table 1).

The St George's Respiratory Questionnaire is a 50-item questionnaire developed for patients with 50 chronic airflow limitation, including asthma [Jones, 1992; Nelsen, 2017]. The SGRQ is a QoL instrument that assesses symptoms, physical activity, and the effect of the disease on the patient's life and can therefore provide a wider perspective on treatment effectiveness in patients with severe asthma compared with more targeted questionnaires such as the ACQ [Chupp, 2017]. The SGRQ is scored from 0–100, with higher scores indicating a worse HRQOL; a four-point reduction in score is considered to be the minimal clinically important difference (MCID), defined as the individual patient score change over a predetermined period [Jones, 2002]. The questions are designed to be self-completed by the participant. This will be completed electronically according to the SoA (Section 1.3; Table 1).

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3; Table 1).

8.3.1. Physical examination/history directed physical examination

- A complete physical examination will include, at a minimum, assessments of the Skin, Eyes, cardiovascular (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 recorded in the eCRF.
- 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. ECGs

- Twelve-lead ECGs will be obtained at the time points specified in the SoA (see Section 1.3; Table 1) using an ECG machine, provided centrally by GSK via a third party vendor, that automatically calculates the heart rate and measures PR interval, QRS duration, QT, and QTc intervals.
- The QTcF formula must be used for *each* individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled. Refer to Section 7.1.2 for the QTcF formula.
- If a routine ECG demonstrates a prolonged QT interval, obtain 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 discontinued from the study intervention (but not from the study). Refer to 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 tests

- See Section 10.2 for the list of clinical safety laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3; Table 1).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study until the Follow-up visit/call should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - In the absence of a diagnosis, abnormal laboratory findings assessments (e.g. Elevated Liver Enzymes) or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (see Section 10.3.1 and Section 10.3.2).
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - 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 in the eCRF.

8.3.5. Pregnancy testing

- A urine/blood pregnancy test must be performed for all female participants of childbearing potential before the administration of the first dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- See Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted as per the SoA (See Section 1.3; Table 1) during the study.
- A serum pregnancy test will be conducted for all WOCBP at the screening visit (Visit 0), EoS visit (Visit 6), and the ED Visit. In addition, for all WOCBP a highly sensitive urine pregnancy test should be performed within 24 hours prior to administration of study intervention and HRCT scans at the scheduled study visits as specified in the SoA (Section 1.3; Table 1): at Visit 1, Visit 2, Visit 3, Visit 4, and Visit 5 and at the Follow-up Visit . In the case of Visits 1 and 4 if the HRCT scan and dosing occur more than one day apart, two urine pregnancy tests will be required to establish the absence of prgenancy prior to the scan and study dosing, respectively.
- A final urine pregnancy test should be conducted for all WOCBP, 35 weeks after the last administered dose of study intervention.

- Participants should have a urine pregnancy test at the Follow-up Visit/call (Week 61). Participants who withdraw early from the study should have a urine pregnancy test, 9 weeks after the ED Visit. A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6. Study Safety monitoring

Participant safety will be continuously monitored by the medical monitor, designated Safety Lead (or delegate) throughout the study. Pertinent findings and conclusions are shared with the product's Safety Review Team (SRT) for review of the overall benefit risk profile of the product. The GSK SRT will review 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.

8.4. Adverse events, serious adverse events, and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up (see Section 7). This includes events reported by the participant, or, when appropriate, by legally authorised representative, or caregiver/surrogate).

Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

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 and/or Section 10.6.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

All AEs/SAEs will be collected from the start of study intervention until the follow-up visit/call at the time points specified in the SoA (Section 1.3; Table 1). However, any AE/SAE assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a participant consents to participate in the study.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, 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 Section 10.3 and/or Section 10.6. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records per the local country requirements. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.8 for contact information.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

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 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5 and/or Section 10.6.4.4.

8.4.4. AESIs

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 10).
- Type III hypersensitivity (immune complex disease/vasculitis) reactions.

- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.5. Regulatory reporting requirements for SAEs/AESIs

- Prompt notification by the investigator to the sponsor of an SAE/AESI is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor partner will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigators must report to the sponsor pregnancies, medication errors, abuse and misuse.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Table 6 Timeframes for submitting SAE and pregnancy reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	paper/electronic AEs report	24 hours*	Paper/electronic AEs report
Pregnancies	24 hours*	paper pregnancy notification report/electronic pregnancy report	24 hours*	Paper pregnancy follow-up report/electronic pregnancy report

AE = Adverse event; SAE = Serious adverse event.

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

‡ Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.6. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 35 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 the sponsor within 24 hours of learning of the female participant pregnancy.
- 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, fetal 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. See Table 6 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.1 and Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention.

8.4.7. CV 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 eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.4.8. Contact information for reporting SAEs and pregnancies

Table 7 Contact information for reporting SAEs and pregnancies

Study contact for questions regarding SAEs, pregnancies and SAEs linked to device deficiencies	
Contact GSK's local and/or medical contacts	
Contacts for reporting SAEs, pregnancies and SAEs linked to device deficiencies Available 24/24 hours and 7/7 days oax37649@gsk.com	

GSK = GlaxoSmithKline Biologicals SA; SAE = Serious adverse event.

8.4.9. Participant card

The investigator (or designee) must provide the participant/participant's LAR(s) with a "participant card" containing information about the clinical study. The participant/participant's LAR(s) must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.4.10. Medical device deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill 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.

If the site(s) uses non-sponsor medical devices, i.e., medical devices not provided by GSK, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly.

The definition of a medical device deficiency can be found in Section 10.6.

Note: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.4.10.1. Time period for detecting medical device deficiencies

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

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.10.2. Follow-up of medical device deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- 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.

8.4.10.3. Prompt reporting of device deficiencies to the 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 medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor electronically. If this primary method is unavailable, then alternative method such as fax should be utilized (see Appendix 6 for details).
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.10.4. Regulatory reporting requirements for device deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill 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. Biomarkers

8.5.1. Serum Biomarkers

Serum samples will be collected to evaluate the effect of depemokimab over time on exploratory biomarkers and may be used to investigate the biological responses associated with disease and compared to clinical and/or imaging endpoints. Biomarkers may include but not limited to T2 cytokines including IL-5, Il-4 and periostin. Samples will be collected according to the schedule described in the SoA (Section 1.3) and as detailed in laboratory manual provided separately to sites. Samples may be stored for a maximum of 20 years (or according to local regulations) from the last participant's last visit and may be used for additional analysis to gain a deeper understanding of the impact of Depemokimab on pathways of interest relating to asthma or related diseases.

8.5.2. Fractional exhaled Nitric oxide (FeNO)

Airway inflammation will be evaluated using a standardized single-breath FeNO test in accordance with the SoA (Section 1.3; Table 1) to assess the change from baseline in FeNO levels in response to depemokimab. The standard single exhalation technique recommended by the ATS will be followed [Dwiek, 2011]. Standardized equipment (NIOX VERO®) will be supplied by CLARIO and they will be responsible for ensuring that the equipment and procedures for the measurement of FeNO are validated prior to the start of the study.

8.5.3. Nasal brushing for RNA

Nasal brushing samples will be collected, handled and stored at the timepoints specified in the SoA (Section 1.3; Table 1) and as described in the laboratory manual. Samples will be collected to investigate the effect of depemokimab overtime on the transcriptome of upper airway cells using bulk RNA sequencing [Poole, 2014; Jackson, 2022]. The impact of depemokimab on nasal epithelial biology will be evaluated and the predictive value of the baseline biology evaluated both in relationship to clinical outcome, as in the study by Jackson et al [Jackson, 2022], and in relationship to imaging outcome. Samples may be stored for up to 20 years (or according to local regulations) from the participant's last visit.

8.6. Bronchoscopy sub-study assessments

8.6.1. Bronchial biopsy

Bronchial biopsies will be taken from proximal airway carinae during bronchoscopy at timepoints described in the SoA (Section 1.3; Table 1) and as described in the lab manual. Samples will be collected, handled and stored as detailed in the laboratory manual to investigate the effect of depemokimab (comparison of findings pre- and post-depemokimab) on tissue protein and transcriptome expression, applying techniques such as spatial transcriptomics coupled with proteinomics as well as separate assessment by immunohistochemistry or immunofluorescence. Samples may be stored for up to 20 years (or according to local regulations) from the last participant's last visit.

8.6.2. Bronchial brushing for RNA

Bronchial brushing samples will be collected at the timepoints specified in the SoA (Section 1.3; Table 1) and as described in the laboratory manual. Samples will be collected separately from both the proximal airways and from the distal airways to investigate the effect of depemokimab overtime on the transcriptome of lower airway cells using RNA sequencing technologies. Samples may be stored for up to 20 years (or according to local regulations) from the last participant's last visit.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to first participant first visit and it will include a more technical and detailed description of the statistical analyses described in this section.

Any changes to the original planned analysis given in this section of the protocol will be described in the SAP and/or the Clinical Study Report and included in a Protocol Amendment.

9.1. Statistical hypotheses/comparisons

The primary objective is to describe the change from baseline (Week 0) in total mucus plug volume measured at TLC at Week 26 following treatment with 100 mg depemokimab.

The null hypothesis of no change from baseline (Week 0) in total mucus plug volume, detectable by qHRCT at Week 26 following treatment with 100 mg depemokimab, shall be tested. A two-sided significance level of 5% will be used for the test.

9.1.1. Multiplicity Adjustment

No multiplicity adjustment is planned.

9.2. Analysis sets

Table 8 Analysis sets

Analysis Set	Definition/Criteria	Main analyses in scope
Screened	• All participants who were screened for eligibility.	• Study population
Assigned	• All participants who were assigned to study intervention in the clinical study.	• Study population
Safety	• All participants who received at least 1 dose of study intervention.	• Safety
FAS	• All participants who received at least 1 dose of study intervention and have at least one post-treatment efficacy assessment.	• Efficacy
PP	• All participants in the FAS for whom there were no major protocol deviations that impact the primary analyses.	• Efficacy and demography

FAS = Full Analysis Set; PP = Per Protocol

9.3. Statistical analyses

9.3.1. General considerations/definitions

The primary analysis will be conducted when all participants complete their Week 26 assessment. The EoS analysis will be conducted when all participants complete Week 52 assessment.

The study's efficacy analysis population will be the FAS and the PP shall be used for the supplementary analysis. All continuous variables (including qHRCT endpoints, pre-BD FEV_1, pre-BD FVC, post-BD FEV_1, post-BD FVC, ACQ-5 and SGRQ scores) will be summarized using number of non-missing values, median, mean, SD, minimum, and maximum as well as lower and upper quartiles, depending on the distributions of the data. Mean changes from baseline in continuous variables will be reported, including asymptotic 95% confidence intervals and standard errors (assuming normal distribution for all continuous variables). Categorical data (e.g., ACQ-5 asthma control category) will be summarized as the number and percentage among participants with non-missing data

Full details of these analyses will be described in the SAP.

9.3.1.1. Data handling strategy for ICEs

For each estimand of interest, data considerations and the estimation method for intercurrent events' handling strategies are shown in Table 9.

A multiple imputation approach will be used to impute data that are missing or ignored for analysis because of ICEs handling strategy. For the hypothetical strategy, outcomes that are observed after occurrence of an ICE will be excluded from analyses. These excluded outcomes, together with outcome data that are missing will be imputed under Missing At Random (MAR) mechanism for missingness assuming that the treatment effect of participants with an ICE will be the same as those without an ICE. For the treatment policy strategy, missing data shall be imputed using the multiple imputation method and the participant who experience an ICE shall be analyzed irrespective of the ICE.

Monotone missing (unobserved or ignored) data following occurrence of an ICE will be imputed depending on the strategy for handling the specific ICE as detailed in Section 3. A sequential imputation procedure will be used; whereby data at each timepoint are imputed one at a time. Details of the imputation model for each strategy will be provided in the SAP.

For instances where data are unobserved for reasons not relating to an ICE, then multiple imputation will be implemented assuming MAR mechanism as well. This will also include a sensitivity analysis that will entail a tipping point analysis for the endpoints of interest.

Table 9. Data considerations and estimation approach for ICE handling strategies

ICE Handling Strategy	Scenario of Post-ICE Outcome Data	Estimation Method-Multiple Imputation
Hypothetical	Observed data to be set to missing (ignored data). Unobserved data (truly missing).	For both missing and ignored data scenarios we assume that participants continue as remaining on treatment. Imputation model is based on observed data from participants without the ICE and with similar ICE.
Treatment policy	Observed data to be included in analysis as collected and analyzed regardless of whether participants are still on randomized intervention. Unobserved data will be imputed.	Imputation model is based on post-ICE data of participants with same ICE who provide data (if available). If no or insufficient observed post-ICE data, impute assuming Missing At Random (MAR).

Hypothetical Handling Strategy:

Under the hypothetical strategy, data observed after an ICE will not be used in the analysis and will be ignored. Outcome data of participants whose data have been ignored due to an ICE will be imputed assuming a scenario where the ICE had not occurred. This implies that participants who experienced an ICE will be assumed to have outcomes similar to those in the same treatment arm who did not experience the ICE. This assumes data are MAR, where participants whose data have been discarded are assumed to be similar as other participants in their respective treatment arm who did not experience an ICE.

Treatment Policy Handling Strategy: Under the treatment policy strategy, data collected after an ICE occurrence will be included in the analysis as observed.

9.3.2. Primary endpoint(s)/estimand(s) analyses

Refer to Section 3.

9.3.2.1. Main analytical approach

The primary endpoint i.e., change from baseline in total mucus plug volume at TLC at Week 26, will be analyzed using a Mixed Model Repeated Measures (MMRM) analysis.

The repeated-measures analysis will be based on the restricted maximum likelihood method (REML) assuming an unstructured covariance structure to model the within subject errors. In case unstructured covariance structure leads to non-convergence, compound symmetry structure will be used.

The model shall include the timepoints (measured in visits) as the fixed effects, participant as the random effect and total mucus plug volume at baseline, Week 26 and Week 52 as response. Although the primary endpoint is measured at Week 26 and change from baseline in total mucus volume at Week 52 is a secondary endpoint, both of them will be analyzed in one MMRM model. The least square (LS) mean and the 95% CI of the change from baseline (differences in the least squares means) at Week 26 and Week 52 will be provided.

Full details of all statistical analyses, assumptions underlying the fitted models, structure of the imputation model and multiple imputation parameters setting will be provided in the SAP.

9.3.2.2. Sensitivity analyses

A sensitivity analysis to assess the impact of missing data will be performed only if there is sufficient off-treatment data (i.e. data collected following treatment discontinuation prior to study withdrawal). A multiple imputation approach will be used using this off-treatment data to impute missing data.

9.3.2.3. Handling of Missing Data

Missing data or data excluded due to intercurrent events shall be handled using the appropriate strategy as mentioned in Table 9. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. Further details of the missing data analysis shall be provided in the SAP.

9.3.2.4. Supplementary analysis

A supplementary analysis shall be performed for the primary objective, where participants who do not experience any ICE (similar to a per-protocol population) shall be analysed.

9.3.3. Secondary endpoint(s)/estimand(s)] analyses

9.3.3.1. Efficacy analysis

For the key (first) and second secondary objective, i.e., change from baseline in airway wall thickness at TLC at Week 52 and Week 26 respectively, a MMRM analysis will be used to determine if there is a significant difference in the change from baseline values. The fixed and the random effects shall be the same as those used in the primary analysis.

Airway wall thickness at baseline, Week 26 and Week 52 shall be used as the response in this analysis. Similar to the primary analysis, the change from baseline at Week 26 and Week 52 shall be analyzed in one MMRM model.

For the third secondary endpoint, i.e., change from baseline in total mucus plug volume at Week 52, the MMRM model referred in the primary analysis shall be used to determine if there is a significant change from baseline.

The fourth and fifth secondary endpoint i.e., change from baseline in other qHRCT endpoints (i.e., mucus segment score, air trapping at FRC, specific airway volume at TLC and FRC and airway wall area percentage at TLC), an MMRM model shall be used for analysis for each endpoint. The response variable shall be the qHRCT endpoint values at baseline, Week 26 and Week 52. The fixed and the random effects shall be those used in the primary analysis.

The sixth and the seventh secondary endpoint i.e., change from baseline in pre-BD FEV_1 and post-BD FEV_1 at Week 26 and Week 52, shall be analyzed in one MMRM model similar to the analysis described above.

9.3.3.2. Safety analyses

Safety analyses will be performed using the safety analysis set. Adverse events will be coded using the most recent version of the MedDRA that will have been released for execution by the Sponsor/designee.

Safety data will be presented using descriptive statistics unless otherwise specified.

The AEs will be presented by system organ class and/or preferred term covering number and percentage of participants reporting at least 1 AE and number of AEs where appropriate. An overview of AEs will present the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention. Separate AE tables will be provided taken into consideration relationship as assessed by the Investigator, intensity, seriousness, death, and AEs leading to discontinuation of study intervention. An additional table will present number and percentage of participants with the most common AEs.

9.3.4. Tertiary/Exploratory endpoint(s)/estimand(s)] analyses

Specific details of tertiary/exploratory endpoint analysis will be described in the SAP.

9.3.5. Exploratory analyses

Clinical validation of the effect sizes for the total mucus plug volume and airway wall thickness obtained from this study data will be conducted by comparing the investigational treatment group with relevant external placebo data from other similar clinical trials, once available in published form. This comparison may serve to establish the treatment effect relative to a well-documented placebo response. The external placebo data will be carefully selected from studies with comparable populations, endpoints and study designs to ensure its relevance.

Further statistical details shall be provided in the SAP.

9.4. Interim analyses

An interim analysis will be performed when 62 (which is 60% of enrolled sample size of 103) enrolled study participants complete Week 26 efficacy assessment. The purpose of the interim analysis is for sample size re-estimation, i.e., to continue the study after re-estimating the sample size after maintaining the conditional power at the end of study of 90% or to stop for futility at the interim.

In addition to the interim analysis as described above, there shall be two planned analyses: a Week 26 analysis and a Week 52 final analysis. The Week 26 analysis (also called the primary analysis) shall be performed when all participants complete their Week 26 assessment and similarly the Week 52 analysis (also called the EoS or the key secondary analysis) shall be performed when all participants complete Week 52 assessment. Both the primary and EoS analysis shall contain efficacy and safety assessments until that duration. The safety tables in the EoS analysis shall be segmented by periods: baseline to week 26, week 26 to week 52, and baseline to week 52. There shall be separate reports at the end of primary and EOS analysis.

9.4.1. Sequence of interim and other planned analyses

The sequence of the analyses are as follows:

1. The interim analysis shall be performed when 60% participants of the planned/ upfront sample size of 103 participants have completed Week 26 assessment. The interim analysis shall determine whether to stop for futility; or continue the trial with the planned/ upfront or increased sample size.
2. The primary analysis shall be performed when all participants (sample size determined by the interim results) have completed Week 26 assessments.
3. The final analysis (also called EoS analysis or key secondary analysis) shall be performed when all participants (sample size determined by the interim results) have completed Week 61 assessments.

9.4.2. Statistical considerations associated with the interim analyses

The interim analysis is performed to either stop the trial early due to futility, thereby exposing less participants to an ineffective treatment; or to continue the trial with the upfront or increased sample size in the case when the drug shows promise at the interim stage. A sample size re-estimation (SSRE) procedure shall be used to compute the total sample size. The interim data shall be reviewed by the sponsor who shall take the decision based on airway wall thickness (key secondary endpoint) observed at the interim.

The details of the sample size re-estimation at interim stage (and the upfront sample size) are given in Section 9.5 below.

9.5. Sample size determination

The sample size is so chosen to maintain **at least 90%** power at **5%** level of significance for both the primary and the key secondary endpoint. To detect an effect size of 0.48 in the primary endpoint (total mucus plug volume at Week 26), 48 participants need to be enrolled. To maintain similar power to detect an effect size of 0.32 in the key secondary end point (airway wall thickness at Week 52), 103 participants need to be enrolled. Hence, 103 participants shall be enrolled into the study to maintain at least 90% power for both endpoints. The chosen value of 0.48 (0.32, respectively) corresponding to the primary (key secondary, respectively) endpoint are the effect sizes that we expect to observe in this study. The estimates for the effect sizes for both endpoints were obtained from our imaging vendor. We borrowed effect sizes from two single arm studies and one randomised control trial, all of them involving investigational biologic therapies targeting type 2 inflammation. The estimate of the effect size of airway wall thickness at Week 52 is actually the effect size at Week 26. However, due to paucity of data for Week 52, we conservatively assume that the effect sizes for the two timepoints are equal.

The final estimate was obtained as the weighted average of the three effect sizes using the inverse variance as the weights. Since we plan a single arm study, the effect sizes used from the randomized control trial was the change from baseline in the active arm.

Despite a thorough review of relevant prior data, there remains considerable uncertainty about the change from baseline in the key secondary endpoint, i.e., airway wall thickness. To mitigate the risk of an underpowered study, we will use a sample size re-estimation approach [Chang, 2012] conducted at an appropriate interim time. The optimal interim time was computed as 60% (i.e. at 62 participants) of the initial upfront sample size. This choice minimizes the expected sample size of the study (see [Gallo, 2014] for details of the method and [Lu Mao, 2014; Lu Mao, 2021] for the description of the R package grpseq used in the simulation).

Therefore, the study will start with an up-front enrolled sample size of 103. An interim analysis is planned when 60% (i.e. 62 participants) of the enrolled participants complete Week 26 assessment.

Note: The ideal interim timing should be when 62 enrolled participants complete their Week 52 assessments. However, this would extend the interim analysis timing to the extent that almost all study participants are expected to be recruited by this time. Therefore, the interim analysis timing of 26 weeks was chosen to enable early decision making and expose less participants to depemokimab and ionizing radiation in case the study stops for futility.

Depending on the computed value of the conditional power (CP) at the interim (CP is defined as the power to detect an effect size of 0.48 in the airway wall thickness at Week 26 at the end of the study, when all participants complete Week 26 assessment, given the values observed at interim), the enrolled sample size may be increased up to a maximum of **150** using the below rule:

1. If CP $\geq$ 90%, we will continue with initial sample size (no increase required)
2. If 30% $\leq$ CP < 90%, we will increase the sample size to achieve a 90% CP, with a maximal enrolled sample size of 150 (that is, if the re-estimated enrolled sample size exceeds 150, we will continue with 150 enrolled participants)

A nonbinding futility stop is planned if CP<30%. No reduction in sample size or stopping due to efficacy is permitted at interim, to avoid inadequate data to examine other endpoints.

Note: the sample size re-estimation procedure is based on the interim value of the airway wall thickness at Week 26. This is to ensure that we have enough sample size to power the airway wall thickness at Week 52 at the end of study (assuming equal effect sizes at Week 26 and Week 52). The primary endpoint (total mucus volume at Week 26) has a large

effect size; therefore, we shall always have enough sample size to power the primary endpoint at the end of the study.

Table 9 below highlights few scenarios corresponding to the different values of change from baseline in airway wall thickness observed at interim and the decision for the next stage [Gallo, 2014; Lu Mao, 2014].

Table 10. Describing decisions for different interim values of airway wall thickness

Observed z-statistic at IA[a] (n = 62)	Conditional power (CP)	Total enrolled sample size [b]	Conditional power with new enrolled sample size	Decision
2.04	0.92	103	0.90	Continue with planned sample size
1.73	0.85	112	0.90	Continue with increased sample size
1.41	0.75	131	0.90	
1.18	0.65	147	0.90	
0.70	0.42	190[c]	0.77	Continue with increased sample size but restrict it to 150
0.47	0.31	204[c]	0.68	
-0.47	0.05	61	NA	Stop the trial for futility (non-binding)

a. The observed z-statistics at IA is defined as the mean change from baseline in airway wall thickness at Week 26 calculated for 50 participants divided by the standard error of the estimate.
b. Total enrolled sample size refers to the total sample size required to maintain a power of 90% for airway wall thickness at the end of study period.
c. The total enrolled sample size shall be restricted to 150.

Note: The column 'Total enrolled sample size' is inflated by a factor of 1.0068 to recoup the power loss due to the non-binding futility stop rule.

The details of the sample size re-estimation procedure shall be provided in the SAP.

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
  - Applicable ICH 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 IRB/IEC 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, as applicable:
  - 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/IEC.
  - Notifying the IRB/IEC of SAEs 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 the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants/participants' legally authorized representative (LAR) and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their LAR(s) will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection (e.g., HIPAA and GDPR requirements), where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant/participant's LAR(s).
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant or their LAR.

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

10.1.4. Recruitment strategy

Prior to selecting a site for inclusion in the study, data will be gathered to understand the numbers of participants that they may be able to enroll from their own patients and networks. These items will provide basic information such as site contact information and capabilities with right equipment and tools that are designed to assist with recruitment. In addition, a third-party vendor and the sponsor will develop several items designed to help the potential participant understand the study including, for example, a SoA table to represent the visit tests and procedures, user manuals for specific procedures to help site staff walk patients through during consenting process.

Recruitment will be monitored throughout the study and mitigation plans put in place if needed.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant/participants' LAR(s) must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant/participants' LAR(s), that their data will be used as described in the informed consent.
- The participant/participants'/LAR(s) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

- A SRT is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.7. Dissemination of clinical study data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 6 months of primary/study completion date (pediatric population) and within 12 months of primary/ study completion date (adult population). Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- GSK will provide the investigator with the participant-level line listings for their site only after completion of the full statistical analysis.

- GSK intends to make anonymized participant-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL Plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- 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, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor 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 a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.
- Any source data collected and processed by the third-party vendors during the study are expected to be transferred to the sponsor at the end of the study and retained by the vendors as per the timeframe set with each vendor via master agreement.

10.1.9. Source documents

- There will not be any source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available) as eCRF should not be source data itself. Data entered directly in the eCRF is as per the SoA requirement and based on source documents. Definition of what constitutes source data and its origin can be found in monitoring guidelines.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and site start and closure

Start of study and 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 (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or temporarily 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 temporary 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.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 11 will be performed by the central laboratory/by the local laboratory.
- All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
- Local laboratory results are only 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.
- 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.

- Investigators must document their review of each safety laboratory report.
- The addresses of the clinical laboratories in charge of the testing can be found in the "List of Clinical Laboratories and Key Vendors".

Table 11 Protocol-required safety laboratory tests

Laboratory tests	Parameters	
Hematology	• Platelet count	
	• RBC count	
	• RBC indices	– Mean corpuscular volume – Mean corpuscular hemoglobin – %Reticulocytes
	• WBC count with differential:	– Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
	• Hemoglobin	
	• Hematocrit	
Clinical chemistry[1]	• Blood urea nitrogen/Urea • Potassium • Creatinine* • Sodium • Calcium • Magnesium • Glucose • Creatine phosphokinase	– AST/SGOT – ALT/SGPT – GGT – Alkaline phosphatase[2] – Total bilirubin – Direct bilirubin – Total protein – Albumin
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination and UACR (if blood or protein is abnormal): – Epithelial cells – RBC – WBC – Casts – Crystals – Culture	
Pregnancy testing	• Highly sensitive serum pregnancy test at Screening Visit (Visit 1), EoS Visit (Visit 6) and ED Visit; urine pregnancy tests for all other scheduled visits (as needed for WOCBP)[3]	
Other screening tests	• Follicle stimulating hormone and estradiol (as needed in WONCBP only) • Total IgE If a central laboratory is being used and protocol-required additional local tests are needed, include the last bullet in the other screening tests section of the table (All study-required laboratory) • All study-required laboratory tests will be performed by a central laboratory, with the exception of: • Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories.	

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; eGFR = Estimated glomerular filtration rate; HBsAg = Hepatitis B surface antigen; hCG = Human chorionic gonadotropin; HCV = Hepatitis C virus; IEC = International ethics committee; INR = International normalized ratio; IRB = Institutional review board; RBC = Red blood cell; SGOT = Serum glutamic-oxaloacetic transaminase; SGPT = Serum glutamic-pyruvic transaminase; ULN = Upper limit of normal; WBC = White blood cell; WONCBP = Woman of non-childbearing potential.

1 Details of liver event stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver event stopping criteria and Section 10.5 Liver safety requirements and guidelines]. All events of ALT [or AST] ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT [or AST] ≥3 × ULN and INR >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in 24 hours (excluding studies of hepatic impairment or cirrhosis).

2 If alkaline phosphatase is elevated, consider fractionating.

3 Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

* To assess the kidney function, use the eGFR 2021 calculator.

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 unfavorable 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 (hematology, 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 condition 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.

Events meeting the AE definition
• Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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, admission for routine examination.). • 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. Pre-existing diseases will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death.
b. Is life threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization. • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent 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, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant.
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Is a suspected transmission of any infectious agent via an authorized medicinal product.
h. Other situations: • Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or 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 jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of CV events

CV definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • MI/unstable angina. • Congestive heart failure. • Arrhythmias. • Valvulopathy. • Pulmonary hypertension. • Cerebrovascular events/stroke and transient ischemic attack. • Peripheral arterial thromboembolism. • Deep venous thrombosis/pulmonary embolism. • Revascularization.

10.3.4. Definition of TEAE

TEAE Definition:
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.5. Recording, assessment, and follow-up of AEs, SAEs, AESIs, and pregnancies

10.3.5.1. AE, AESI and SAE recording

- When an AE/AESI/SAE 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/AESI/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 identifier, 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/AESI/SAE.

10.3.5.2. Assessment of intensity

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

- **Mild:**
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:**
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:**
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes 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 their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

10.3.5.5. Follow-up of AEs, AESI and SAEs

- 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, AESI or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem 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.

After the initial AE, AESI and SAE or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESI (as defined in the Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

10.3.5.6. Updating of SAE, AESI and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the study contact for reporting SAEs (see Section 8.4.3).

10.3.5.7. 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 section) 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 offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.8.

SAE reporting to GSK via paper data collection tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/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 timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. WOCBP

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

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. WONCBP

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal).
- Permanently sterile due to one of the following procedures:
    a. Documented hysterectomy.
    b. Documented bilateral salpingectomy.
    c. Documented bilateral oophorectomy.

For permanently sterile individuals 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. If reproductive status is questionable, additional evaluation should be considered.

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

- **Postmenopausal female.**

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

- A high FSH level and low estradiol level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. In the absence of 12 months of amenorrhea, a blood sample for simultaneous FSH and estradiol levels may be collected at the discretion of the investigator to confirm non-reproductive potential when menopausal status is in question according to local laboratory reference range.

- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

Female participants:

Contraceptives[a] allowed during the clinical 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].
• IUD.
• IUS[c].
• Bilateral tubal occlusion/ligation.
• Azoospermic partner (vasectomized or due to a medical cause). – Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP, and the absence of sperm has been confirmed. (e.g., medical assessment of the surgical success for vasectomy). If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: Documentation for a male partner can come from medical history interview with the participant.
Highly effective methods[b] that are user dependent Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]. – Oral. – Intravaginal. – Transdermal. – Injectable.
• Progestogen-only hormone contraception associated with inhibition of ovulation[c]. – Oral. – Injectable.
• Sexual abstinence. – Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

CTFG = Clinical Trial Facilitation Group; IUD = Intrauterine device; IUS = Intrauterine hormone-releasing system; LAM= Lactational amenorrhea method; WOCBP = Woman of non-childbearing potential.

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 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 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 depemokimab 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: Liver safety requirements and guidelines

10.5.1. Liver safety: required actions, monitoring, and follow-up to assess causality of liver event

Liver event study intervention stopping criteria	
ALT absolute	ALT ≥8xULN
ALT increase	Unable to monitor weekly: ALT ≥5xULN but <8xULN that cannot be monitored weekly for 2 weeks. ALT ≥3xULN but <5xULN that cannot be monitored weekly for 4 weeks. Able to monitor weekly: ALT ≥5xULN but <8xULN that persists for 2 weeks. ALT ≥3xULN but <5xULN that persists for 4 weeks. Note: if values reduce to <3xULN or return to within baseline or normal limits for 2 consecutive weekly assessment, weekly monitoring may return to regular per protocol schedule.
Bilirubin[1,2]	ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value)
INR[2]	ALT ≥3xULN and INR >1.5
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required actions, monitoring and follow-up to assess causality of liver event	
Actions and monitoring	**Follow-up to assess causality of liver event**
• Immediately discontinue study intervention. • Report the event to GSK within 24 hours. • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2]. • Perform liver event follow-up to assess causality of liver event. • Monitor the participant liver chemistries (see MONITORING). MONITORING: If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver	• Viral serology[4]. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (IgG or gamma globulins). • Blood sample for PK analysis, obtained within a week of meeting increased liver monitoring criteria after last dose[5]. • CPK and LDH, GGT, GLDH, and serum albumin. • Fractionate bilirubin, if total bilirubin ≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. Also note that the mechanism of action of

Required actions, monitoring and follow-up to assess causality of liver event	
Actions and monitoring	**Follow-up to assess causality of liver event**
event follow-up to assess liver event causality within 24 hours. • Monitor participants twice weekly until liver chemistries reduce to <3xULN for ALT, <2xULN for total bilirubin or ≤1.5 for INR or return to or remain within baseline or normal limits. • A specialist or hepatology consultation is recommended. For all other criteria (bilirubin <2xULN and INR ≤1.5): • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within 24-72 hours. • Monitor participants weekly until liver chemistries reduce to <3xULN for ALT or return to or remain within baseline or normal limits. RESTART and/or RECHALLENGE • Do not restart and/or rechallenge participant with study intervention since not allowed per protocol; continue participant in the study for any protocol-specified follow-up assessments.	depemokimab leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the 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, Type1 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. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease, complete liver imaging form. • Liver biopsy may be considered and discussed with local specialist if available, for instance: – In patients when serology raises the possibility of 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.

AIH = Autoimmune hepatitis; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CPK = Creatine phosphokinase; CRF = Case report form; DNA = Deoxyribonucleic acid; DILI = Drug-induced liver injury; GGT = Gamma glutamyl transferase; GLDH = Glutamate dehydrogenase; GSK = GlaxoSmithKline Biologicals SA; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HDV = Hepatitis D virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; INR = International normalized ratio; LDH = Lactate dehydrogenase; PCR = Polymerase chain reaction; PK = Pharmacokinetic; RNA = Ribonucleic acid; SAE = Serious adverse event; ULN = Upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. 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 total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline

value) or ALT ≥3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); 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 IgM antibody; HBsAg and HBcAb (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant known to be HBsAg and/or HBcAb positive prior to onset of the liver event or subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed and if this is feasible)].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to 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 laboratory manual.

10.5.2. Liver safety: liver chemistry increased monitoring criteria with continued study intervention

Liver event 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, stabilize (i.e., ALT or AST <3xULN, and no increases in total bilirubin and INR) or return to or remain within baseline or normal limits. • If at any time participant meets the liver event 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, stopping criteria have not been met but any of the monitored liver chemistry (ALT, AST, alkaline phosphatase, total bilirubin and INR) remains abnormal/above baseline, monitor participants twice monthly until they stabilize or return to within baseline or normal limits. Alternatively, the monitoring can return to standard as per protocol when the investigator and medical monitor agree that values are stable or no longer significantly abnormal (this may require local investigation of potential causes for liver chemistry abnormality).

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GSK = GlaxoSmithKline Biologicals SA; INR= International normalized ratio; ULN = Upper limit of normal.

10.6. Appendix 6: Medical device AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions 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 the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.6.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device 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 unfavorable 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 except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as 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.

10.6.2. Definition of medical device SAE, SADE, and USADE

A medical device SAE is any serious AEs 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 hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal 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 ADE that has resulted in any of the consequences characteristic of an SAE. • 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 defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the /IB (see Section 2.3).

10.6.3. 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 inadequacy of the information supplied by the manufacturer.

10.6.4. Recording and follow-up of medical device AEs and/or SAEs and device deficiencies

10.6.4.1. Medical device 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 identifier, 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.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.6.4.2. Assessment of intensity

See Section 10.3.5.2.

10.6.4.3. Assessment of causality

See Section 10.3.5.3.

10.6.4.4. Follow-up of medical device AE/SAE and 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.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.6.5. Reporting of medical device SAEs

Medical Device 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) 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 offline, then the site can report this information on a paper SAE form (see next table) or to the GSK medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.8.

Medical device SAE reporting to GSK via paper data collection tool

- Email/Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK medical monitor.
- In rare circumstances and in the absence of email/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 Section 8.4.8**.**

10.6.6. 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 fulfill 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 the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Section 8.4.8**.**

10.6.7. Reporting of medical device deficiencies for associated person

- **Reporting to GSK**

If an Associated Person (e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter.

If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.

- Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form.
- If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours. See Section 8.4.8 for reporting.
- 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.

10.7. Appendix 7: Country-specific requirements

Not applicable

10.8. Appendix 8: HRCT And Radiation guidance

Image acquisition

High-Resolution Computed tomography is the imaging modality used for image analysis as HRCT is currently still accepted as the gold standard to evaluate structural characteristics of the airways and lung parenchyma. Compared to chest radiography and magnetic resonance imaging, chest CT offers images with higher resolution and greater detail to distinguish between different tissues. For this study, participants will undergo chest high-resolution (HRCT) scans with gating to ensure the scans are taken optimally at the correct breathing levels: Total Lung Capacity (TLC) and Functional Residual Capacity (FRC). Scans are performed at three study visits: baseline (V1), Between Week 24 to Week 26 (V4) and Between Week 50 to Week 52 (V6). To minimize radiation exposure, low radiation scanning protocols will be provided to the participating sites.

Radiation Guidance

The CT procedures incorporated into this study design are aligned with the directives presented in the European Union (EU) guidance [Directorate-General, 1998]. Participants will be informed of the risks associated with the CT procedure before entering the study.

In this study, extra attention will be paid to reduce radiation by providing low radiation scanning protocols tailored to the specific scanner available at participating sites. Low radiation scanning protocol guidance will be provided to each participating sites prior to any participant's scan visits. Participating site will be required to set up a study-allocated CT scanner with a low radiation scanning protocol and conduct a phantom scan using this protocol. The phantom scan will be sent to FLUIDDA, who will be supporting this study for quantitative analysis for review and confirmation for the low radiation CT scanner settings. All study team personnel involved in the CT scanning procedure will also undergo training to ensure quality and consistency of the HRCT scans are maintained across study centers. Study centers will only be certified for the CT scanning procedure after the phantom scan is approved by FLUIDDA and all relevant study team personnel have successfully completed their training.

The following is FLUIDDA's method for calculating radiation exposure from the CT scan procedure using FLUIDDA's recommended CT scanner settings.

CT-Expo

The software CT-expo is used to give an estimation of the radiation dose a participant will get from a chest HRCT scan at TLC/FRC. CT-expo's calculations are based on computational methods which were used to evaluate the data collected in both German surveys on CT exposure practice in 1999 and 2002 [Stamm, 2014]. A comprehensive description of these methods can be found in the book 'Radiation Exposure in Computed Tomography' [Nagel, 2002]. Based on a selection of CT scanner brands and models from four manufacturers, the estimated radiation exposure using the low radiation scanning protocols recommended for this study can be found in Table 12 (Appendix 9). Specific settings that were used in CT-expo are described in Table 13 (Appendix 9).

When using CT-expo, the typical total error in dose calculation is ±10 to ±15% for those quantities which can also be measured ($CTDI_{vol}$, $CTDI_w$ [weighted CT dose index], DLP_w [dose length product]) and ±20 to ±30% for those quantities which can only be derived by using conversion coefficients (effective dose). The CT-expo manual states that the typical total error for $CTDI_{vol}$ lies within a range of 15%. Scanner's estimation for the CTDIvol also contains a certain error, varying from -22% to 15% depending on the scanner type [Irvine, 2014]. Taking this information into consideration, the values for CT-expo's calculation and the scanner's estimation are within the error range, providing support that the estimations from CT-expo gives a good indication for the radiation dose a participants will receive.

Using the software CT-Expo, an estimation on the radiation dose can be made for a male participant (with a length of 170 cm, a weight of 70 kg [154 lbs] and a trunk diameter of 28.3 cm), the effective dose for an HRCT scan, averaged over all scanner types mentioned above, would be 2.2 mSv. Each participant will undergo 6 scans (2 scans per visit, 3 visits) which will result in an average exposure of 2.2*6 = 13.2 mSv over a time period of 52 weeks. This dose is within the accepted radiation dose range for biological research (1 to 10 mSv) [Directorate-General, 1998].

It is noteworthy that while a HRCT scan taken with the recommended low radiation protocol in this study is higher than a standard chest x-ray or mammogram at 0.02 mSv and 0.13 mSv respectively, the average estimated radiation exposure received by participants in this study for 6 HRCT scans at 2.2 mSv (based on the scanner brands and models in Table 12 [Appendix 9]) is approximately 3.6 times lower than 6 standard chest CT scans which would expose a person to 48 mSv of radiation (8 mSv per scan) [USEPA].

An average US citizen receives an annual natural background radiation exposure from natural sources of 3.1 mSv [USNRC]. Participants completing this study will therefore receive an equivalent of 4.3 years background radiation based on the average estimated radiation exposure in Table 12 (Appendix 9). Based on the estimated total amount of radiation exposure for each participant at each time point, the potential benefits of the study are also expected to be Category IIB following the European Union (EU) guidance document targeting the diagnosis, cure, or prevention of disease [Irvine, 2014].

Further calculations on the relative risk increase were conducted and demonstrated a relative risk increase of 0.055 % for the 13.2 mSv received from all scans in the current study, based on the detriment adjusted nominal risk coefficient for an adult at 4.2% per Sv as published by the International Commission on Radiological Protection (ICRP) in 2007 [ICRP, 2007].

There are potential risks associated with CT scans (as outlined in the above paragraphs) due to the exposure of ionizing radiation. The radiation related risks are exclusively stochastic effects, as the name implies, and are effects that occur by chance specifically as it relates to a fatal malignancy. The doses estimated in this protocol of ~13.2 mSV are well below the threshold for deterministic effects, which generally starts at above 2000 mSV.

Structure segmentation

The HRCT images are imported into a medical imaging processing software package, Mimics, to reconstruct the lung lobes, airways and pulmonary vasculature. A combination of automatic AI-based segmentation algorithms and manual correction is used to correctly identify voxels. The following structural endpoints can be derived from these segmentations: airway wall thickness, total mucus plug volume and score, air trapping, airway volume, blood vessel distribution, lobar volume, airway wall area percentage and airway radius.

Computational Fluid Dynamics

After reconstructing the patient-specific geometrical models of the respiratory system, flow behavior is simulated using computational fluid dynamics (CFD). These simulations allow us to assess functional endpoints including internal airflow distribution, regional airway resistance, ventilation mapping, and aerosol deposition of inhaled medication. As this technique is based on computational simulations, it does not require any inhalation of a tracer to derive this quantitative metrics.

10.9. Appendix 9: Radiation Dose Calculations

In Table, the radiation dose is listed as effective dose and volume computed dose index ($CTDI_{vol}$) for multiple scanners from five manufacturers including General Electric (GE), Philips, Siemens, and Toshiba/Canon. The settings that were used to perform the calculations in the CT-expo software are provided in Table 13.

Table 12. $CTDI_{vol}$ and effective dose estimation calculated with CT-expo

Scanner type	Effective dose (mSv)	$CTDI_{vol}$ (mGy)	Scanner selected in CT-expo
GE Discovery HD750	2.7	4.6	*Not applicable*
GE Lightspeed VCT	2.3	4.5	*BS large*
GE Optima CT 660	2.7	4.9	*Large body*
GE Revolution CT	1.9	3.7	Large body
GE Revolution Apex	1.8	3.9	Large body
GE Revolution Ascend	2.5	4.7	Large body
Philips Brilliance EVO	2.7	4.6	Large body
Philips Brilliance 64	1.8	3.2	Brilliance 60/64
Philips Brilliance iCT	1.9	3.4	Series adult
Phillips Ingenuity	1.9	3.3	*Not applicable*
Philips Incisive	2.4	4.1	*Not applicable*
Siemens Somatom Perspective	2.5	4.5	*Not applicable*
Siemens Somatom Perspective AS	1.7	3.6	AS series
Siemens Somatom Definition Edge	1.5	3.4	Not applicable
Siemens Somatom Definition Flash	1.8	3.4	tube A
Siemens Somatom Sensation	1.8	3.1	Not applicable
Siemens Somatom Force	1.7	3.6	BS normal
Siemens Somatom Go.Top	2.3	4.8	go.All/TOP (BS normal)
Siemens Somatom Drive	1.6	3.2	BS normal
Toshiba/Canon Aquilion Prime	2.5	4.1	Prime (BS medium)
Toshiba/Canon Aquilion ONE	3.2	5.8	Premium, ONE, VISION (BS medium)

Table 13. Specific settings that were used in CT-expo

Settings	Definition	Settings Used
U (kV)	Kilovolts	100
I (mA)	Electrical tube current in mA	200
T (s)	Acquisition time per slice or rotation time (spiral scans)	0,6
N*hcol (mm)	Beam width	40
TF (mm)	Table feed per rotation	55
h_{rec} (mm)	Reconstructed slice thickness	0,6
Spiral mode	*Not applicable*	On
Longitudinal dose modulation	*Not applicable*	On
Gender	*Not applicable*	Male
Scan range (cm)	*Not applicable*	40-70
ICRP	International Commission on Radiological Protection	103

The calculations for the effective dose strictly apply only for an average male participants with a length of 170 cm, a weight of 70 kg (154 lbs) and a trunk diameter of 28.3 cm. The effective dose is dependent on participants size, so these calculations are just an indication. The $CTDI_{vol}$ refers to standardized cylindrical phantoms made from PMMA of diameter 32 cm, so different participant dimensions will not impact it. Spiral scans require additional data at the start and at the end of the spiral. Since the spiral mode is on, an over ranging correction is introduced, which will increase the effective dose.

10.10. Appendix 10: 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 summarized as follows:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced 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., generalized hives, itch-flush, swollen lips-tongue-uvula).
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence).
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    – Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP.

Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline.

10.11. Appendix 11: Spirometry and Reversibility

Sites are recommended to advise the participants to take the following measures prior to spirometry, to aid in providing accurate results.

- Avoid eating a large meal for 2 hours before the test.
- Avoid vigorous exercise for 30 minutes before the test.
- Avoid alcohol on the day before the test.
- Wear loose fitting clothing.

Following are some of the recommendations to avoid errors while assessing reversibility (site's preferred method of conducting reversibility may differ):

- Once a subject has signed the ICF, the site should ask the subject when they last took their LABA/LAMA and SABA. If it was within the past 12 hours for LABA/LAMA or 6 hours for SABA, then the site should ask the subject to return to the site for V0 (Screening) assessments on another day when the subject has withheld from LABA/LAMA for >12 hours and SABA for >6 hours.
- For post bronchodilator assessments, 4 puffs of albuterol/salbuterol (SABA) to be delivered using a spacer at 30 second intervals.
- Spirometry should be performed approximately 15 minutes after SABA administration.
- Ensure patient is fully rested prior to pre- and post-bronchodilator spirometry (and rest patient 2-3 minutes between blows if this helps).
- At each visit, spirometry should be performed at the same time of day (+/- 1 hour) as the assessment performed at Visit 1 (the baseline assessment).

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