CLINICAL STUDY PROTOCOL

Primary study intervention(s)	Depemokimab
Other study intervention(s)	Placebo
Study identifier	222725
EU CT number	2024-520417-41
Approval date	05 Aug 2025
Title	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of depemokimab in adult participants with COPD with Type 2 inflammation
Compound number/Name	GSK3511294
Brief title	Depemokimab as an **E**xtended treatme**N**t **DUR**ation biologic in **A**dults with COPD and type 2 inflammation **(ENDURA-2)**
Sponsor	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Sponsor signatory	Jeff Min Senior Director, Respiratory Clinical Research

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

Based on TMF-14732712 Protocol v4.0.

Protocol Amendment 2 Investigator Agreement

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

Study identifier	222725
EU CT number	2024-520417-41
Approval date	05 Aug 2025
Title	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of depemokimab in adult participants with COPD with Type 2 inflammation
Investigator name	
Signature	
Date of signature	
(DD Month YYYY)	

Protocol Amendment Summary Of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	05 Aug 2025
Amendment 1	18 April 2025
Original Protocol	24 March 2025

Amendment 2 (05 Aug 2025)

Overall rationale for the current Amendment:

In Protocol Amendment 2, text regarding the requirement to collect all adverse events from the time of the signing of the ICF and throughout the study has been clarified, irrespective of suspected relationship to study treatment. A change in estimand has been implemented for the primary and secondary endpoints. Additional changes have been made for clarification of study procedures.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
1.2 Schema	The requirement for participants to be on SoC therapy for 6 months prior to Visit 0 has been changed to Visit 1	To be consistent with Section 5.1.4 COPD Maintenance Therapy INC#6
1.3.1 SoA for the first 52 weeks; 8.1.3.1. Screening Visit 0; 8.1.3.2 Critical procedures performed at Screening Visit 1 and 8.4.1 Time period and frequency of collecting AE, SAE and other safety information	All AEs and SAEs must be collected from the signing of the ICF, throughout the study and/or until the Follow-Up visit.	Clarification of the collection of all AEs and SAEs from the signing of the ICF and throughout the study, irrespective of suspected relationship to study treatment.
3.1 Estimands and 9.3.1 Key elements of analysis plan	Change in strategy for handing the ICE of use of another respiratory biologic for COPD for the primary and secondary endpoints	The ICE of use of another respiratory biologic for COPD will be handled using a composite strategy.
8.5 Pharmacokinetics	Deleted description of genetic assessment from the PK section.	Clarification that genetic analysis will not be performed on PK samples. Genetic sample collection is described in Section 8.7 Genetics.
10.8.1 Other countries	Section 10.8.1 Other countries has been added “In countries where medical records systems automatically associate the term “asthma” with use of inhaled corticosteroids, the Investigator should ensure and attest that these participants do not have asthma, and that COPD is the cause of the lung disease in the source documentation.	To clarify that in countries where systems automatically associate the term “asthma” with inhaled corticosteroids, the investigator must attest that COPD is the cause of the lung disease and that the participant does not have asthma.
Global	Correction of grammar, formatting, or spelling	To correct minor errors and improve readability.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Definition
ADA	Antidrug antibodies
ADE	Adverse device effect
AE	Adverse event
AECOPD	Acute exacerbations of COPD
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
ATS	American Thoracic Society
AxMP	Auxiliary medicinal product
BEC	Blood Eosinophil Count
BiPAP	Bi-Level Positive Airway Pressure
BMI	Body mass index
BP	Blood pressure
CASIS	COPD and Asthma Sleep Impact Scale
CAT	COPD assessment test
CFR	Code of Federal Regulations
CI	Confidence Interval
CONSORT	Consolidated standards of reporting trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRF/eCRF	Case report form/electronic case report form
CRP	C-reactive protein
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ED	Emergency department
eDiary	Electronic Diary
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EoS	End-of-study
EQ-5D-3L	European Quality of Life (EuroQol) 5 Dimension 3 Level
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
EXACT	Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes
FAS	Full analysis set
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in one second

Abbreviation	Definition
FSFV	First participant first visit
FTIH	First-time in human
FU	Follow-up
FVC	Forced vital capacity
GCP	Good clinical practices
GCSP	Global Clinical Safety and Pharmacovigilance
GDPR	General data protection regulation
HCP	Healtcare provider
HDV	Hepatitis D
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
IB	Investigator's brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroid
ICSR	Individual case safety reports
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
IV	Intravenous
LA	Long-acting
LABA	Long-acting beta2-adrenergic receptor agonist
LAMA	Long-acting muscarinic receptor antagonist
LFT	Liver function test
LS	Least-sqaures
LSLV	Last participant last visit
LTOT	Long term oxygen therapy
MACE	Major adverse cardiovascular event
MAR	Missing at random
MIDD	Model-informed drug development
MDI	Metered Dose Inhaler
mMRC	Modified Medical Research Council
MSDS	Material safety data sheet
NAb	Neutralizing antibodies
NIPPV	Non-invasive positive pressure ventilation

Abbreviation	Definition
PARC	Pulmonary and activation-regulated chemokine
PD	Pharmacodynamic
PDE3	Phosphodiesterase enzyme-3
PDE4	Phosphodiesterase enzyme-4
PFS	Prefilled safety syringe
PGx	Pharmacogenomics
PI	Personal information
PK	Pharmacokinetic
PP	Per Protocol
PRN	Pro re nata
PRO	Patient reported outcome
QTc	QT interval corrected
QTcF	QT interval corrected with Fridericia's formula
QTL	Quality tolerance limit
RNA	Ribonucleic acid
RTSM	Randomization and Trial Supply Management
RWD	Real World Data
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDAC	Statistical data analysis center
SEA	Severe eosinophilic asthma
SGRQ	St. George's respiratory questionnaire
SGRQ-C	St. George's respiratory questionnaire for COPD patients
SoA	Schedule of activities
SoC	Standard of care
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
T2	Type 2 immune response
TEAE	Treatment-emergent adverse event
TM	Telemedicine
TSLP	Thymic stromal lymphopoietin
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Definition of Terms

Term	Definition
AxMP	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorized AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004. Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator, and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Combination product	Combination product comprises any combination of: • drug • device • biological product. Each drug, device and biological product included in a combination product is a constituent part.
Comparator	Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
eDiary	Electronically recorded patient data and automated data entries on, for example, a handheld mobile device, tablet, or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
ICE	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.
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

Term	Definition
	from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
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.
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 [term is relevant to Japanese regulations only]	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: participant.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
PGx	The ICH E15 Guidance for Industry defines PGx as "the study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of PGx, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (PK, safety, efficacy, or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not PGx.
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

Term	Definition
	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.
Q26W	Once every 26 weeks
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
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.
Self-contained study	Study with objectives not linked to the data of another study.
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).
SoC	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.
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. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Subcohort	A group of participants for whom specific study procedures are planned as compared with other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule) at the time of enrollment.
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 adverse drug reactions that are both serious and unexpected are participant to expedited reporting.
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 randomized, double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of depemokimab in adult participants with COPD with Type 2 inflammation

Brief title: Depemokimab as an **E**xtended treatme**N**t **DUR**ation biologic in **A**dults with COPD and type 2 inflammation **(ENDURA-2)**

Rationale: Depemokimab is being developed as a LA SC injectable anti-IL-5 therapy at a reduced dosing frequency (Q26W) without compromising on efficacy and safety as compared to current anti-IL-5 therapies. The aim of this study is to investigate the efficacy and safety of depemokimab 100 mg SC given Q26W for a minimum of 52 weeks and a maximum of 104 weeks treatment period, as an add-on therapy in participants with uncontrolled moderate to severe COPD with an eosinophilic phenotype. Further details of the rationale are in Section 2.1.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of depemokimab 100 mg SC compared with placebo, given Q26W	• Annualized rate of moderate/severe exacerbations
Secondary	
• To evaluate depemokimab 100 mg SC compared with placebo on additional efficacy endpoints and symptoms	• Time to first moderate/severe exacerbation • Change from baseline in SGRQ total score (measured using the SGRQ-C) at Week 52 • Change from baseline in E-RS: COPD total score at Week 52

Objectives and endpoints for pre-specified pooled analysis across Studies 222714 and 222725 (this study)

Objectives	Endpoints*
Secondary: Pre-specified pooled analysis across studies 222714 and 222725 (this study)	
• To evaluate depemokimab 100 mg SC compared with placebo on pooled efficacy endpoint	• Annualized rate of exacerbations requiring Emergency Department visit or hospitalization • Annualized rate of severe exacerbations

Refer to Section 3 for additional information on objectives, endpoints and estimands.

Overall design: This is a randomized, placebo-controlled, parallel group, double-blind multicenter trial evaluating depemokimab 100 mg SC compared with placebo given Q26W as a liquid formulation in a PFS injection. The study treatment period will be for a minimum of 52 weeks and a maximum of 104 weeks duration.

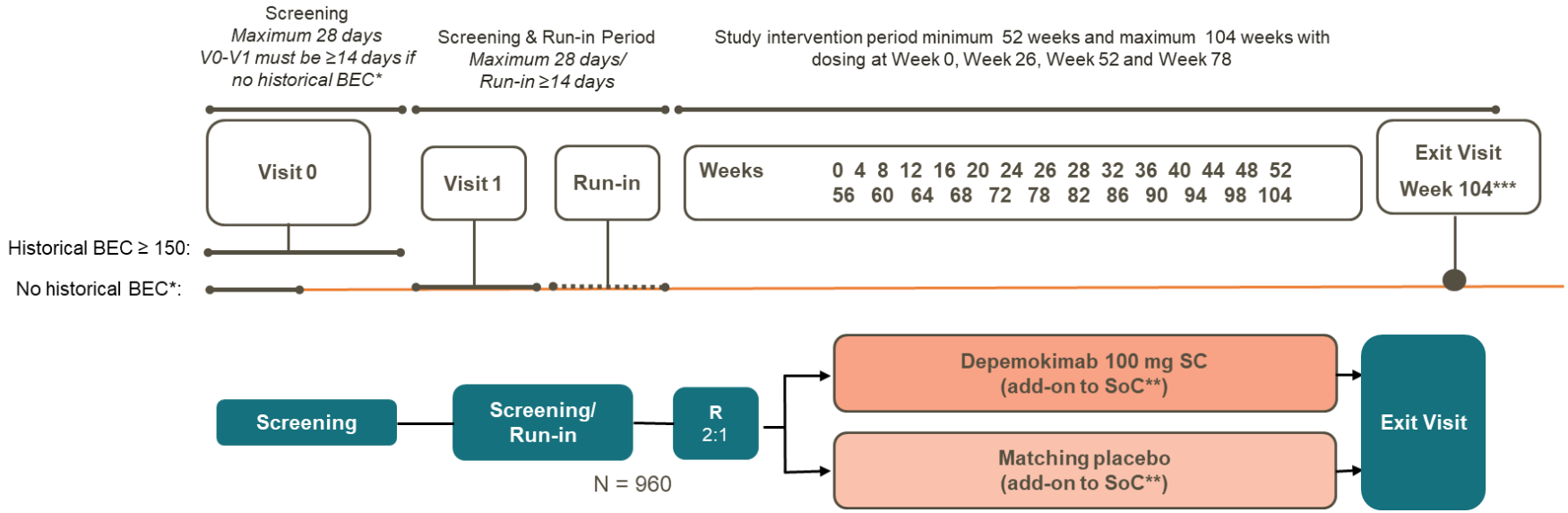
Refer to Section 4.1 for additional information on overall study design.

Number of participants: 960 participants in total (randomization 2:1) will be enrolled in this study.

Data monitoring/other committee: An unblinded interim analysis for futility is planned and will be performed by an SDAC in conjunction with an IDMC to maintain study integrity.

1.2. Schema

Figure 1 Study design overview 222725



BEC: Blood Eosinophil Count; N: Number of participants; R: Randomization; SC: Subcutaneous; SoC: Standard of Care
*Documented evidence of elevated BEC at 2 time-points that are ≥ 14 days apart.
**SoC = optimized standard-of-care COPD maintenance therapy, defined as ICS plus LAMA plus LABA. Participants are required to be on SoC therapy for 6 months prior to Visit 1.
*** The Exit Visit will be scheduled for at least 26 weeks following the last administered dose for a participant. The Exit visit may take place at either Week 52, 78 or 104, according to a participant's planned study duration, and is aligned with the date the last randomized participant is scheduled to complete their Week 52 Visit. The FU visit will be 9 weeks after the Exit Visit.

1.3. Schedule of activities

1.3.1. SoA for the first 52 weeks

Table 1 Schedule of activities for the first 52 weeks

Protocol Activity	Screen-ing	Screening/ Run-in	Intervention Period (Visit Window is ± 7 days)															Follow-up/ Withdraw (±7 days)		Notes
Visit	**V0[a]**	**Visit 1[a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16[n]**	**WS[c]**	**FU**	Bold text = In-clinic visits R* = Randomization; WS = withdraw from study; FU = Follow-up The visit scheduled should be adhered to within the window +/- 7 days
Study Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**61**	
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**			
Distribution of Participant card	X																			
Eligibility Assessments																				
Informed Consent[a]	X																			
Genetic sample Informed Consent[d]	X	(X)																		(X)=assessment may be conducted at Visit 1 if not conducted at Visit 0
Inclusion/Exclusion	X	(X)																		(X)=assessment may be conducted at Visit 1 if not conducted at Visit 0
Demography/child bearing status	X	(X)																		(X)=assessment may be conducted at Visit 1 if not conducted at Visit 0
Medical history		X																		Including CV history, CV risk factors, COPD and exacerbations (see Section 8.1.3.2.)
Pre- and post-bronchodilator Spirometry		X																		Centralized spirometry, one retest is allowed with approval from medical monitor

Protocol Activity	Screen-ing	Screening/ Run-in	Intervention Period (Visit Window is ± 7 days)															Follow-up/ Withdraw (±7 days)		Notes
Visit	**V0[a]**	**Visit 1[a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16[n]**	**WS[c]**	**FU**	Bold text = In-clinic visits R* = Randomization;
Study Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**61**	WS = withdraw from study; FU = Follow-up
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**			The visit scheduled should be adhered to within the window +/- 7 days
Parasite Screening[e]		X																		
eDiary registration and training		X																		Conduct thorough eDiary training at Screening Visit 1 and throughout the study as needed.
CAT		X																		
Randomization Criteria			X																	
Efficacy Assessments																				
Review of exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pre-bronchodilator Spirometry			X	X		X				X							X	X		Centralized spirometry, one retest is allowed for each visit, performed at the same time as the assessment at Visit 2 (± 2 hour)
Post-bronchodilator Spirometry			X														X	X		Centralized spirometry, one retest is allowed for each visit
Review of eDiary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		To be documented in source
Provide medical problems and healthcare utilization worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Review medical problems and healthcare utilization worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		To be verified by the site via a phone call for remote/decentralized assessments To be documented in source

Protocol Activity	Screen-ing	Screening/ Run-in	Intervention Period (Visit Window is ± 7 days)															Follow-up/ Withdraw (±7 days)		Notes
Visit	**V0[a]**	**Visit 1[a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16[n]**	**WS[c]**	**FU**	Bold text = In-clinic visits R* = Randomization; WS = withdraw from study; FU = Follow-up The visit scheduled should be adhered to within the window +/- 7 days
Study Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**61**	
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**			
HRQoL: PRO and Health Outcome Assessments																				
EXACT Daily Symptom Diary		←==========Daily==========→																		
CAT			X							X							X	X		
SGRQ-C			X	X		X				X				X			X	X		
EQ-5D-3L			X							X							X	X		
CASIS			X							X							X	X		
mMRC			X																	
Clinician rated response to therapy						X				X				X			X	X		
Patient rated response to therapy						X				X				X			X	X		
PGI-S of COPD			X														X	X		
PGI-C in COPD																	X	X		
PGI-S of cough			X			X				X				X			X	X		
PGI-S of sputum			X			X				X				X			X	X		
PGI-S of dyspnea			X			X				X				X			X	X		
Additional eligibility and in study safety assessments																				
Concomitant Medication Assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical Examination[g]		X		X	X	X				X		X		X			X	X		
Vital Signs and pulse oximetry		X	X	X	X	X				X		X		X			X	X		
12-lead ECG		X	X							X							X	X		

Protocol Activity	Screen-ing	Screening/ Run-in	Intervention Period (Visit Window is ± 7 days)															Follow-up/ Withdraw (±7 days)		Notes
Visit	**V0[a]**	**Visit 1[a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16[n]**	**WS[c]**	**FU**	Bold text = In-clinic visits R* = Randomization; WS = withdraw from study; FU = Follow-up
Study Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**61**	
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**			The visit scheduled should be adhered to within the window +/- 7 days
Pregnancy (β-HCG blood) test (WOCBP only)[h]		X															X	X		The pregnancy test (β-HCG blood) at V16 is only required if the participant is exiting the study at this stage.
Urine Pregnancy Test (WOCBP only)[h]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	The pregnancy test may be conducted at home or in-clinic
FSH / Estradiol (WONCBP only)		X																		This test is performed to confirm WONCBP status
Hematology with differential[i, j]	X	X	X	X	X	X				X	X	X		X			X	X		For dose administration days (V2/Wk0 and V9/Wk26) obtain prior to dosing. Blinded differential will be performed V2 onwards.
Clinical Chemistry including liver chemistry	X	(X)	X	X	X	X				X	X	X		X			X	X		(X)=assessment may be conducted at Visit 1 if not conducted at Visit 0
Complement C3 and C4			X	←==========														==========→		Additional C3 and C4 sample may be taken in the case of an event potentially representing type III hypersensitivity
Immunogenicity sample			X			X				X				X			X[p]	X		For dose administration days (V2/Wk0 and V9/Wk26) obtain prior to dosing.
AE/SAE[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	This assessment can be conducted by phone call or in-clinic.

Protocol Activity	Screen-ing	Screening/ Run-in	Intervention Period (Visit Window is ± 7 days)															Follow-up/ Withdraw (±7 days)		Notes
Visit	**V0[a]**	**Visit 1[a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16[n]**	**WS[c]**	**FU**	Bold text = In-clinic visits R* = Randomization;
Study Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**61**	WS = withdraw from study; FU = Follow-up
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**			The visit scheduled should be adhered to within the window +/- 7 days
Review COPD symptoms			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		This assessment can be conducted by phone call or in-clinic. Review status to be documented in source.
Smoking Status																				
Smoking Status		X								X							X	X		Smoking history (substance use) to be collected during screening visit
Smoking Cessation Counselling		X																		To be documented in source data
Laboratory Assessments																				
Genetics sample[l]			←==========Collect at Visit 2 or any visit after==========→																	
Biomarkers																				
Clinical Biomarkers																				
CRP			X																	
Eotaxin-3			X																	
FeNO			X																	
Fibrinogen			X																	
IgE			X																	
PARC			X																	
Exploratory systemic (blood/serum/plasma) biomarkers																				
Serum T2 cytokines and proteome			X																	
Exploratory Biomarkers in airway samples																				

Protocol Activity	Screen-ing	Screening/ Run-in	Intervention Period (Visit Window is ± 7 days)														Follow-up/ Withdraw (±7 days)		Notes
Visit	**V0[a]**	**Visit 1[a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16[n]**	**WS[c]**	**FU**	Bold text = In-clinic visits R* = Randomization;
Study Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**61**	WS = withdraw from study; FU = Follow-up
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**			The visit scheduled should be adhered to within the window +/- 7 days
Nasal epithelium (brushing) transcriptomics		X															X	X		
Study treatment																				
Administer study treatment[l]			X							X							X			HCP administered in-clinic using PFS
eCRF/worksheets/other																				
Provision/ dispensing of Rescue medication		X	X			X				X				X			X			
Register Visit in the IRT	X	X	X			X				X				X			X	X		All visits will be in the eCRF
eDiary close out																	X	X		Applies only if this is an exit visit
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pharmacokinetics (PK) sub-study (approximately n=300)																				
PK sub-study Informed Consent	X																			
PK sample				X		X				X				X			X[o]	X		PK sub-study only: PK samples at Week 26 and 52 will be collected pre-dose
Real-world data linkage																				
Token generation			X																	Token will be generated for eligible and consenting participants who are randomized and enrolled into the study

AE = Adverse event; CASIS = COPD and Asthma Sleep Impact Scale; CAT = COPD assessment test; COVID = Coronavirus disease; CRP = C-reactive protein; CV = Cardiovascular; eCRF = electronic case report form; ECG = Electrocardiogram; ED = Emergency department; eDiary = electronic Diary; EXACT= Exacerbations of Chronic Pulmonary Disease Tool; FeNO = Fractional exhaled nitric oxide; FU = Follow-up; HCG= Human Chorionic Gonadotropin; HRQoL = Health-Related Quality of Life; ICF = Informed consent form; IgE= Immunoglobulin E; IRT = Interactive Response Technology; mMRC= modified Medical Research Council; PARC= Pulmonary and activation-regulated chemokine; PD= Pharmacodynamics; PGI-C= Patient Global Impression of Change; PGI-S= Patient Global Impression of Severity; PK = Pharmacokinetics; PRO= Patient-reported outcome; SAE = Serious adverse event; SGRQ-C = St. George's respiratory questionnaire for COPD; TM = Telemedicine; V = Visit; Wk= Week; WOCBP = Women of childbearing potential; WS = Withdraw from study.

a. The period between screening Visit 0 and Visit 1 is a maximum of 28 days. If a participant has a history of an eosinophil count that meets the eligibility criteria, screening Visits 0 and 1 may be conducted on the same day. Otherwise, screening visits 0 and 1 must be conducted at least 14 days apart. Informed Consent must be obtained prior to initiating any study assessments. The randomization visit (Visit 2) must be performed at least 14 days after screening Visit 1, up to a maximum of 28 days. Note: Participants must have BEC of ≥300 cells/µL (analyzed by a central laboratory) and one additional BEC ≥150 cells/µL confirmed prior to randomization into the study. The laboratory assessment may be repeated twice. Under exceptional circumstances, the extension of visit windows for the screening/run-in period is permissible but only with advance written permission from the Medical Monitor.
b. Randomization Visit 2 is up to 4 weeks after Screening Visit 1. Results from Screening Visit 0 and Visit 1 procedures must be available for review of randomization criteria. All assessments at Visit 2 are to be conducted prior to administration of study treatment.
c. Participants who prematurely withdraw from the study should attend an in clinic WS Visit 26 weeks after the last administered dose of study treatment (i.e., at Week 26, Week 52, Week 78 or Week 104) and a follow up visit/call 35 weeks after the last administered dose of study treatment for AE/SAE assessments and pregnancy assessments. Note this includes any participants who discontinue study treatment and remain in the study but subsequently withdraw from the study.
d. Informed Consent for optional genetics research must be obtained before collecting a sample.
e. Parasitic Screening is only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months. Site staff should use local laboratories for the parasitic test.
f. Ensure maintenance COPD medications and vaccinations from the year prior to Screening Visit 0, all medications within the 3 months prior to Screening Visit 0 and all current medications are reviewed. 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 screening or receives during the study must be recorded. Any prior use or experience with a respiratory biologic (regardless of duration) will be recorded.
g. A complete physical exam as well as measurement of height (cm) and weight (kg) should be conducted at Screening Visit 1. For subsequent visits, a brief physical exam only should be conducted. Height (cm) will be measured at screening (Visit 1) only. Body weight (kg) will be measured at screening (Visit 1) and at Visit 16 (if this is an Exit Visit) or Early Discontinuation/ WS visits.
h. Pregnancy testing is only required for women of childbearing potential (WOCBP). A serum pregnancy test will be performed at screening Visit 1 and at an Exit Visit (in line with Section 8.3.5), in subsequent visits a urine pregnancy test will be performed. In case of positive urinary test, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. Pregnancy will lead to definitive treatment discontinuation in all cases.
i. To be randomized, participants must have mandatory hematology test performed at screening and meet the BEC randomization criteria (Section 5.2.8.1). If a participant does not meet the eligibility cut-off for BEC criteria, up to 2 retests are permitted prior to Visit 2
j. For hematology samples collected after Randomization, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, the total white blood counts will be reported throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.
k. All AEs and SAEs will be collected from the signing of the ICF until the Exit Visit/Study withdrawal and/or Follow-Up visit.
l. The genetics sample can be collected at Visit 2 or any visit after.

m. The study treatment (depemokimab or placebo) is to be administered 6-monthly (Q26W) in-clinic (after all scheduled assessments are complete) at the designated study site by way of a scheduled visit. Participants will be monitored in-clinic for a minimum of 2 hours following each administration of the study treatment.
n. Participants will remain in the study for at least 52 weeks and either up to 104 weeks or until a scheduled visit that aligns to the date the last randomized participant is scheduled to complete their Week 52 (Exit Visit).
o. PK sub study only: PK samples may be collected up to 4 weeks prior to the Exit Visit if requested by the Sponsor.
p. Immunogenicity samples may be collected up to 4 weeks prior to the Exit Visit if requested by the Sponsor.

1.3.2. SoA for Weeks 52 to 104

Table 2 Schedule of activities for Weeks 52 to 104

Protocol Activity	Intervention Period and Exit Visit (visit window is ±7 days)													Follow-up/ Withdraw (±7 days)		Notes
Visit	V16[a]	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28 EXIT[b]	WS[c]	FU	Bold text = In-clinic visits WS = withdraw from study; FU =Follow up. The visit scheduled should be adhered to within the window +/- 7 days
Study week	52	56	60	64	68	72	78	82	86	90	94	98	104	78 or 104	87 or 113	
Study Day	364	392	420	448	476	504	546	574	602	630	658	686	728			
Efficacy Assessments																
Review of exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pre-bronchodilator Spirometry	X						X						X	X		Centralized spirometry, one retest is allowed for each visit, performed at the same time as the assessment at Visit 2 (± 2 hour)
Post-bronchodilator Spirometry	X												X	X		Centralized spirometry, one retest is allowed for each visit
Review of eDiary	X	X	X	X	X	X	X	X	X	X	X	X	X	X		To be documented in source.
Provide medical problems and healthcare utilization worksheet	X	X	X	X	X	X	X	X	X	X	X	X				
Review medical problems and healthcare utilization worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X	X		To be verified by the site via a phone call for remote/decentralized assessments To be documented in source
HRQoL: PRO and Health Outcome Assessments																
EXACT Daily Symptom Diary	X															
CAT	X						X						X	X		
SGRQ-C	X			X			X			X			X	X		
EQ-5D-3L	X						X						X	X		
CASIS	X						X						X	X		
Clinician rated response to therapy	X						X						X	X		
Patient rated response to therapy	X						X						X	X		
PGI-S of COPD	X												X	X		
PGI-C in COPD	X												X	X		

Protocol Activity	Intervention Period and Exit Visit (visit window is ±7 days)													Follow-up/ Withdraw (±7 days)		Notes
Visit	**V16**[a]	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28 EXIT**[b]	**WS**[c]	**FU**	Bold text = In-clinic visits WS = withdraw from study; FU =Follow up. The visit scheduled should be adhered to within the window +/- 7 days
Study week	**52**	**56**	**60**	**64**	**68**	**72**	**78**	**82**	**86**	**90**	**94**	**98**	**104**	**78 or 104**	**87 or 113**	
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**546**	**574**	**602**	**630**	**658**	**686**	**728**			
PGI-S of cough	X						X						X	X		
PGI-S of sputum	X						X						X	X		
PGI-S of dyspnea	X						X						X	X		
Additional eligibility and in-study safety assessments																
Concomitant Medication Assessment[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical Examination[e]	X			X			X			X			X	X		
Vital Signs and pulse oximetry	X			X			X			X			X	X		
12-lead ECG	X						X						X	X		
Pregnancy (β-HCG blood) test (WOCBP only)[f]													X	X		
Urine Pregnancy Test (WOCBP only)[f]	X	X	X	X	X	X	X	X	X	X	X	X			X	The pregnancy test may be conducted at home or in-clinic
Hematology with (blinded) differential	X			X			X			X			X	X		For dose administration days (Visit16/Wk52 and Visit 22/Wk78) obtain prior to dosing.
Clinical Chemistry including liver chemistry	X			X			X			X			X	X		
Complement C3 and C4	←==========												==========→			Additional C3 and C4 samples may be taken in case of an event potentially representing type III hypersensitivity
Immunogenicity sample	X			X			X			X			X[g]	X		For dose administration days (V16/Wk52 and V22/Wk78) obtain sample prior to dosing,
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	This assessment can be conducted by phone call or in-clinic.
Review COPD symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X		This assessment can be conducted by a phone call or in-clinic.

Protocol Activity	Intervention Period and Exit Visit (visit window is ±7 days)													Follow-up/ Withdraw (±7 days)		Notes
Visit	**V16**[a]	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28 EXIT**[b]	**WS**[c]	**FU**	Bold text = In-clinic visits WS = withdraw from study; FU =Follow up. The visit scheduled should be adhered to within the window +/- 7 days
Study week	**52**	**56**	**60**	**64**	**68**	**72**	**78**	**82**	**86**	**90**	**94**	**98**	**104**	**78 or 104**	**87 or 113**	
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**546**	**574**	**602**	**630**	**658**	**686**	**728**			
																Review status to be documented in source.
Smoking Status																
Smoking Status	X						X						X	X		
Smoking Cessation Counselling													X	X		To be documented in source.
Biomarkers																
Exploratory systemic (blood/serum/plasma) biomarkers																
Nasal epithelium (brushing) transcriptomics	X												X	X		
Study treatment																
Administer study treatment[h]	X						X									HCP administered in-clinic using PFS
eCRF/worksheets/other																
Provision/ dispensing of Rescue medication	X			X			X			X			X			
Register Visit in the IRT system	X			X			X			X			X	X		
eDiary close out													X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

AE = Adverse event; CASIS = COPD and Asthma Sleep Impact Scale; CAT = COPD assessment test; COVID = Coronavirus disease; CRP = C-reactive protein; CV = Cardiovascular; eCRF = electronic case report form; ECG = Electrocardiogram; ED = Emergency department; eDiary = electronic Diary; EXACT = Exacerbations of Chronic Pulmonary Disease Tool; FeNO = Fractional exhaled nitric oxide; FU = Follow-up; HCG= Human Chorionic Gonadotropin; HRQoL = Health-Related Quality of Life; ICF = Informed consent form; IEC = Independent Ethics Committee; IgE = Immunoglobulin E; PARC = Pulmonary and activation-regulated chemokine; PD = Pharmacodynamics; PGI-C= Patient Global Impression of Change; PGI-S= Patient Global Impression of Severity; PK = Pharmacokinetics; PRO = Patient-reported outcome; SAE = Serious adverse event; SGRQ-C= St. George's respiratory questionnaire for COPD; TM = Telemedicine; V = Visit; Wk = Week; WOCBP = Women of childbearing potential; WS = Withdraw from study

a. Procedures listed for Visit 16 at Week 52 only apply to study participants receiving treatment beyond 52 weeks (i.e., Week 52 to a maximum of Week 104). For these participants, a dose of IMP must be taken at Week 52.

b. The Exit Visit should be at either Week 52, Week 78 or Week 104 and should occur at least 26 weeks following the last administered dose and be aligned to the date the last randomized participant is scheduled to complete their Week 52 Visit. No further study treatment is to be administered at the Exit Visit. In the instance that the Exit Visit occurs at Week 52 or Week 78, all predefined Exit Visit assessments are to be conducted instead of the predefined assessments for the scheduled visit.

c. Participants who prematurely withdraw from the study should attend an in clinic WS Visit 26 weeks after the last administered dose of study treatment (i.e., at Week 26, Week 52, Week 78 or Week 104) and a follow up visit/call 35 weeks after the last administered dose of study treatment for AE/SAE assessments and pregnancy assessments. Note this includes any participants who discontinue study treatment and remain in the study but subsequently withdraw from the study.
d. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving during the study must be recorded
e. A complete physical exam including weight should be conducted at Visit 16 (Week 52) and Visit 28 (Exit Visit, Week 104) and a brief physical examination at intervening visits.
f. Pregnancy testing is only required for women of childbearing potential (WOCBP).
g. Immunogenicity samples may be collected up to 4 weeks prior to the Exit Visit if requested by the Sponsor.
h. The study treatment (depemokimab or placebo) is to be administered 6-monthly (Q26W) in-clinic (after all scheduled assessments are complete) at the designated study site by way of a scheduled visit. Participants will be monitored in-clinic for a minimum of 2 hours following each administration of the study treatment.

2. INTRODUCTION

2.1. Study rationale

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction [Celli, 2022]. COPD is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung. Exposure to noxious particles or gases predominantly due to cigarette smoking is an important risk factor for COPD worldwide. Other risk factors include occupational and environmental exposures, respiratory infections, socio-economic status and genetic predisposition. While the disease course is marked by progressive deterioration in airflow, it is punctuated by AECOPD which contribute to the overall disease severity and which increase in frequency as the disease worsens [Vogelmeier, 2017; Barnes, 2015]. In addition to the increased risk of morbidity and mortality associated with COPD exacerbations, these events place a significant economic burden on healthcare systems which is predicted to increase with the increasing global disease prevalence [Halpin, 2017; Perera, 2012; Toy, 2010].

A subset of COPD patients have evidence of Type 2 inflammation characterized by elevated blood and sputum eosinophils; circulating Th2 cells; ILC2 and elevated Type 2 cytokines (IL-4, IL-5 & IL-13) [Barnes, 2015; Christenson, 2015]. Up to 40% of COPD patients have an inflammatory pattern that includes elevated sputum eosinophils [Brightling, 2005; Saha, 2006]. In these patients, the BEC has been identified as a predictor of response to therapies targeting type 2 inflammation. IL-5 is a dominant cytokine driving T2 pathological inflammation through multiple cell types [Bischoff, 1990; Maspero, 2021; Ochi, 2000; Stone, 2010]. Based on the observation that airway eosinophilic inflammation is associated with COPD exacerbations [Bafadhel, 2011; Bafadhel, 2017], and that reducing Type 2 inflammation would attenuate COPD exacerbations, the mepolizumab COPD program was designed to evaluate whether anti-IL-5 therapy could reduce exacerbations in a COPD patient population meeting a blood eosinophil threshold with a history of exacerbations despite receiving ICS-based triple maintenance therapy.

MEA117106 and MEA117113 were two Phase 3A studies of mepolizumab in COPD participants who were uncontrolled despite maximum inhaled therapy [Pavord, 2017]. These studies compared treatment with mepolizumab to placebo when added to maximum inhaled SoC (ICS plus LABA plus LAMA). These studies demonstrated that mepolizumab given at a dose of 100 mg SC Q4W resulted in clinically relevant rate reductions in moderate/severe exacerbations of 18% (MEA117106 high stratum) and 20% (MEA117113) compared with placebo in participants with peripheral BEC of ≥150 cells/µL at Screening or ≥300 cells/µL in the prior 12 months. A greater response (24% reduction in the rate of moderate/severe exacerbations compared with placebo) was observed in participants with a higher cutoff of BEC ≥300 cells/µL at Screening – this population is similar to the population evaluated in the Phase 3 MATINEE (208657) study of mepolizumab in participants with uncontrolled COPD. Mepolizumab

administration in COPD was generally safe compared with placebo, with an AE profile similar to the known profile for mepolizumab in other approved indications, with no new safety concerns.

Depemokimab is being developed as a LA SC injectable anti-IL-5 therapy at a reduced dosing frequency (Q26W) without compromising efficacy and safety profile compared to current investigational anti-IL-5 therapies. The single ascending dose depemokimab FTIH study (Study 205722) investigated safety, tolerability, immunogenicity, PK and PD of depemokimab administered SC in participants with mild to moderate asthma, who were controlled on low-medium daily dose of ICS and/or ICS plus LABA, and short acting bronchodilators. Data from Study 205722 showed that the engineered changes to the antibody have resulted in reduced clearance, extended half-life, and extended pharmacology (allowing for SC administration Q26W, therefore dosing twice a year) compared with mepolizumab, combined with an acceptable safety profile [GSK Study Report 2019N411063].

The efficacy and safety of depemokimab has been evaluated in two replicate Phase 3 trials, SWIFT-1 and SWIFT-2. in which 792 patients underwent randomization and 762 were included in the full analysis; 502 were assigned to receive depemokimab and 260 to receive placebo. The annualized rate of exacerbations was 0.46 (95% CI, 0.36 to 0.58) with depemokimab and 1.11 (95% CI, 0.86 to 1.43) with placebo (rate ratio, 0.42; 95% CI, 0.30 to 0.59; P<0.001) in SWIFT-1 and 0.56 (95% CI, 0.44 to 0.70) with depemokimab and 1.08 (95% CI, 0.83 to 1.41) with placebo (rate ratio, 0.52; 95% CI, 0.36 to 0.73; P<0.001) in SWIFT-2. No significant between group difference in the change from baseline in the SGRQ score was observed in either trial, so no statistical inference was drawn on subsequent secondary end points. The proportion of patients with any adverse event was comparable in the depemokimab group and the placebo group in SWIFT-1 (73% for both) and SWIFT-2 (72% and 78%, respectively). There were no deaths and no serious adverse events that were considered by the investigator to be related to depemokimab or placebo [Jackson, 2024]

The aim of studies 222714 and 222725 is to investigate the efficacy and safety, over a 52- to 104-week treatment period of depemokimab 100 mg SC administered Q26W as an add-on therapy in participants with moderate to severe COPD with type 2 inflammation characterized by an eosinophilic phenotype. These studies are designed to confirm the benefits of depemokimab treatment on the primary outcome of moderate/severe exacerbations as well as to inform on outcomes which are less frequent such as exacerbations requiring ED visits or hospitalization as well as additional important HRQoL data.

Based on the results of 205722, MEA117113, MEA117106, MATINEE studies and feedback from health authorities, the inclusion criteria for this study focus on moderate to severe COPD participants with an eosinophilic phenotype who are more likely to benefit from depemokimab treatment.

2.2. Background

Persistent eosinophil inflammation is a feature of up to 40% of patients with severe COPD [Brightling, 2005; Saha, 2006]. and in severe asthma [Chung, 2014]. Only one mAb targeting eosinophil inflammation in COPD with an eosinophilic phenotype has received marketing authorization; dupilumab (Dupixent) a dual inhibitor of IL-4 and IL-13 signalling has been shown to reduce the rate ratio for the annualized rate of moderate or severe exacerbations by about 30% (rate ratio 0.70 [95% CI, 0.58 to 0.86]) and an improvement in prebronchodilator FEV1 increased from baseline to week 12 by a LS mean of 160 ml (95% CI, 126 to 195) with dupilumab and 77 ml (95% CI, 42 to 112) with placebo (LS mean difference, 83 ml; 95% CI, 42 to 125; P<0.001), a difference that was sustained through week 52 [Bhatt, 2023]. In a replicate Phase 3 trial, dupilumab was shown to reduce the rate ratio for the annualized rate of moderate or severe exacerbations by about 34% (rate ratio 0.66 (95% CI 0.54 to 0.82; P<0.001) and an improvement in prebronchodilator FEV1 increased from baseline to week 12 by an LS mean of 139 ml [95% CI, 105 to 173] as compared with placebo (least-squares mean change, 57 ml [95% CI, 23 to 91]), with a significant least squares mean difference at week 12 of 82 ml (P<0.001) and at week 52 of 62 ml (P=0.02) [Bhatt, 2024]. Several mAbs are being evaluated in Phase 3 trials for COPD. MATINEE, evaluating mepolizumb as add-on treatment in individuals with COPD has completed and marketing authorization is under review.

Several mAbs targeting eosinophil inflammation have received marketing authorization for asthma with an eosinophilic phenotype, including 3 targeting either IL-5 or its receptor (IL-5R): mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All three, by utilizing blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations, and improve lung function and HRQoL, in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL-5/5R is provided by depemokimab asthma studies (SWIFT 1 and 2); long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data in real-world evidence settings for mepolizumab [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence, have demonstrated that treatments targeting the IL-5 pathway are both highly effective and well-tolerated. Based on this established efficacy and safety, anti-IL-5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimized care with Step 4 or Step 5 treatment (medium and high dose ICS); anti-TSLP tezepelumab is also recommended [GINA, 2020]

Depemokimab is a humanized, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, depemokimab contains 7 amino acid substitutions to the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region and 3 amino acid changes (YTE) in the Fc region. The resulting antibody has increased affinity and half-life. Evidence to date indicate that these amino acid changes extend the pharmacokinetics (PK) and pharmacology of depemokimab to enable less frequent dosing with an anticipated similar efficacy and safety profile relative to mepolizumab (administered chronically).

LA alternatives that can be administered on a less frequent basis are recognized as successful approaches for chronic indications. As a LA anti-IL-5 therapy, depemokimab is anticipated to have an efficacy and safety profile that is similar to those of the currently approved therapies in its class, but with a single administration Q26W, as opposed to the current regimen of Q4W for mepolizumab and reslizumab, or Q8W for benralizumab (Q4W for the first 3 doses).

A detailed description of the chemistry, pharmacology, and safety of depemokimab is provided in the current IB [GSK Document Number RPS-CLIN-132006].

2.3. Benefit-risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of depemokimab may be found in the IB [GSK Document Number RPS-CLIN-132006].

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention - Depemokimab (GSK3511294)		
• Allergic reactions including anaphylaxis.	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 9) 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 IB "Safety in Clinical studies" section. 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].	• Daily monitoring of SAEs by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. • Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 9). • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An IDMC will review unblinded safety data at regular intervals. • Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose. • Use of dedicated eCRF pages to collect information on systemic reactions.
• 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	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed (Section 5.2). • Daily monitoring of SAEs will be done by Medical Monitor; regular systematic review of adverse event

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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].	(AE)/SAE data from ongoing studies will be performed by a GSK safety review team. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a rheumatologist (member of the IDMC). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.1.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1). • Use of dedicated eCRF page to collect information on type III hypersensitivity (immune complex disease/ vasculitis).
• 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 "Safety in Clinical studies" section. Further information is summarized in section 6 of the IB titled 'Summary of Data and Guidance for the Investigator'.	• 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. • The IDMC will review unblinded safety data at regular intervals. • Use of dedicated eCRF page to collect information on local injection site reactions.
• Risk of depemokimab affecting an unborn baby.	• Reproductive studies have not been conducted with depemokimab; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages in sexually mature males. No cell or stage specific abnormalities were noted. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism (as shown in pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of mAbs into semen due to the inability of large molecular weight proteins such as depemokimab to access pivotal cells in the	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (Section 5.2.8.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing potential must be using a highly effective contraceptive method from at least 14 days prior to first dose and until 35 weeks after the last administered dose as described in Section 10.4.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	testes [Setchell, 1975; Pollanen, 1989; Pollanen, 1995; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).
• Potential risk of mild discomfort and/or minor nasal bleeding during nasal epithelium collection (nasal brushing)	• Brushing of the inferior nasal turbinate to collect upper airway cells (i.e., nasal brushing) is a common, minimally invasive, diagnostic (e.g., ciliary dysfunction) and research procedure that has been performed in healthy volunteers and participants from infancy to adult age; [Mosler, 2008; Hamizan, 2019; Fawcett, 2023; van Nijnatten, 2023]. It is considered a well-tolerated procedure with potential reported risks of mild discomfort, reflex lacrimation, sneezing, and/or possible minor nasal bleeding during the procedure that are self-limited. Significant bleeding from a nasal brushing procedure is considered extremely rare.	• Technique to be performed by appropriately trained staff. The potential mild side effects described are self-limited and minimized by the short duration of the procedure with the brushing itself anticipated to take less than 10 seconds. • If the procedure is deemed by the investigator to be intolerable or inappropriate for an individual participant, it may be omitted. If any of the samples are not successfully taken at the baseline visit, that procedure should not be performed at any subsequent study visit.

2.3.2. Benefit assessment

Current clinical data from anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as COPD and asthma with an eosinophilic phenotype. Mepolizumab 100 mg SC (Q4W) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. Additionally, mepolizumab 100 mg SC (Q4W) is under review with multiple global health authorities as an add-on maintenance treatment for COPD with an eosinophilic phenotype. The safety profile of mepolizumab is favorable.

As a LA anti-IL-5 mAb, depemokimab is anticipated to provide the same clinical benefit without compromising on the safety profile compared with mepolizumab and others in its class and with the added benefit of an extended duration of action and sustained control of inflammation, requiring less frequent SC dosing (Q26W). As such, depemokimab may offer the convenience of an improved dosing schedule.

2.3.3. Overall benefit-risk conclusion

Taking into account the measures taken to minimize risk to participants from this study, the potential risks identified in association with depemokimab are justified by the anticipated benefits that may be afforded to participants with COPD.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of depemokimab 100 mg SC compared with placebo, given Q26W	• Annualized rate of moderate/severe exacerbations
Secondary	
• To evaluate depemokimab 100 mg SC compared with placebo on additional efficacy endpoints and symptoms	• Time to first moderate/severe exacerbation • Change from baseline in SGRQ total score (measured using the SGRQ-C) at Week 52 • Change from baseline in E-RS: COPD total score at Week 52
Other Exploratory*	
• To evaluate depemokimab 100 mg SC compared with placebo on additional PRO efficacy measures	• Change from baseline in CAT score at Week 26, Week 52, Week 78, and Week 104 • CAT score responders (≥2 unit reduction in CAT score from baseline) at Week 26, Week 52, Week 78, and Week 104 • Other endpoints as detailed in Appendix 10
• To evaluate depemokimab 100 mg SC compared with placebo on lung function	• Change from baseline in pre-bronchodilator FEV1 and FVC at Week 4, Week 12, Week 26, Week 52, Week 78 and Week 104 • Change from baseline in post-bronchodilator FEV1 at Week 52 and Week 104
• To evaluate depemokimab 100 mg SC compared with placebo on health outcome endpoints	• Change from baseline in EQ-5D-3L at Week 26, Week 52, Week 78 and Week 104 • Healthcare utilization for COPD including hospitalization, ED, and physician office/clinic visits
• To evaluate depemokimab 100 mg SC compared with placebo with respect to patient and clinician rating of symptom severity and change, and response to therapy	• Patient-rated response to therapy, clinician-rated response to therapy, PGI-C in COPD, and change from baseline in PGI-S at Week 52 and Week 104 for cough, sputum, dyspnea, and COPD
• To evaluate depemokimab 100 mg SC compared with placebo on sleep	• Change from baseline in CASIS total score at Week 26, Week 52, Week 78, and Week 104
Biomarkers, Pharmacodynamics and Pharmacokinetics	
• Biomarkers • To explore the association of baseline biomarkers with treatment response	• Baseline clinical biomarkers (FeNO, Eotaxin-3, PARC, Fibrinogen, CRP, IgE) • Baseline serum T2 cytokines and/or proteome
• To explore the pharmacodynamic response and the association with treatment response for exploratory systemic and airway biomarkers	• Change from baseline for selected exploratory biomarkers • Nasal epithelium brushing transcriptomic profile
• Pharmacodynamics • To investigate the PD effects of depemokimab	• Ratio to baseline in absolute BEC at discrete time-points during the 104-Week treatment period
• Pharmacokinetics (sub-study) • To investigate the PK of depemokimab (subgroup of participants)	• Depemokimab plasma concentration at discrete time-points during the 52-Week treatment period
Safety	
• To evaluate the safety of depemokimab 100 mg SC Q26W versus placebo in	• Incidence of AEs/SAEs

Objectives	Endpoints
participants with COPD with an eosinophilic phenotype	• Incidence of adjudicated SAE reports and adjudicated MACE (CV death, heart failure, non-fatal myocardial infarction, or non-fatal stroke) • Change from baseline in vital signs including BP, body temperature, pulse rate • Change from baseline in ECG values • Immunogenicity as measured by the incidence of ADA and NAb to depemokimab • Change from baseline in Laboratory parameters, including (hematological, and clinical chemistry parameters) and hepatobiliary laboratory abnormalities • Mortality (all cause including respiratory and cardiovascular causes of death)

AE = Adverse event; ADA = antidrug antibodies; CRP = C-reactive protein; EXACT = Exacerbations of Chronic Pulmonary Disease Tool; ECG = Electrocardiogram; (E-RS: COPD = Evaluating Respiratory Symptoms in COPD; FeNO = Fractional exhaled nitric oxide; HRQoL = Health-Related Quality of Life; IgE = Immunoglobulin E; MACE = major adverse cardiovascular event; NAb = neutralizing antibodies; PARC = Pulmonary and activation-regulated chemokine; PD = Pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = Pharmacokinetics; SAE = Serious adverse event; SC = subcutaneous; SGRQ-C = St. George's respiratory questionnaire for COPD
*Other exploratory objectives and endpoints are presented in Appendix 10.

Objectives and endpoints for pre-specified pooled analysis across Studies 222714 and 222725 (this study)

Objectives	Endpoints
Secondary: Pre-specified pooled analysis across studies 222714 and 222725 (this study)	
• To evaluate depemokimab 100 mg SC compared with placebo on pooled efficacy endpoint	• Annualized rate of exacerbations requiring ED visit or hospitalization • Annualized rate of severe exacerbations

3.1. Estimands

3.1.1. Primary estimand

The primary clinical question of interest is the reduction in annualized rate of moderate/severe COPD exacerbations with depemokimab 100 mg SC compared with placebo, both given Q26W added to SoC, in participants with moderate to severe COPD experiencing frequent exacerbations and characterized by BEC, regardless of treatment discontinuation for any reason, changes in background medication or use of a prohibited medication and incorporating the use of another respiratory biologic for COPD.

- **Treatment comparison:** depemokimab 100 mg SC versus placebo (both as add-on treatment to optimized SoC)
- **Population:** Participants with moderate to severe COPD experiencing frequent exacerbations and characterized by BEC.
- **Primary endpoint:** Annualized rate of moderate/severe exacerbations
- **Summary measure:** Ratio of the annualized rates of moderate/severe exacerbations between depemokimab and placebo

- **Intercurrent events (ICE) anticipated**:
  - Premature discontinuation of study treatment – to be handled using a treatment policy strategy (i.e., regardless of the ICE occurring)
  - Change in background medication or use of a prohibited medication – to be handled using a treatment policy strategy (i.e., regardless of the ICE occurring)
  - Use of another respiratory biologic for COPD – to be handled using a composite strategy
- **Rationale for estimand:** Interest lies in evaluating the treatment effect based on the intention to treat a participant irrespective of their compliance to the planned course of treatment, changes in background medication or use of prohibited medication. A composite strategy was chosen for the ICE of use of another respiratory biologic for COPD recognizing the possibility of participants being prescribed alternative biologics that become available in their respective countries, and the impact that receiving such alternative respiratory biologics may have on the occurrence of exacerbations.

3.1.2. Secondary estimands

The secondary estimands are defined as follows:

- **Treatment comparison:** depemokimab 100 mg SC versus placebo (both as add-on treatment to optimized SoC)
- **Population:** Participants with moderate to severe COPD experiencing frequent exacerbations and characterized by BEC.
- Secondary endpoints:
  - Time to first moderate/severe exacerbation.
  - Change from baseline in SGRQ total score (measured using the SGRQ-C) at Week 52.
  - Change from baseline in E-RS: COPD total score at Week 52.
- Summary measure:
  - Hazard Ratio for Time to first moderate/severe exacerbation.
  - Difference in mean change from baseline in SGRQ total score (measured using SGRQ-C) at Week 52.
  - Difference in mean change from baseline in E-RS: COPD total score at Week 52.
- **Intercurrent events (ICE) anticipated**: The same set of ICEs will be addressed using the same strategies as for the primary estimand above.

3.1.3. Secondary estimands for pre-specified pooled analysis across Studies 222714 and 222725 (this study)

The secondary estimands for the pre-specified pooled analysis are defined as follows (Refer to Section 3):

- **Treatment comparison:** depemokimab 100 mg SC versus placebo (both as add-on treatment to optimized SoC)
- **Population:** Participants with moderate to severe COPD experiencing frequent exacerbations and characterized by BEC.
- **Secondary endpoint:**
  - Annualized rate of exacerbations requiring ED visit or hospitalization.
  - Annualized rate of severe exacerbations.
- Summary measure:
  - Ratio of the annualized rates of exacerbations requiring ED visit or hospitalization.
  - Ratio of the annualized rates of severe exacerbations.
- **Intercurrent events (ICE) anticipated**: The same set of ICEs will be addressed using the same strategies as for the primary estimand above.

4. STUDY DESIGN

4.1. Overall design

This is a randomized, placebo-controlled, parallel group, double-blind multicenter trial evaluating depemokimab 100 mg SC compared with placebo given Q26W as a liquid formulation in a PFS injection. The study treatment period will be a minimum of 52 weeks up to a maximum duration of 104 weeks. Rescue therapy will be provided to the participants during the study.

Study inclusion criteria require a BEC of ≥300 cells/µL at Screening Visit 0 or Visit 1 as well as an additional BEC of ≥150 cells/µL (either historical in the previous 12 months or taken during screening). If a participant does not meet the eligibility cut-off for BEC criteria, up to 2 retests are permitted prior to Visit 2. Participants must have a history of regular use of triple maintenance COPD therapy (as defined in Inclusion Criteria, Section 5.1) for at least 6 months prior to Screening Visit 1. Participants are also required to have a history of at least 2 moderate COPD exacerbations that were treated with systemic corticosteroids (IM, IV or oral), or at least 1 severe exacerbation requiring hospitalization in the 12 months prior to Screening Visit 1 and at least one of the exacerbations must have occurred while treated with ICS plus LAMA plus LABA.

All participants will continue optimized maintenance inhaled COPD therapy throughout the entire duration of the study regardless of intervention arm assignment.

Excluding screening and run-in periods, participants will remain in the study for at least 52 weeks and either up to 78 or 104 weeks, whichever visit aligns to the date of the last randomized participant is scheduled to complete their Week 52. The timing of the last randomized participant into the study will thus affect the timing of the Exit Visit for participants enrolled beyond 52 weeks. All participants will be expected to complete at least 52 weeks of the study. The last randomized participant will be scheduled to complete only 52 weeks of the study.

The study will consist of a screening Visit 0 and Visit 1, a run-in period (≥14 days) and a study intervention period (minimum 52 weeks and maximum of 104 weeks) (Figure 1). After the run-in period, participants will be randomized in a 2:1 ratio using an IRT system in a blinded manner to receive either up to four doses of depemokimab 100 mg (Q26W), or placebo by SC injection. The doses of study intervention will be administered in the clinic and after all scheduled assessments are complete: the first dose at randomization visit (Visit 2, Week 0, Day 1), the second at Visit 9 (Week 26), the third and fourth doses will be administered at Visit 16 (Week 52) and Visit 22 (Week 78). Participants will be assessed at each scheduled visit (16 study visits) during the 52-Week treatment phase and for an additional 12 visits from Week 52 to Week 104.

If the participant has a qualifying historical BEC≥150 cells/µL, Visit 0 may occur anytime from 0 to 28 days (0 to 4 weeks) before Visit 1. If the participant does not have a qualifying historical BEC, Visit 0 and Visit 1 must occur at least 14 days apart to allow for the appropriate time between eosinophil measurements. Assessments may be conducted at Visit 1 if not conducted at Visit 0.

Randomization Visit 2 must be performed at least 14 days after the start of Screening Visit 1. Results from Screening Visit 1 procedures must be available for review of randomization criteria. To be randomized, participants must demonstrate having elevated BEC at two time-points (≥300 cells/μL for one time-point and ≥150 cells/μL for the other) at least 14 days apart.

Screening and Visits 2 to 5, 9, 10, 11, 13, 16, 19, 22, 25 and 28 are designated to be conducted in-clinic. All other visits are designated as decentralized/remote visits which may be conducted virtually (TM, secure video conferences, phone calls, or a web portal and/or mobile application). Decentralized/remote visits may be conducted in-clinic if this is a preferred option by the participant or deemed medically necessary by the investigator. Study procedures that can be conducted through decentralized/remote visits are those listed in the SoA (Section 1.3) table at Visit 6 and onwards (excluding the Exit Visit). The following procedures should be conducted in the clinic: (i) spirometry, (ii) clinician rated response to therapy, and (iii) complete physical examinations.

Informed consent must be obtained prior to initiating any study assessments.

A follow-up visit will be conducted 9 weeks after the Exit Visit, which may be conducted in-clinic or via a phone call.

An IDMC will be utilized to ensure external objective review of the data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (see Section 8.3.8).

4.2. Scientific rationale for study design

Population: This study is designed to evaluate the efficacy and safety of depemokimab 100 mg SC as an add-on therapy in participants with moderate to severe uncontrolled COPD with an eosinophilic phenotype. Participants should have uncontrolled COPD, as evidenced by repeat exacerbations, despite treatment with optimized background triple therapy. The concurrent use of these medications (i.e., ICS plus LABA plus LAMA) is often termed ‘triple inhaled maintenance therapy’. For participants who continue to exacerbate despite the use of triple inhaled therapy (approximately 40% of participants on inhaled triple therapy), there are limited additional maintenance treatment options. Additional adjunctive therapies, such as chronic macrolides or PDE3/PDE4 inhibitors, are also permitted as part of an optimized COPD regimen.

Participants are also required to have the requisite elevated BEC (see Randomization criterion 1, Section 5.2.8) that is indicative of moderate to severe COPD with an eosinophilic phenotype. This population has been shown to benefit from add-on anti-IL-5 therapies such as mepolizumab [Pavord, 2012; Ortega, 2014; Chupp, 2017] and is therefore anticipated to benefit from depemokimab.

BEC at screening: A Screening BEC threshold of ≥300 cells/µL at Screening Visit 0 or Visit 1 as well as an additional BEC ≥150 cells/µL (either historical in the previous 12 months or taken during screening), has been selected as a criterion to identify participants likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous trials with mepolizumab.

Primary efficacy endpoint: A primary efficacy endpoint of annualized rate of moderate/severe exacerbations has been selected as a robust and clinically relevant measure of the direct benefit of depemokimab to a population with severe uncontrolled moderate to severe COPD with an eosinophilic phenotype. An exacerbation of COPD is defined as an event characterized by increased dyspnea and/or cough and sputum that worsens in <14 days which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution or other insults to the airways [GOLD, 2025]. In the current study, the definition of moderate/severe exacerbations (see Section 8.2.1), i.e., clinically significant exacerbations treated with systemic corticosteroids (IM, IV, or oral) and/or antibiotics, or resulting in hospitalization or death, is consistent with previous trials with mepolizumab [Pavord, 2012; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Placebo-controlled design: An established randomized, double-blind and parallel-group study design will allow for a robust determination of participant response to depemokimab on established background therapy. As such, the comparator arm in this study will be placebo plus continued maintenance COPD treatment. A 2:1 randomization will be used in order to limit the number of participants randomized to placebo treatment and to provide more safety information on depemokimab. All participants will continue to receive their optimized maintenance COPD therapy throughout the entire duration of the study regardless of intervention arm assignment, as defined in Inclusion Criteria Section 5.1.

Study duration: The study treatment period will be a minimum of 52-weeks up to a maximum of 104 weeks, which should allow sufficient time to assess whether depemokimab 100 mg SC, administered as up to 4 repeat doses 26 weeks apart (at Week 0 [randomization] and at Weeks 26, 52, and 78), can reduce the annualized rate of clinically significant exacerbations to a similar extent to what has been observed with other anti-IL-5 mAbs compared to placebo. The study will also provide 12 to 24-months of safety data with repeat dosing.

Run-in period: The run-in period (≥14 days) allows for the assessment of participant understanding and compliance with the daily eDiary, to establish Baseline symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Data collection after discontinuation from study intervention: The protocol objective is to collect data over the full study period, whether participants continue on study intervention or in the case of premature discontinuation from study intervention. However, the decision to continue in the study after premature discontinuation from study intervention remains the prerogative of the participant. Participants who agree to

continue in the study after premature discontinuation from study intervention (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned minimum 52-week up to a maximum of 104 weeks participation and follow up contact 9 weeks later, to enable capture of post-intervention information.

4.2.1. Patient input into design

Participant involvement in the study design was obtained from 50 patients (10 in US, 10 in UK, 10 in Argentina, 10 in Germany and 10 in China) using an online qualitative survey containing 43 questions over a period of 2 weeks. Based on the participant feedback and assessment of burden, the following elements were incorporated into the study design:

- The frequency of PROs and Patient Global Impressions (PGI) were reduced,
- The frequency of biomarker sample collection was reduced.
- Patients provided favorable feedback on the hybrid trial model, allowing for home visits and virtual/telemedicine visits at key assessments which will reduce the burden of onsite visits and offer some flexibility in visit timing for the participant's schedule

4.3. Justification for dose

Using MIDD principles, the dose and dosing frequency of depemokimab that matches the blood eosinophil pharmacology observed in the mepolizumab Phase 3 studies (MEA117106 and MEA117113) was determined to be 100 mg administered SC Q26W. The same dose regimen was used for the asthma (206713 and 213744) and CRSwNP Phase 3 clinical studies (217095 and 218079) based on similar principles.

The dose rationale for this study is supported by FTIH study 205722 (single SC doses of depemokimab ranging from 2 mg to 300 mg), which was designed to collect robust blood eosinophil pharmacology data (including washout) in an eosinophilic population (mild to moderate asthma and a BEC ≥200 cells/µL at screening) and to inform dose selection in late-phase development using MIDD principles [Wang, 2019; Marshall, 2019]. The precedence of using blood eosinophil reduction as a predictor of efficacy was originally established in severe asthma with an eosinophilic phenotype. Two mepolizumab Phase 3 studies in asthma, demonstrated consistently reduced annualized exacerbation rate by approximately 50%, with associated reductions in BEC of 84% in the MENSA trial [Ortega, 2014] and 78% in the MUSCA trial [Chupp, 2017], compared with placebo. In the COPD population, a similar reduction in blood eosinophils at Week 52 of 78% and 80% (compared with placebo) was observed in studies MEA117113 and MEA117106 high stratum following mepolizumab 100 mg SC Q4W. A higher 300 mg dose was tested in study MEA117113, however this higher dose was associated with only a minimal increase in the BEC reduction (84% compared with placebo) with no evidence of increased efficacy.

Since depemokimab targets the same IL-5 epitope as mepolizumab, establishing the same reduction in BEC as mepolizumab via the same IL-5 neutralization is expected to provide comparable clinical efficacy in COPD with an eosinophilic phenotype with a previous history of two moderate or 1 severe exacerbation in the past 12 months. This hypothesis has already been established in SEA where the depemokimab dose of 100 mg Q26W demonstrated sustained reductions of BEC in the positive Phase 3 studies (SEA SWIFT 1&2 [Jackson, 2024]) comparable to mepolizumab.

A PK-blood eosinophil model previously developed based on mepolizumab data was updated to reflect the comparably longer half-life and enhanced IL-5 binding affinity of depemokimab. The PK and IC50 parameters were re-estimated based on the data from the depemokimab FTIH Study. The impact of the baseline BEC on the maximum achievable drug inhibitory response was assumed to be the same between mepolizumab and depemokimab. The baseline value in the model was adjusted to reflect the expected typical value in the depemokimab Phase 3 population with a baseline BEC ≥300 cells/µL. The model predicted BEC and percentage change from baseline at Week 52 following administration of 100 mg SC depemokimab Q26W are shown in Table 4 together with the observed data from the combined MEA117106 and MEA117113 subpopulation with ≥300 cells/µL at baseline who received 100 mg SC mepolizumab Q4W. The predictions show that the percentage decrease from baseline at the selected depemokimab dose of 100 mg SC Q26W is expected to result in a similar suppression of eosinophils as observed in the MEA117106 and MEA117113 studies following 100 mg SC mepolizumab Q4W. Similar levels of eosinophils suppression were predicted at higher doses.

Table 4 Predicted geometric mean (95% Prediction Interval) and percent reduction of BEC at end of treatment (Week 52) for depemokimab, compared with end of treatment observed in mepolizumab pivotal Ph3 trials in COPD (MEA117106, MEA117113)

	Depemokimab 100 mg SC Q26W	Mepolizumab 100 mg SC Q4W
		METREO and METREX combined ≥300 cells/µL sub-population
Geometric mean (cells/µL)	92.9	50
95% prediction interval (cells/µL)	44.9 – 192	9-279
Reduction as ratio to baseline (%)	80%	83%

Note: Baseline BEC 470 cells/µL reflects geometric mean for the participants with baseline BEC ≥300 cells//µL in the Phase 3 pivotal trials METREO and METREX (studies MEA117113 and MEA117106).
Geometric mean and ratio to baseline refer to the mepolizumab 100 mg SC Q4W arm (showing the subset of participants with baseline eosinophil ≥300 cells/µL). 95% prediction interval is computed as mean+/-1.96*sd in the log-space and back-transformed.

In addition, given the precedented safety profile of IL-5 neutralization comparable to placebo, targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of depemokimab.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all visits up to and including the Exit Visit (which occurs 26 weeks after their last scheduled dosing visit of the study) or the last scheduled procedure shown in the SoA (Section 1.3). This last visit for each participant is considered their EoS visit, regardless of whether all doses of study intervention were received.

Once the final participant completes their 26-week dosing visit, no additional dosing should take place for any participants in the study. This means that all subsequent scheduled dosing visits for other participants will instead be considered their Exit Visits.

The EoS is defined as the date of the last visit (as defined above) related to primary and secondary endpoints, and follow-up. If EoS is not equal to 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:

5.1.1. Age

- Participants must be ≥40 to ≤80 years of age, at the time of signing the ICF. **INC#1**

5.1.2. Blood eosinophils

- An eosinophilic phenotype with elevated BEC at two time-points at least 14 days apart **INC#2**
    - If the participant has a documented historical BEC of ≥150 cells/µL in the 12 months prior to Screening Visit 0, they must have at least one additional BEC of ≥300 cells/µL from a sample collected at Screening Visit 0 or Screening Visit 1.

    or

    - If historical BEC is not available, the participant must have at least one BEC ≥300 cells/µL and the other ≥150 cells/µL among the samples collected at Screening Visit 0 or Screening Visit 1.

5.1.3. Type of participant and disease characteristics

- Moderate to severe COPD with frequent exacerbations, defined as: **INC#3**
    - A clinically documented history of COPD as defined by the American Thoracic Society/European Respiratory Society for at least 1 year
    - A post-salbutamol FEV1/FVC ratio of <0.70 and a post-salbutamol FEV1 >30% and ≤80% predicted normal values calculated with GLI-Global Race Neutral equations in line with the ATS recommendations [Bowerman, 2023] at screening
    - A well-documented history (e.g., medical record verification, including capturing of all prior biologic use) of at least 2 moderate or 1 severe exacerbation in the 12 months prior to screening
        i. At least one qualifying exacerbation must have occurred while participant is on ICS plus LAMA plus LABA
        ii. Moderate exacerbations must have been treated with systemic corticosteroids

iii. Severe exacerbations are those requiring hospitalization or observation >24 hours in ED /urgent care facility

- CAT score ≥10 at Visit 1. **INC#4**
- Smoking status: Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Screening. Former smokers are defined as those who have stopped all smoking (including tobacco, marijuana, or e-cigarettes) for at least 6 months prior to Screening Visit 1 **INC#5**

5.1.4. COPD maintenance therapy

- Participants should be on optimized inhaler therapy, defined as ICS plus LAMA plus LABA either as multiple inhalers or a single combination inhaler* for at least 6 months prior to Screening Visit 1. **INC#6**

  *Note: Where intolerance or safety risk is documented for ICS, dual therapy LABA plus LAMA is allowed with prior discussion with the study medical monitor.

- Participants on adjunctive COPD therapies such as chronic macrolide antibiotics, PDE4 or PDE3-4 inhibitors, or chronic oral corticosteroids (up to 15 mg prednisone equivalent per day) may participate, provided they have been on these medications for 6 months, and on a stable dose for at least 3 months immediately prior to Screening Visit 1. These participants should remain on these therapies for the duration of the study. **INC#7**

5.1.5. Weight

- BMI ≥16 kg/m^2 **INC#8**

5.1.6. Sex

- Male or eligible female. **INC#9**

Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

  i. Is a woman of non-childbearing potential (WONCBP), OR

  ii. Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, from at least 14 days prior to the first dose of study intervention until at least 35 weeks after the last administered dose of study intervention.

  A WOCBP must have a negative highly sensitive serum pregnancy test at Screening (Visit 1) and a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention.

The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Note: If the 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.

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

5.1.7. Informed Consent

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF including tokenization, in this protocol. **INC#10**

5.2. Exclusion criteria

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

5.2.1. Medical conditions

5.2.1.1. Asthma

- Patients with a current or prior physician diagnosis of asthma* are excluded. **EXC#1**
- *A diagnosis of asthma should be based on both a history of typical respiratory symptoms combined with evidence of variable expiratory airflow limitation at the time of diagnosis consistent with GINA 2024 or other accepted guidelines.

5.2.1.2. Lung Disease

- Other clinically significant lung disease: The Investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with α1-antitrypsin deficiency as the underlying cause of COPD are excluded. Also excluded are participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases. **EXC#2**
- COPD stability: Participants with pneumonia, COPD exacerbation, or lower respiratory tract infection within the 4 weeks prior to Screening Visit 1 are excluded. **EXC#3**

- Lung resection: Participants with a history of, or plan for lung volume reduction surgery / endobronchial valve procedure are excluded. **EXC#4**
- Pulmonary rehabilitation: Participants in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1 are excluded. Participants who are in the maintenance phase of a pulmonary rehabilitation program may participate. **EXC#5**
- Continuous oxygen: Patients requiring oxygen supplementation for more than 12 hours per day are excluded. Non-continuous (i.e., 12 hours or less per day) oxygen is permitted up to 2 L/min at screening. **EXC#6**
- Cor pulmonale – resulting in right heart failure, severe pulmonary hypertension are excluded. **EXC#7**.
- Chronic hypercapnia requiring NIPPV use (including BiPAP or CPAP) are excluded. **EXC#8**

5.2.1.3. Other

- Unstable cardiovascular disease or arrhythmia. **EXC#9**
- Vasculitis: Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment. **EXC#10**
- Eosinophilic disease: Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic syndromes including EGPA (also known as Churg-Strauss Syndrome), or Eosinophilic Esophagitis. **EXC#11**
- Parasitic Infection: Participants with a known, pre-existing parasitic infection within 6 months of Screening (Visit 1). **EXC#12**
- Malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior to Screening Visit 1 (Participants that had localized carcinoma of the skin or cervix which was resected for cure will not be excluded). **EXC#13**
- **Immunodeficiency:** A known immunodeficiency other than that explained by use of corticosteroids (e.g., HIV). **EXC#14**
- **Liver disease:** Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice. **EXC#15**

  NOTE: Stable non-cirrhotic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B (in whom HDV has been excluded) or C are acceptable if participant otherwise meets entry criteria
- **Other concurrent medical condition**: Participants with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Clinically significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the

participant at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study. **EXC#16**

5.2.2. Prior/Concomitant therapy

- Previous exposure to mAb(s) targeting IL-5/5R, IL-4R/IL-13, IL-33, or TSLP within 6 months or 5 half-lives (whichever is longer), prior to Screening Visit 1. **EXC#17**
- Previous documented treatment failure or non-response to anti-IL-5/5R or anti-IL-4R/IL-13 therapy. **EXC#18**
- Other mAbs: Participants who have received any mAb within 5 half-lives of Screening Visit 1. **EXC#19**
- Investigational medications: Participants who have received an investigational drug within 30 days of Screening Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product). **EXC#20**
- Oral corticosteroids: Participants who have received short term use of oral corticosteroids within 4 weeks of Visit 1. **EXC#21**

5.2.3. Prior/Concurrent clinical study experience

- Previous randomization in the present study. **EXC#22**
- Concurrent enrollment in another clinical trial. **EXC#23**

5.2.4. Diagnostic assessments/Cardiac Safety exclusion criteria

- 12-lead ECG at Screening Visit 1: Participants with a QTcF >450 msec (or QTcF >480 msec in participants with bundle branch block). **EXC#24**
- Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.

  Note: Where a single ECG demonstrates a prolonged QTcF interval, obtain two more ECGs readings at a minimum of 2 minutes apart over a brief recording period (e.g., 5 to10 minutes), the average of the triplicate QTcF measurements should be used to determine eligibility.

5.2.5. Other exclusion criteria

- Hypersensitivity: Participants with a known allergy or sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic. **EXC#25**

- Non-compliance: Participants at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits. **EXC#26**
- Questionable validity of consent: Participants with, conditions that will limit the validity of informed consent to participate in the study, e.g., uncontrolled psychiatric disease or intellectual deficiency. **EXC#27**
- Drug or alcohol abuse: A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1. **EXC#28**
- Affiliation with Investigator Site: Is an Investigator, sub-Investigator, study coordinator, employee of a participating Investigator or study site, or immediate family member that is involved in this study. **EXC#29**

5.2.6. Liver safety exclusion criteria

Liver chemistry test: Participants who meet the following based on results from sample taken at Screening Visit 1: **EXC#30**

- ALT >2x ULN
- 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.
- Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice.

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

5.2.7. Exclusion criteria specific to the collection of nasal epithelium (nasal brushing) biomarker samples

- Participants with structural nasal abnormalities (such as deviated nasal septum) or nasal polyps, history of frequent nose bleeding or recent nasal surgery (within 3 months of Screening Visit 1), CSF leak or any abnormality that in the opinion of the Investigator may interfere with the nasal sample collection procedures. **EXC#31**
- Participants receiving medications which increase bleeding risk (vitamin K antagonist, direct oral anticoagulant or antiplatelet agents) or those with severe coagulopathy. Low-dose aspirin is permitted. **EXC#32**

Note: Participants who do not qualify for nasal epithelium sample collection may still participate in the study.

5.2.8. Randomization criteria

At Visit 2, those participants who continue to meet the inclusion/exclusion criteria and who meet the randomization inclusion/exclusion criteria will be randomized and commence the study intervention period until the target of approximately 960 randomized participants is reached.

5.2.8.1. Randomization inclusion criteria

1. **BEC:** Participants must have elevated BEC as described in the inclusion criteria Section 5.1.2. Note: The laboratory assessment may be repeated twice, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion prior to Visit 2 (see Section 5.1.2, INC#2).
2. **eDiary compliance:** Compliance with completion of the eDiary defined as completion of all questions on 5 or more days out of the 7 days immediately preceding Visit 2.

5.2.8.2. Randomization exclusion criteria

1. **COPD stability:** Participants who have pneumonia, exacerbation, lower respiratory infection during the Run-in period.

   Note: Participants may temporarily delay randomization for up to 6 weeks (see Section 5.5) with written approval from the study Medical Monitor.
2. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator, which would impact participant safety and/or study efficacy measures (see Section 5.2.6, EXC#30).
3. **LFT:** Participants who meet the following based on results from sample taken at Screening Visit 1:
   - ALT >2x ULN
   - Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
4. **Pregnancy:** Participants who are pregnant or breastfeeding. Participants should not be randomized if they plan to become pregnant during the time of study participation.
5. Participants with a QT interval, from the ECG conducted at Visit 2, i.e., QTcF >450 msec (or QTcF >480 msec in participants with bundle branch block) (Section 5.2.4, EXC#24).
6. Participants are excluded if an abnormal ECG finding of the 12-lead ECG conducted at Visit 2 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.

5.3. Lifestyle considerations

No lifestyle restrictions are required for this study.

5.4. Screen failures

- Screen/run-in failures occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAE.

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

Screen Failures (Visit 0)	Screen Failures (Visit 1)	Run-in Failures
Participants who are assigned a participant number at the time of signing the informed consent (screening Visit 0) but do not progress to the screening Visit 1	Participants who complete at least one additional Visit 1 (Screening Visit 1) procedure but do not enter the run-in period.	Participants who enter the run-in period but are not subsequently randomized.

- Individuals who do not meet the criteria for participation in this study may be rescreened; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor. Rescreened participants should be assigned a new participant identifier for every screening/rescreening event. Previously assigned participant identifier(s) are to be recorded in the participants' eCRF.

5.5. Criteria for temporarily delaying randomization

- Participants who experience a clinically significant COPD exacerbation (as defined in Section 8.2.1), pneumonia or lower respiratory tract infection during the run-in period should receive appropriate treatment, have their randomization visit delayed and remain in the run-in period (up to 6 weeks) until the investigator considers the participant to have returned to their baseline COPD status for at least 7 days.
- A participant who is not eligible to continue in the study at the end of the run-in period, should be considered a run-in failure but may be rescreened after consultation with the medical monitor (Section 5.4)

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study interventions administered

Table 5 Study interventions administered

ARM Name	Depemokimab 100 mg	Placebo
Intervention label	Depemokimab	Placebo
Intervention name	Depemokimab 100 mg SC	Placebo
Intervention description	100 mg Q26W (Week 0, Week 26, Week 52, Week 78)	Placebo Q26W (Week 0, Week 26, Week 52, Week 78)
Type	Biologic	NA
Dose formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloride solution in single-use PFS
Unit dose strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage level(s)	100 mg once Q26W (Week 0, Week 26, Week 52, Week 78)	Placebo once Q26W (Week 0, Week 26, Week 52, Week 78)
Route of administration	SC injection	SC injection
Use	IMP	Placebo
Authorized AxMP/Unauthorized AxMP	N/A	N/A
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labeling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Prefilled safety syringe, IMP=Investigational Medicinal Product, N/A=not applicable

6.1.1. Medical devices

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

  - The safety syringe device components are manufactured by Becton Dickinson. The safety syringe device components are assembled with the pre-filled syringe at GSK, Barnard Castle.

- Instructions for medical device use will be provided in a Pharmacy Manual. All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Sections 8.4.10, and Section 10.7) 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 or the 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.
- 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 MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Assignment to study intervention

- Eligible participants will be centrally randomized using an IRT system. The randomization schedule will be generated using the GSK validated randomization software RandAll NG. Treatment balance will be controlled within country. Participants will be assigned to study intervention in accordance with the randomization schedule. Once a randomization number has been assigned to a participant, it cannot be reassigned to any other participant in the study.

- At Visit 2 (Week 0), those participants who meet the randomization criteria will be randomized in a 2:1 ratio to receive one of the following study treatments in addition to their stable maintenance COPD treatment:
  - Depemokimab 100 mg SC
  - Placebo SC
- Study intervention will be administered in the clinic at Visit 2 (Week 0) and Visit 9 (Week 26), Visit 16 (Week 52) and Visit 22 (Week 78) as per the SoA (Section 1.3).

6.4. Blinding

- This is a double-blind study in which participants/care providers/investigators/outcomes assessors are blinded to study intervention. All participants will be centrally assigned to randomized study intervention using an RTMS/IRT.
- The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.
- If the investigator is unable to access the RTMS/IRT system, they can contact the GSK helpdesk based on the information provided in the pharmacy manual.
- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, depemokimab and placebo will be administered from PFSs that will be identical in appearance.
- If a participant's intervention code is unblinded by the investigator or treating physician (typically for the purpose of safety), that participant will continue with all study visits and will not receive the second or subsequent dose of study intervention at Week 26, Week 52 and Week 78. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF (see Section 7.1). In the event of an inadvertent unblinding which is not related to a safety concern, the participant will continue with all study visits and dose administrations
- To maintain the blind, select haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomization samples will not be reported to the site or the central study team. Sites should also allocate an unblinded member of the study team to redact this information from other data sources such as local lab results.

GSK's GCSP staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4.1. Controlled early access to unblinded PK and PKPD data

Designated independent representative(s) may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development using scrambled (random assignment of participant identification numbers) PK and PKPD unblinded datasets, including baseline demographic characteristics. No AE or efficacy data will be included.

6.5. Study intervention compliance

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

Participants will be monitored in clinic for a minimum of 2 hours post-dose of each injection 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

Dose modification is not allowed.

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

There are no plans to provide depemokimab following study completion.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition whether or not GSK is providing specific post-study treatment.

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 and study 208021 in healthy Chinese participants [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 48 days) of depemokimab.
  - Closely monitor the participant for any AE/SAE and laboratory abnormalities 35 weeks following the last administered dose.
  - Document the quantity of the excess dose as well as the duration of the overdose.
- 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 COPD therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study and any prior use or experience with a respiratory biologic regardless of duration must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Rescue medicine

Participants will be supplied with the short-acting bronchodilator salbutamol MDI or nebules as rescue medication.

Although the use of rescue/auxiliary medications is allowable (at any time during the study), the use of rescue medications should be withheld, if possible, for at least 4 hours prior to the spirometry assessments (see SoA [Section 1.3] and Section 8.1.3). Rescue medication usage will be recorded in the eDiary.

6.9.2. Permitted medications and non-drug therapies

The COPD medications listed below are permitted during the treatment period while the participant is on study intervention. The requirements for study inclusion with regards to this medication list are described in detail in Section 5.2.2.

- If taken as SoC therapy prior to Visit 1 the following are permitted:
  - inhaled corticosteroids
  - inhaled long-acting muscarinic antagonists or inhaled long-acting beta 2-agonists
  - chronic macrolide antibiotics
  - methylxanthines
  - PDE-3 and/or PDE -4 inhibitors
  - oral corticosteroids (chronic use only) up to 15 mg prednisone equivalent per day
  - leukotriene receptor antagonists (e.g., montelukast)
  - Note: if taken at Visit 1, these therapies should be continued throughout the duration of the study
- Oral or injectable corticosteroids (course ≤28 days) only for the short-term treatment of COPD exacerbations and/or pneumonia
- Antibiotics (short course ≤14 days) for the short term treatment of COPD exacerbations and/or pneumonia
- Mucolytics such as acetylcysteine
- LTOT: To be eligible to enter the study participants who are on LTOT must be using at a flow rate of ≤2 L/minute at rest over 12 hours or less per day. Non-continuous (i.e., 12 hours or less per day) oxygen is permitted up to 2 L/min at screening. However, oxygen therapy may be adjusted as deemed medically` necessary at any time during the study. Oxygen therapy must be captured on the concomitant medication page of the eCRF.
- Maintenance phase of pulmonary rehabilitation treatment (participants are not allowed to initiate treatment during the study).

- Rescue medication for PRN use e.g., salbutamol or ipratropium.

The following non-COPD medications are permitted during the study (for example):

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Corticosteroid administered via topical, ophthalmic or localized injection routes (e.g., intra-articular and epidural)
- Vaccinations (influenza vaccine, pneumonia vaccine, shingles vaccine, COVID-19 vaccine etc.).
    - Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Vaccines (including those given during the study and in the year prior to Visit 0) will be captured on the concomitant medication pages of the eCRF
- Allergy immunotherapy
- Antibiotics for short-term treatment (≤14 days) of acute infections. Long term treatment with antibiotics is not allowed
- Systemic and ophthalmic beta-blockers
- Smoking cessation treatments
- Cough suppressants
- Anti-depressants and anxiolytics
- NIPPV for conditions other than chronic hypercapnia

Note: Immunosuppressants for conditions other than COPD are allowed if they have been stable for the 3 months prior Screening Visit 1 and after discussion with the study Medical Monitor.

6.9.3. Prohibited medications and non-drug therapies

Medications noted as part of exclusion criteria are prohibited for the duration of the treatment period. Eligible participants are expected to continue their Baseline maintenance COPD medications during the run-in period and throughout the intervention period. Where spirometry is performed (See SoAs in Section 1.3), participants will refrain from taking their morning dose of their maintenance COPD medications until instructed to do so by clinic personnel.

Rescue medication (i.e., salbutamol or ipratropium) must also be withheld for at least 4 hours before visits when spirometry is performed (see SoAs in Section 1.3), and prior to reversibility testing.

COPD medications and non-drug therapies that are prohibited during the randomized phase of the study:

- Acute phase of pulmonary rehabilitation (at any time during the study including Run-in)
- Lung volume reduction surgery/endobronchial valve insertion
- Long term (>14 days) antibiotic therapy (antibiotics used for ≤14 days for acute infections or for exacerbations or pneumonia are allowed)
- mAbs
- Any prior use or experience with a respiratory biologic regardless of duration will be recorded
- Chronic oral corticosteroids for non-COPD treatment
- Experimental anti-inflammatory drugs (non-biologicals) or other investigational products (biologic or non-biologic) within either 30 days or five drug half-lives prior to Visit 1, whichever is longer
- Other investigational products (participants must have not received investigational products for 1 month or 5 half-lives prior to Visit 1, whichever is longer)
- Radiation therapy is excluded for 12 months prior to Visit 1 and throughout the study

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

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

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 7.1.1)
- ECG: Meets any of the protocol-defined QTc stopping criteria (see Section 7.1.2)
- Pregnancy: Positive pregnancy test (see Section 8.4.6)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 9)
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.1.5).
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant except for an inadvertent unblinding which is not related to a safety concern (see Section 6.4.1).

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

- The investigator will make every effort to encourage the participant to remain in the study and to continue with all remaining study visits, including the Exit and FU Visits as detail Section 4.4 and Section 7.2.
- The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

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

AE = Adverse event.

- Participants will be provided with the option to continue their scheduled visits in clinic and designated decentralized/remote visit. The required study assessments will depend on whether the participant is attending the visit in-clinic or a designated decentralized/remote visit. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed.
- If for any reason, the participant later chooses to withdraw from the study, a WS Visit (see Section 7.1) should be conducted according to the SoA (Section 1.3).

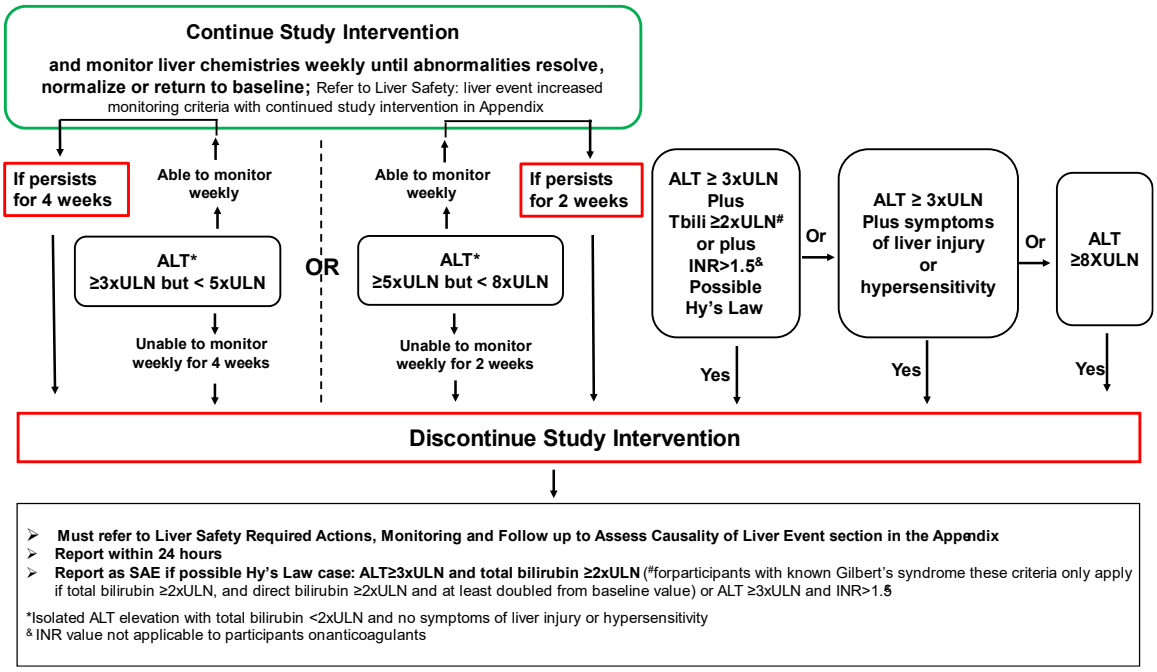
7.1.1. Liver event stopping criteria

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 chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

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



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

Refer to Section 10.6.1 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 10.6.2 for required liver event increased monitoring criteria with continued study intervention.

7.1.2. QTc stopping criteria

If either of the criteria mentioned below are met, the participant (s) must be discontinued. However, it should be confirmed with 2 additional ECGs, using the average of the triplicate QT interval to determine discontinuation.

- QTcF >500 msec OR uncorrected QT >600 msec

  OR

- Increase 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

QTc= QT interval corrected.
Note: QTcF is the QT interval corrected for heart rate according to Fridericia's formula that is selected for this study. It is either machine-read or manually over-read when not automatically machine read. This specific formula must be used to determine eligibility and discontinuation for an individual participant.

7.1.3. Temporary discontinuation

For this study, a temporary discontinuation refers to a delayed administration for the second dose or subsequent dosing of study intervention at Week 26, Week 52 and Week 78. The reason for a delay in dosing and for temporary discontinuation will be documented in the eCRF

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

7.1.4. Rechallenge

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 (see Appendix 6).

7.1.5. Criteria for follow-up of potential Type III hypersensitivity

- 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, immunogenicity, C3, and C4 samples may be taken at the time of the event along with haematology, clinical chemistry and urinalysis.
- Symptoms potentially suggestive of vasculitis include but are not limited to:
  - persistent* fever
  - 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

  (*where persistent is considered to be a duration of ≥2 days)
- 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 Study Medical Monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.
- Unscheduled PK, immunogenicity, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional serologic tests (e.g., ANA, 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.

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.

- Participants who prematurely withdraw from the study should attend:
  - a WS Visit, 26 weeks after the last administered dose of study intervention (at Week 26, Week 52, Week 78, or Week 104) AND
  - a FU 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.
- 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 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.
- The primary reason for participant withdrawal from the study will be documented in the CRF/eCRF based on the list below:

Reasons
AE
Death
Lack of efficacy
Lost to follow-up
Participant reached protocol-defined stopping criteria
Physician decision
Physician decision to start an approved respiratory biologic

Reasons
Pregnancy
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Withdrawal by participant
Other

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/other contact methods, 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.
- A final attempt will be made to contact the participant for a safety follow-up 35 weeks after the last administered dose of study intervention.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 CRF/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).
- As detailed in the SoA (Section 1.3), participants should make every effort to complete the follow-up visit/call on the scheduled day. The visit may be completed within 7 days of the scheduled time-point.
- Every effort should be made to reduce missing data throughout the study.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue to receive the second scheduled dose of study intervention, if applicable.
- 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.
- If allowed by country regulation/ethics, some study assessments may be conducted virtually (TM, secure video conferences, phone calls, or a web portal and/or mobile application); however, onsite visits are required as per the SoA (Section 1.3).
- Laboratory results that could unblind the study (e.g., haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Participants should be provided a quiet space in which to complete PROs, prior to other assessments and procedures. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. Family or friends should not influence the answers. Site staff should encourage participants to complete all questions.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- The order of key assessments and procedures during any given clinic visit should be as follows:
    1. Questionnaires/PROs
    2. Vital signs
    3. 12-lead ECG
    4. Spirometry
    5. Laboratory samples (only for screening visits 0 and 1 the site may collect the laboratory samples first to facilitate the collection of an early sample for the BEC; for all other visits, this order of key assessments should be followed)
    6. Intranasal biomarker samples
    7. Administration of study intervention
- No study procedures are to be performed before the participant is consented.

8.1. Administrative and general 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 trial participants, and to determine if the trial 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 /study start in the eCRF.

8.1.3. Screening and critical baseline assessments

8.1.3.1. Screening Visit 0

- During Screening Visit 0, site staff must obtain informed consent to the study participant. Informed consent for an optional genetic sample, where permitted, is also obtained at this visit.
- Informed consent for the PK sub-study, Tokenization and for genetic sampling can also be obtained at this visit.
- A mandatory hematology blood sample is collected at this visit and will be used to assess Inclusion Criterion 2 (BEC ≥300 cells/μL at Screening Visit 0).

- A participant number will be assigned at the time the ICF is signed. No study related procedures may be performed until the ICF document has been signed by the participant.

During Screening Visit 0, the following assessments are performed:

1. Demography including year of birth, gender, race, childbearing potential and ethnicity
2. Childbearing status for all women (can be conducted at Visit 1 instead, if necessary); for WOCBP, contraception should be started at least 14 days prior to receiving the first dose of study intervention (see Appendix 4)
3. COPD and all concomitant medications review
4. Hematology blood sample (for eosinophil count) is collected:
    - In order to meet the INC#2 (Section 5.1.2), a mandatory hematology test is performed at Screening Visit 0 and Visit 1 and will be analyzed by a designated central laboratory.
    - To be randomized, participants must demonstrate having elevated blood eosinophils at two time-points at least 14 days apart:
        - If the participant has a documented historical BEC of ≥150 cells/μL in the 12 months prior to Screening Visit 0, they must have at least one additional BEC of ≥300 cells/μL from a sample collected at Screening Visit 0 or Screening Visit 1.

        or

        - If historical BEC is not available, the participant must have at least one BEC ≥300 cells/μL and the other ≥ 150 cells/μL among the samples collected at Screening Visit 0 and Screening Visit 1.
    - Historical BEC: Where several historical BECs are obtainable, the highest BEC should be recorded in the eCRF.
        - A historical blood eosinophil measurement must meet the following: It must have been measured between 12 months and 14 days prior to Visit 0 and it must not have been measured within 14 days of a COPD exacerbation.
        - If the historical documented BEC is associated with a COPD exacerbation, then this eosinophil count cannot be used for inclusion in the study but should be recorded in the eCRF.
    - The screening hematology assessment may be repeated twice, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion prior to randomization Visit 2. Participants who do not meet the eosinophil inclusion criteria prior to the randomization visit, will be considered a screen failure.
5. Review of inclusion/exclusion criteria

    Note: This review should include a review of concomitant medication and asthma history (see Section 5.2.1.1).

8.1.3.2. Critical procedures performed at Screening Visit 1

A Screening BEC ≥300 cells/µL at Screening Visit 0 or Visit 1 as well as an additional BEC ≥150 cells/µL (either historical in the previous 12 months or taken during screening) must be available prior to randomization. Participants who do not meet the inclusion criteria of BEC ≥300 cells/µL will be considered screen failures.

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

- Medical history including COPD (including date of diagnosis and COPD type (emphysema or chronic bronchitis), COPD exacerbation history, smoking status, smoking cessation counselling, previous and/or current medical conditions.
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening as well as family history of premature cardiovascular disease.
- Spirometry including bronchodilator responsiveness (see Section 8.2.9).
- If a participant fails the spirometry test due to artifacts (e.g., cough, early termination, poor effort, equipment failure) one retest is allowed during the run-in period with an approval from the medical monitor.
- A hematology blood sample must be drawn from participants who do not have documentation of a historical BEC ≥150 cells/µL in the 12 months prior to Screening Visit 0.
- Screening Visit 1 spirometry including pre- and post-albuterol/salbutamol responsiveness testing; one retest is allowed with approval from the medical monitor (see Section 8.2.9).
- Parasitic screening as described in the SoA (Section 1.3).
- Concomitant medication review; COPD maintenance medications from the year prior to Screening Visit 1 and all other medications within the 3 months prior to Screening Visit 1.
- Complete physical examination including height and weight
- 12-Lead ECG
- CAT score
- Vital signs and pulse oximetry at this visit only
- Urine pregnancy test if applicable
- Clinical chemistry
- Register and train participant on the use of eDiary. Instruct participant to complete the daily evening eDiary from Screening Visit 1 and throughout the study
- Review inclusion/exclusion criteria assessments
- Review exacerbations
- Review and record all AEs that have occurred since Screening Visit 0

- Provide copy of the medical problems and healthcare utilization worksheet
- Dispense rescue medication
- Record Visit in the RTSM

8.1.3.3. Critical procedures performed at Visit 2 (Randomization, first study intervention Visit)

The following critical assessments will be conducted at Visit 2:

- Review AEs and SAEs
- Review exacerbations during the Run-in period
- COPD and Concomitant medication review
- Review and assess compliance with completing the eDiary during the Run-in period
- Vital signs and 12-Lead ECG
- Review randomization inclusion and exclusion criteria (Section 5.2.8)
- Urine pregnancy test, if applicable
- Hematology, clinical chemistry, immunogenicity, FeNO, and blood biomarkers
- CAT, SGRQ-C, EQ-5D-3L, CASIS, mMRC and PGI-S for cough, sputum, dyspnea, and COPD questionnaires in eDiary
- Spirometry
- Review COPD symptoms
- Provide and review medical problems and healthcare utilization worksheet
- Provision / dispensing of rescue medication
- Optional genetics sample can be collected at Visit 2 or any visit after.
- Register and randomize participant in the RTSM
- Administer study intervention as per SoA (Section 1.3)

8.1.4. Tokenization at randomization

To link traditional study data to RWD, a common, universal ID (herein named a “token”) that is unique to each study participant, persistent, and available in real-world datasets is necessary. A token is a universal, deidentified key that can be used to reference participants across datasets.

Tokenization and RWD linkage also enables clinical trial data to be used to answer unanticipated questions and eliminate the need for follow-up studies, expediting future results. By linking tokenized clinical trial data with RWD (e.g., prescription data, Electronic Health Records , medical claims, etc.), GSK can further elucidate any potential safety signals and understanding of the benefits of clinical trial interventions in the real

world. Ultimately, the time and costs saved will benefit participants awaiting the development of treatments and ensure GSK can get a more holistic, longitudinal view of trial participants.

As part of their participation in the trial, participants will be offered the consent for tokenization and linking of their clinical trial data. Outside of tokenization and linking of their clinical trial data, no additional study procedures beyond what is outlined in this clinical study protocol, would be completed as result of their participation.

Participation in tokenization is optional and participants who decline to participate in the tokenization process will still be able to participate in the clinical study. The trial participant's tokenized data will be available for linking to other future data for 5 years from after the study ends or until they withdraw their consent for future data linking, whichever comes first. The participant will be instructed of the withdrawal consent process with information provided in the ICF.

Process:

Step 1: Trial participants will be provided with a description of the purpose of the trial/study, as well as the description and purpose of tokenization and RWD linkage through the informed consent workflow. The ICF for trial tokenization may be the same as for the overall trial, or a separate ICF.

Step 2: A trial participant may or may not choose to provide consent for trial tokenization. If consent is not provided, tokens will not be generated for that participant. If consent is provided, token generation will proceed as described in step 3.

Step 3: The consenting participant's Subject ID and PII will be input in the trial tokenization tool. The output of this process will generate tokens, which are stored securely in GSK's data lake, to be made available for linking to RWD at a later date. PII is processed in compliance with trial regulations and never stored with the token or made available to GSK

Step 4: When appropriate, GSK may link de-identified, tokenized real-world datasets to trial data, to complete applicable analyses. The combined Trial data plus real-world dataset will be certified as de-identified, to support regulatory requirements.

8.2. Efficacy assessments

Planned time-points for all efficacy assessments are provided in the SoA (Section 1.3).

The primary and secondary efficacy endpoints are described below.

8.2.1. Exacerbations

The symptoms used to ascertain an exacerbation of COPD are:

- worsening of two or more of the following major symptoms for at least two consecutive days:
  - dyspnea
  - sputum volume
  - sputum purulence (color)

  or
- worsening of any one of the major symptoms together with any one of the following minor symptoms for at least two consecutive days:
  - sore throat
  - colds (nasal discharge and/or nasal congestion)
  - fever (oral temperature >37.5°C) without other cause
  - increased cough increased wheeze

The severity of each exacerbation is based on the maximum level of care needed for each event:

- Moderate exacerbations are defined as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. *
- Severe exacerbations are defined as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥24 hours) or result in death.

  * The dose and type will be according to the local practice.

If a participant is determined to have an exacerbation it should be treated per protocol as described in Section 8.2.2.

8.2.2. Treatment of exacerbations

If in the opinion of the Investigator/treating physician, the exacerbation is severe enough to warrant the need for oral corticosteroids (with or without antibiotics) the following guidelines should be used.

- The duration of treatment with oral corticosteroids should typically be ≤14 days (dose and type according to local practice)
- If in the opinion of the Investigator/treating physician the duration of corticosteroid use will extend beyond 14 days, consultation with the study Medical Monitor is recommended. Durations exceeding 28 days are considered chronic use (Section 6.9.2).

- Any course of oral corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation.

If, in the opinion of the Investigator/treating physician, there is evidence of respiratory bacterial infection that warrants treatment with antibiotics the following guidelines should be followed:

- The duration of treatment with antibiotics should be 5 to 14 days (dose and type according to local practice).
- If in the opinion of the Investigator/treating physician the duration of antibiotic use will extend beyond 14 days, consultation with the study Medical Monitor is recommended. Durations exceeding 14 days are considered long term use (Section 6.9.3). If first line antibiotic treatment fails and additional antibiotics are used, the total duration of antibiotic treatment will be considered.
- Any course of antibiotics started within 7 days of finishing a previous course will be considered as treatment for the original exacerbation (i.e., a single exacerbation).

  Note: Use of antibiotics for the treatment of upper or lower respiratory tract infection is not considered a COPD exacerbation unless worsening of COPD symptoms are documented by the Investigator in the participant's medical notes. All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF. Exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of an SAE.

8.2.3. SGRQ

SGRQ total score will be measured using the SGRQ for COPD [SGRQ-C]. The SGRQ-C is a 40-item participant questionnaire, designed to measure health impairment by addressing the frequency of respiratory symptoms (questions 1-7) and the participant's current state (questions 8-14). Higher scores indicate greater impairment of health. The SGRQ-C is derived from the original SGRQ and produces scores equivalent to the SGRQ instrument [Meguro, 2007]. The SGRQ-C is designed for supervised self-administration which means that the participant should answer the questionnaire by themselves, but that site staff can provide support if required. There is no specified recall period for the instrument. It is appropriate for site staff to help clarify a question; it is important that answers are not provided by the site staff. If participants have difficulty reading questions, they may be read out loud. The participant's response should not be challenged.

Participants must complete the SGRQ-C while in the clinic for their scheduled study visit. The SGRQ-C should be administered per the order programmed in the eDiary and before any other study procedures at Randomization (Visit 2) and at additional visits indicated in the SoA (Section 1.3).

8.2.4. Daily symptom diary

Using the eDiary, participants will complete a daily symptom diary (each evening) consisting of items from EXACT, rescue medication use and nighttime awakenings. Participants will be trained to use the eDiary at Visit 1 and will complete the eDiary throughout the study.

8.2.4.1. EXACT

The EXACT symptom diary will be completed daily, in the evening, starting at Screening Visit 1 and up to Week 52. On the date of the Exit Visit, the evening diary for daily symptom reporting will not be completed.

EXACT is a 14-item participant reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of symptoms suggestive of an exacerbation of disease in participants with COPD. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the participant [Leidy, 2010; Leidy, 2011; Mackay 2014]. The EXACT questions will be the first questions presented for completion each evening at bedtime in the eDiary. The daily recording of information allows an assessment of the underlying day to day variability of a participant's symptoms and facilitates the detection of symptom worsening that may be indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100, higher scores indicate more severe symptoms. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the participant becomes more familiar with the tool and the eDiary).

8.2.4.2. E-RS: COPD

E-RS: COPD consists of 11 items from the 14-item EXACT instrument. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e., breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS: COPD has a scoring range of 0 to 40, higher scores indicate more severe symptoms [Leidy, 2014]. Three subscales of the E-RS: COPD are used to describe different symptoms; breathlessness, cough and sputum, and chest symptoms [EXACT PROgram, 2023].

8.2.5. Additional PROS and Other Exploratory Endpoints

Safety and other exploratory PRO endpoints are described below.

Participants must complete all PROs (other than the daily symptom diary) while in the clinic for their scheduled study visit. PROs should be administered per the order programmed in the eDiary and before any other study procedures according to the SoA (Section 1.3).

8.2.5.1. CAT

The CAT [Jones, 2009; Jones, 2012] is a short and simple participant completed questionnaire which has been developed for use in routine clinical practice to measure the health status of participants with COPD. The CAT is an 8-item questionnaire suitable for completion by all participants diagnosed with COPD. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0 to 40. Higher scores indicate greater disease impact.

8.2.5.2. CASIS

CASIS is a 7-item tool assessing sleep impairment associated with respiratory disease and breathing problems. The response options ranged from 1 = never to 5 = very often, and several items are reverse scored. The item scores are summed together to arrive at a total raw score. CASIS raw scores are linearly transformed to a 0-100 total scale score. Recall period for the measure is the previous week, with higher scores indicating greater sleep impairment.

8.2.5.3. mMRC

The participant’s degree of dyspnea to different levels of activity will be rated on the 5-point mMRC scale. The mMRC, administered by an interviewer, asks participants to rate how breathless they are on a 5-point Guttman scale. The recall period for the instrument is one week. Higher scores indicate more breathlessness.

8.2.6. Patient and Physician Global Rating

8.2.6.1. PGI-S for COPD

This single global question will ask participants to rate their severity of COPD on a 4-point scale (mild, moderate, severe, very severe).

8.2.6.2. PGI-S for Cough

This single global question will ask participants to rate their severity of cough in the last week on a 6-point scale (no cough, minimal, mild, moderate, severe, very severe) [Rhatigan, 2023].

8.2.6.3. PGI-S for Phlegm (Sputum)

This single global question will ask participants to rate their severity of phlegm (sputum) production in the last week on a 6-point scale (no phlegm (sputum), minimal, mild, moderate, severe, very severe).

8.2.6.4. PGI-S for Shortness of Breath (Dyspnea)

This single global question will ask participants to rate their severity of shortness of breath in the last week on a 6-point scale (no shortness of breath, minimal, mild, moderate, severe, very severe).

8.2.6.5. PGI-C in COPD

This single global question will ask participants to rate the change in their COPD (overall disease) on a 7-point scale (much better, better, slightly better, no change, slightly worse, worse, much worse).

8.2.6.6. Patient and Clinician Rated Response to Therapy

This single global question will ask the participants and clinicians to rate the participant's response to therapy on a 7-point scale (significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, significantly worse).

8.2.7. Rescue medication use

The number of occasions of rescue medication use will also be captured in the daily eDiary.

8.2.8. Nighttime awakenings

Data regarding nighttime awakenings will also be captured in the daily eDiary.

8.2.9. Pulmonary function testing

Throughout the study, it is preferable that for any individual participant at each study visit, pulmonary function testing be administered by the same pulmonologist or technician in order to ensure consistency in technique. All personnel must be trained on the specific spirometer before administering any tests to any potential or enrolled participant. Spirometry measurements will be obtained using centralized spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All sites will use centralized spirometry equipment. All participants will have pre- and post-bronchodilator spirometry performed at Screening Visit 1 and pre- and post-bronchodilator spirometry at Week 52 and Week 104, at scheduled clinic visits during the treatment period as indicated in SoA (Section 1.3).

8.2.9.1. Spirometry

Spirometry lung function assessments will be performed for all participants at specified visits to assess FEV_1. At least 3 valid spirometry efforts should be attempted (with no more than 8 attempts) using the ATS guidelines [Miller, 2005]. Spirometry assessments will be performed at screening (Visit 1), randomization (Visit 2), and at scheduled in clinic visits according to the SoA (Section 1.3). At each visit, spirometry should be performed at the same time of day (±2 hour) as the assessment performed at Visit 2 (the baseline assessment).

Acceptable spirometry efforts should have a satisfactory start of test and end of test (i.e., a plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005]. In short, an adequate test requires a minimum of three acceptable FVC manoeuvres. Acceptable repeatability is achieved when the difference between the largest and the next largest FVC is ≤0.150 L and the difference between the largest and next largest FEV1 is ≤0.150 L [Graham, 2019]. For those with an FVC of ≤1.0 L, both these values are 0.100 L. If these criteria are not met in three manoeuvres, additional trials should be attempted, up to, but usually no more than, eight maneuvers [Miller, 2005]. Adequate rest periods should be permitted between maneuvers.

The largest FEV1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Additional details about acceptable quality for spirometry testing are provided in the vendor manual.

Spirometry must be performed as follows:

- Started between 6:00AM and 11:00 AM. It is preferable that PFTs be conducted at the same time of day for each individual participant.
    - After completing questionnaires at visits where these assessments are captured (as specified in the SoA Section 1.3)
    - After withholding salbutamol for ≥4 hours

  - After withholding ipratropium for ≥4 hours
  - After withholding the morning dose of maintenance COPD medications
  - Prior to dosing of study intervention
- Participants should refrain from smoking for 1 hour prior to each pulmonary function test.
- Participants should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hours prior to each pulmonary function test.

8.2.9.2. Bronchodilator responsiveness testing

Pre-bronchodilator and post-bronchodilator measurements will be taken at the clinic visits specified in the SoA (Section 1.3).

At the Screening Visit 1, both pre- and post-salbutamol spirometry will be obtained to determine participant eligibility.

Bronchodilator responsiveness testing will be completed as follows:

- Following pre-salbutamol spirometry (a minimum of three acceptable spirometry efforts), the participant will self-administer 4 puffs of salbutamol MDI. Three acceptable spirometry efforts will be obtained approximately 10 to 30 minutes after salbutamol administration.

8.2.10. Pharmacodynamic and biomarker assessments

8.2.10.1. Peripheral BEC

A mandatory hematology test is performed at Screening Visit 0 and Visit 1 and will be analyzed by a designated central laboratory.

To be randomized, participants must demonstrate having elevated blood eosinophils at two time-points at least 14 days apart (see Section 5.1.2, INC#2).

The screening hematology assessment may be repeated twice, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion prior to randomization Visit 2. Participants who do not meet the eosinophil inclusion criteria prior to the randomization visit, will be considered a screen failure.

Peripheral BEC as PD assessments will be collected from all participants.

Blood samples for PK will be collected from a subset of participants (n=300).

A PK sub-study will be conducted to assess the PK profile of depemokimab in COPD population including potential ethnic differences in the PK of depemokimab 100 mg, in liquid formulation, between non--Japanese/non-Chinese participants, Chinese and Japanese participants living in China and Japan, respectively (across studies 222714 and 222725). PK blood samples will be collected from approximately 300 participants (non-Chinese and non-Japanese) globally. This PK assessment will be conducted over the first 52 weeks of the study period only (please refer to SoA Section 1.3 and Section 8.5 Pharmacokinetics).

8.3. Safety assessments

Planned time-points for all safety assessments are provided in the SoA (Section 1.3).

The incidence of AEs and SAEs, change from baseline in vital signs, ECG values and laboratory parameters (including hematological, and clinical chemistry parameters), and hepatobiliary abnormalities will be assessed. The incidence of immunogenicity will be assessed as measured by the presence of ADA. All-cause mortality will be recorded. Refer to Section 8.4 for further details.

AEs, SAEs, and other safety reporting including pregnancy will be captured as per GSK standard procedure.

In addition, the clinical study will also capture AESIs (see Section 8.4.4).

8.3.1. Physical examination/history directed physical examination

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Height and weight will also be measured and recorded in the visits specified in the SoA (Section 1.3).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital signs

Oral, tympanic membrane, or skin temperature, pulse oximetry, pulse rate and blood pressure will be recorded in the eCRF (before blood collection for laboratory tests).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.3. ECGs

A single 12-lead ECG and rhythm strip will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. There will be electronic capture and storage of the data by a validated method. See Section 7.1.2 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary. All results will be recorded after measurement of vital signs and prior to spirometry.

If a routine single ECG demonstrates a prolonged QT interval or an increase in the QT interval which meets withdrawal criteria, obtain two more ECG readings over a brief recording period (e.g., 5-10 minutes), with each recording separated by at least 2 minutes. The averaged QTcF values of the three ECG readings should be used to determine whether the participant should be discontinued from intervention product (but not from the study). Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary. The three ECGs should be scanned and sent to the Medical Monitor.

All ECG measurements will be made with the participant in a supine or semi-supine position having rested in this position for approximately 5 minutes before each reading.

The Investigator, a designated sub-Investigator, or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The Investigator must provide his/her dated signature attesting to the authenticity of the ECG machine interpretation. All ECG printouts should be maintained in the source documents.

If a clinically relevant arrhythmia, infarct pattern or conduction defect is documented at Screening, the Investigator will need to record in eCRF prior knowledge of the ECG pattern.

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). These tests will be performed by a central laboratory.

Local laboratory results are only allowed for parasitic screening. The investigator should decide what type of laboratory test, if any, is necessary.

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 should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor.

- In the absence of a diagnosis, abnormal laboratory findings assessments 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 Sections 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.

To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from any visits post-randomization.

8.3.5. Pregnancy testing

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

A blood pregnancy test must be performed for all female participants of childbearing potential before the administration of the first dose of study intervention and Exit visit. In addition, a urine pregnancy test should be performed for all WOCBP prior to randomization (Visit 2), on a monthly basis at the specified scheduled study visit, and at the FU Visit/call (if applicable) as per the SoA (Section 1.3).

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.

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. A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
- Participants who withdraw early from the study should have a urine pregnancy test, 9 weeks after the Early Withdrawal Visit.

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

8.3.6. Medical problems

Participants will be instructed to record any medical problems and healthcare utilization in a worksheet. These entries will be reviewed by the site staff at each study visit and recorded in the eCRF as AEs as appropriate.

8.3.7. Pneumonia

All pneumonias should be confirmed by the presence of new infiltrate on chest imaging (X-ray and/or CT) and captured on the AE/SAE page of the eCRF.

Investigators and site staff should remain vigilant for the possible development and diagnosis of pneumonia as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For all suspected cases of pneumonia, Investigators should confirm the diagnosis by obtaining a chest image or documentation of the result of chest imaging performed outside of the clinic site. Appropriate therapy should be initiated for confirmed pneumonia.

8.3.8. Study safety monitoring and Independent Data Monitoring Committee

- Participant safety will be continuously monitored by the medical monitor, designated Safety Lead (or delegate) and an IDMC throughout the study.
- The IDMC will be comprised of clinical experts and an unblinded statistician external to GSK. The committee will review unblinded data for both safety and efficacy (for the purposes of futility analyses) at pre-specified time-points during the study. Ad hoc reviews may be convened at the request of either the IDMC or the sponsor.
- Details of the structure and function of the IDMC, pre-specified stopping rules (specific to futility analyses) and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request. In addition to the IDMC, the GSK SRT will review blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.
- Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit risk profile of the product

8.3.8.1. Adjudication Committee

Independent external adjudication committees for all SAE reports and all potential MACE (CV death, non-fatal myocardial infarction [MI], non-fatal stroke, and heart failure) will be utilized in this study to ensure external objective medical review of these events in a blinded fashion. The committee members will remain blinded to study intervention assignment. The adjudication plans are described in the charter, which is available upon request.

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 all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant.

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 Section 10.7.

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

- All AEs/SAEs will be collected from the signing of the ICF until the Follow-Up visit at the time points specified in the SoA (Section 1.3).
- 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 10.7. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined above (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 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 Section 10.7.4.4.

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 9)
- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation
- Pneumonia

Note: pneumonia will be confirmed using an imaging modality at the investigators' discretion (e.g., CT scan, X-ray)

8.4.5. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE 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, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.6.
- 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 will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigators have to report to the sponsor pregnancies, medication errors, abuse and misuse even in an absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the sponsor.
- 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, pregnancy and other events reports to GSK

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

AE = Adverse event; CRF/eCRF = Case report form/electronic case report form; 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

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention
- 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, the time period for reporting pregnancies should align with the time period for postintervention contraception determined in Section 5.1, in line with applicable informed consent.
- 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
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, 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 post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.7. 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 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.
- For death due unequivocally to disease under study/SAEs/event that occurred during the study intervention period, or post-study intervention not related to the study intervention, record death in the Death eCRF.

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 uk.gsk-rd-gcsp-ctsm-admin@gsk.com

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

8.4.9. Participant card

The investigator or designee must provide the participant with a "participant card" containing information about the clinical study. The participant 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/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 10.7.
- Note: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.7 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 10.7.

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 by method. If method is unavailable, then alternative method should be utilized.
- 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. Pharmacokinetics

- Whole blood samples of approximately 3 mL will be collected from a sub-set of participants (n=300) for measurement of plasma/ concentrations of depemokimab as specified in the SoA (Section 1.3).
- The PK sub-study will be conducted to characterize the PK profile of depemokimab 100 mg Q26W, in liquid formulation, in participants with COPD and assess potential ethnic differences between non-Asian participants, Chinese and Japanese participants living in China and Japan, respectively (across studies 222714 and 222725).
- Instructions for the collection, handling, processing, storage and shipment procedures for biological samples will be provided in a central study laboratory manual. The actual date and time (24-hour clock time) of each sample and dose will be recorded in the eCRF. Samples obtained on dose administration dates, Visit 9 (Week 26) and Visit 16 (Week 52), should be drawn prior to dosing.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.
- PK samples will be analysed using an appropriately validated assay method under the supervision of the sponsor.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

Peripheral BEC

- In order to investigate the PD effects of depemokimab, BECs will be measured as part of the standard haematological assessments according to the SoA (Section 1.3). The site staff and central study team will be blinded to each participant's BEC (as well as overall haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomization blood tests. Total white blood cell counts will be available throughout the study.
- Collection, processing, storage and shipping procedures for biomarker and PD samples are provided in the laboratory manual.
- Peripheral BEC as PD assessments will be collected from all participants.

8.7. Genetics

- A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.
- See Section 10.5. Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.

8.8. Biomarkers

- With the participant's consent and where permitted, samples for exploratory biomarkers will be collected according to the schedule specified in the SoA (Section 1.3) and as detailed in the laboratory manual provided separately to sites.
- The samples will be stored after collection and may be analysed for any biomarkers that are thought to play a role in depemokimab response, COPD or related diseases, or to evaluate their association with observed clinical responses to depemokimab. Samples may be stored for a maximum of 20 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to depemokimab. With participants' consent, these samples may be used for further research unrelated to the study, as described in the ICF.
- Blood and/or nasal epithelial samples will be collected for transcriptomic profiling of gene expression using RNA sequencing technology. The same samples may also be used to confirm findings by application of alternative technologies. Samples will be collected according to the schedule described in the SoA.

- Collected samples may be used for biomarker assay life-cycle management if necessary.

8.8.1. Clinical biomarkers

- Clinical biomarkers for baseline stratification will be measured. Samples will be collected according to the SoA (Section 1.3)
- The following biomarkers will be analysed for baseline stratification: FeNO, Eotaxin-3, pulmonary and activation-regulated chemokine (PARC/CCL18), fibrinogen, CRP and total IgE.
    a. FeNO* is a non-invasive measure of type 2 airway inflammation in respiratory diseases including asthma and COPD [Dweik, 2011; Donohue, 2014]. The standard single exhalation FeNO test recommended by the ATS will be followed [Dweik, 2011; ATS/ERS, 2005] according to the schedule specified in the SoA.
    b. Elevated serum IgE levels is a hallmark of atopic disease, including in respiratory diseases, and is often associated with exacerbations and lung function decline in COPD [Lommatzsch, 2022].
    c. Increased levels of other inflammatory biomarkers like CRP and fibrinogen, are also associated with poor outcomes in COPD [Dahl, 2001; Dahl, 2007; Agustí, 2012].
    d. PARC/CCL18 is a lung-predominant inflammatory protein found in serum, with 3 important findings. Two large cohort studies and an intervention study examined the pulmonary and activation regulated chemokine. PARC/ CCL-18 is upregulated in COPD. PARC/CCL-18 concentrations were independently associated with future risk of cardiovascular hospitalization and mortality and cardiovascular and total mortality. In the prednisolone interventional study, short-term steroid use modified serum PARC/CCL-18 levels. Together, these data suggest that PARC/CCL-18 may be a useful candidate blood biomarker in COPD.

8.8.2. Exploratory biomarkers

Whole blood, serum, and nasal epithelium (brushing) samples will be collected for exploratory biomarker research, where permitted, and as specified in the SoA.

These samples will be tested as described below, in order to profile the patient population, explore the association of baseline biomarkers with clinical response, or gain a deeper understanding of the impact of depemokimab on disease pathways and processes.

Exploratory biomarkers may be analysed and reported separately from the main CSR.

Serum protein biomarkers

Baseline serum levels of inflammatory cytokines or other proteins will be assessed using suitable immunoassays to characterize the profile of the study patient population.

Nasal epithelium brushing transcriptomics

Nasal brushing samples will be analysed by RNA sequencing or alternative technologies, to characterize nasal epithelial gene expression profile at baseline and explore changes in response to treatment. Given the overlap in expression between lower and upper airways both in healthy and disease states, including COPD, and in response to treatment [Boudewijn, 2017; van Nijnatten, 2023; Faiz, 2020], this data is expected to enable the profiling of the patient population and provide airway-relevant insights into the mechanism of action of depemokimab and its impact on disease processes.

NOTE: The nasal brushing procedure is described in detail in the laboratory manual. If this procedure is deemed by the investigator to be intolerable or inappropriate for an individual participant, it may be omitted (see exclusion criteria for nasal brushing collection in Section 5). Participants who are not eligible for nasal epithelium (brushing) collection may still participate in the study. If samples are not successfully collected at the baseline visit, the procedure should not be performed at any subsequent study visit.

8.9. Immunogenicity assessments

- Samples for evaluating antibodies against depemokimab will be collected at time points specified in the SoA (Section 1.3). Additionally, serum samples should also be collected at the Exit Visit or the final in-clinic visit for participants who withdraw early from the study. The actual date and time of each blood sample collection will be recorded. Details for immunogenicity blood sample collection, processing, storage and shipping procedures are provided in the Laboratory Manual.
- Sample analysis will be performed under the control of GSK's Biomarker & Bioanalytical Platforms (BBP) group, using a tiered analysis approach. The presence of anti-depemokimab binding and NAbs will be determined in serum samples using validated bioanalytical methods, which includes screening, confirmation, titer and NAb analysis. Additional analysis may be performed (e.g., selectivity, cut points, cross- validation), and further immune response characterization may also be performed as needed.

8.10. Medical resource utilization and health economics

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

All unscheduled COPD-related health care utilization will be recorded by participants in a worksheet and collected in the eCRF by the Investigator and study-site staff for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected about unscheduled use of health care resources associated with COPD exacerbations may be used to conduct exploratory economic analyses and will include:

- Number of telephone contacts, specialist nurse visits, visits to a physician's office, home visits (day and night time), outpatient visits, visits to urgent care, visits to the ED, and hospitalizations associated with the participant's exacerbations
- Duration of hospitalization (total days or length of stay, including duration by wards [e.g., intensive care unit, general ward])

The resource utilization worksheet used by the participant to record all COPD-related health care contacts experienced since the last visit will be collected and reviewed by the Investigator or designee at the visits indicated in Section 1.3. The Investigator or designated staff should ask the participant if any of the health care contacts that are recorded on the worksheet were due to a COPD exacerbation. The Investigator can refer to his/her records to verify or supplement information given by the participant, if necessary. If any unscheduled healthcare contact is due to a COPD exacerbation, then the Investigator should ensure completion of the COPD Exacerbation section of the eCRF.

8.10.1. EuroQol questionnaire (EQ-5D-3L)

- The EuroQol 5 Dimension 3 Level (EQ-5D-3L) questionnaire will be completed via eDiary by participants at randomization and at scheduled visits as indicated in the SoA (Section 1.3). The EQ-5D-3L is a standardised instrument for use as a measure of health utility. It is designed for self-completion and is cognitively simple, taking only a few minutes to complete. The recall period for the instrument is one day. The EQ-5D-3L is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (no problems, some problems, and extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a vertical response scale (EQVAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQVAS which best represents their own health on that day. EQ-5D-3L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.
- Participants must complete the EQ-5D-3L while in the clinic for their scheduled study visit. The EQ-5D-3L should be administered per the order programmed in the eDiary and before any other study procedures at Randomization (Visit 2) and at additional visits indicated in the SoA (Section 1.3).
- The sponsor may use the collected data to conduct economic analyses.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to unblinding of treatment assignment information and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and key secondary endpoints.

9.1. Statistical hypotheses

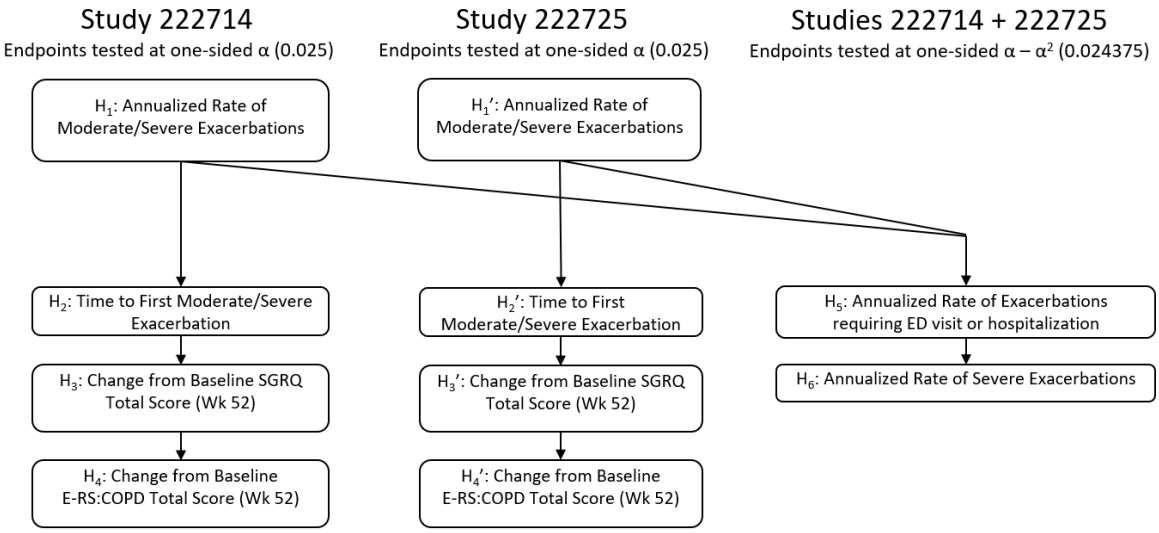
The primary study objective is to test the superiority of depemokimab compared to placebo (both as add on treatment to SoC) as assessed by the annualized rate of moderate/severe exacerbations. The null hypothesis of no difference in annualized rate of moderate/severe exacerbations between depemokimab and placebo will be tested at the two-sided α=0.05 (one-sided α=0.025).

9.1.1. Multiple testing strategy

Hypotheses to be tested will be structured as shown in Figure 3. The primary endpoint of this study will be tested first and if this comparison is significant at the two-sided 5% level, testing will continue within the study according to the testing procedure detailed in Figure 3. Testing of endpoints will be carried out in a hierarchical manner, dependent on statistical significance having been achieved for the previous endpoint in the hierarchy.

A pre-specified pooled analysis of data from study 222714 and this study (222725) is planned for the secondary endpoint of annualized rate of exacerbations requiring ED visit or hospitalization and the secondary endpoint of annualized rate of severe exacerbations. This pooled analysis will be carried out after both studies have completed and only if statistical significance is achieved for the primary endpoint in both studies. Endpoints in the pooled analyses within the multiple testing strategy will be tested at a one-sided significance level of 2.4375% (α-α^2), where α is the one-sided 2.5% level (2-sided significance level of 4.875%) [Bretz, 2009; Bretz, 2019].

Figure 3 Conceptualization of statistical testing strategy across Studies 222714 and 222725 (this study)



Note: Testing procedure and type-I- control in the planned depemokimab COPD submission which consists of studies 222714 and 222725 (both with identical design). Hypotheses can only be tested in sequential order as indicated by the arrows. α or α-α^2 indicates the significance level at which that hypothesis can be tested. If the null hypothesis for the primary objective (H_1 or H_1') is rejected within a study, study level secondary endpoints will be tested sequentially within the study as long as all preceding hypotheses are rejected. Hypotheses relating to exacerbations requiring ED visit or hospitalization and severe exacerbations will only be tested in the combined data of the 2 studies if the primary null hypotheses of H_1 and H_1' are both rejected. At the study level, the type-I error rate is controlled at ≤ 0.025 (one-sided). At the submission level, the type-I error rate is controlled at ≤ 0.000625 (one-sided, 0.025^2) for the primary hypothesis and at ≤ 0.025 (one-sided) when considering all endpoints.

The primary hypothesis (annualized rate of moderate/severe exacerbations, H_1 and H_1') and the key secondary hypotheses of time to first moderate/severe exacerbation (H_2 and H_2'), SGRQ (H_3 and H_3') and E-RS: COPD (H_4 and H_4') will be tested in hierarchical order within each study (Figure 3). The testing procedure starts with the statistical test of the primary null-hypothesis (H_1 and H_1') and continues down the hierarchy within each study as long as the preceding null hypotheses is rejected in favor of depemokimab in a two-sided statistical test with a p-value ≤ 0.05. At the study level, the type-I error rate is controlled at ≤ 0.025 (one-sided).

If both studies independently reject the primary null-hypothesis (H_1 and H_1') in favor of depemokimab in a two-sided statistical test with p-value ≤ 0.05, the endpoints of exacerbations requiring ED visit or hospitalization (H_5) and severe exacerbations (H_6) will be tested in the pooled dataset of Study 222714 and Study 222725. These pooled endpoints will be tested in hierarchical order as indicated by arrows in Figure 3. The testing procedure continues to the next lower ranking hypothesis as long as the previous null hypothesis can be rejected in favor of depemokimab in a two-sided statistical test with a p-value ≤ 0.04875 (2*[0.025-0.025^2]) [Bretz, 2009; Bretz, 2019]. Provided the primary hypothesis can be rejected in both studies the pooled endpoints can be tested regardless of the outcome of the key secondary hypotheses within each study, and vice-versa.

Under the global null-hypothesis (i.e., no difference between depemokimab and placebo), the testing procedure controls the type-I error rate (one-sided) at the study-level to ≤0.025, and at the submission level to ≤0.000625 (=0.025^2). Considering all possible configurations of true and false positive null hypotheses, the type-I error control at the level of the submission is ≤0.000625 for the primary objective, and ≤0.025 for all hypotheses.

The type-I error is controlled by the testing procedure. All confidence intervals and p-values in the study report will be presented without adjustments.

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
Randomized	• All participants who were randomly assigned to study intervention in the study	• Study population
Full Analysis Set (FAS)	• All randomized participants who received at least 1 dose of study intervention • Data will be reported according to the randomized study intervention • This population will serve as the primary population for analyses of efficacy endpoints.	• Efficacy • Study population
Safety	• All randomized participants who receive at least 1 dose of study intervention. • Participants will be analyzed according to the treatment received for more than 50% of treatment administrations. • This population will serve as the primary population for analyses of safety endpoints.	• Safety
PK	• All participants in the Safety Analysis Set who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values). • Data will be reported according to the actual study intervention received.	• PK

NQ = Non-quantifiable; PK = Pharmacokinetic;

9.3. Statistical analyses

9.3.1. Key elements of analysis plan

- This section provides a summary of the planned statistical analyses of the primary and secondary endpoints. The statistical analysis plan will include further technical details and detailed descriptions for all planned analyses.
- All efficacy analyses will be performed on the FAS. Safety analysis will be performed on the Safety Analysis set.
- Unless otherwise stated, Baseline will be defined as the latest assessment prior to randomization (Visit 2).

- Efficacy data reported by participants from the start of treatment up to the Exit Visit will be included in analyses unless stated otherwise. The study is designed to continue to collect data for the primary and secondary efficacy endpoints for participants who prematurely discontinue from study intervention.

9.3.1.1. Primary endpoint /estimand analyses

Details of the primary estimand is described in Section 3. The primary endpoint for this study is the annualized rate of moderate/severe exacerbations.

Table 9 Primary endpoint /estimand analyses

Endpoint	Statistical Analysis Methods
Primary: Annualized rate of moderate/severe exacerbations	Primary Estimand The primary estimand will use a treatment policy strategy to handle the ICEs of treatment discontinuation for any reason, change in background medication, and use of prohibited medication. All efficacy data collected for participants, including data collected following the ICE, will be included in the analysis. A composite strategy will be used for the ICE of use of another respiratory biologic for COPD. Efficacy data collected following the occurrence of the ICE will be replaced with the annualized rate corresponding to the 95th percentile of the distribution of the annualized rate of moderate/severe exacerbations in the placebo arm (single imputation) multiplied by the time remaining post-ICE or the subject's own observed exacerbations following the ICE, whichever is worse. Full details will be provided in the SAP. Primary analysis The annualized rate of moderate/severe exacerbations will be analyzed using a negative binomial model with covariates of smoking status (current vs previous smoker), number of exacerbations in the previous year, baseline disease severity (as %predicted post-bronchodilator FEV1) and geographic region and loge(time in study) as an offset. Missing data due to study withdrawal will be considered MAR. Sensitivity Analysis Sensitivity analysis will be conducted to investigate the assumption of missing data due to study withdrawal being MAR. This will include an analysis where missing data due to study withdrawal is imputed based on off-treatment data collected from participants who continued in the study following early withdrawal from study intervention. In addition, a tipping point analysis, where missing data due to study withdrawal will be imputed based on a plausible range of values for the annualized rate of exacerbations will be carried out. Further details will be provided in the SAP. Additional Estimands The following additional estimands will be included to explore alternative strategies for the intercurrent events for the primary endpoint only. Full details will be provided in the SAP. All ICEs to be handled as treatment policy. A hypothetical strategy will be used for the ICE of use of another respiratory biologic for COPD. Efficacy data collected following the occurrence of the ICE will be censored from the analysis, data following the intercurrent event will be imputed using multiple imputation methods from off treatment data collected prior to starting any respiratory biologic for COPD from patients who have withdrawn from study intervention and continued in the study. Full details will be provided in the SAP. Supplementary Analysis The adjustment for prognostic covariates typically leads to gains in statistical power. A pre-trained prognostic model has a parsimonious utility when predictions for the current trial patients (known as a 'digital-twin') are applied to the current trial analysis.

Endpoint	Statistical Analysis Methods
	A supplementary analysis may be conducted whereby an additional adjustment will be made to the primary analysis model by including a novel prognostic 'super-covariate' score generated on the current trial patients from a statistical/ML model pre-trained on historical COPD trial data that will include at a minimum completed mepolizumab trials. Further details on the development of the prognostic score and on the relevant derivation to obtain the corresponding treatment effect estimates (i.e., marginal or conditional) will be provided in the SAP.

9.3.1.2. Secondary endpoint analyses

Details of the primary estimand is described in Section 3.

The same set of ICEs will be addressed using the same strategies as for the primary estimand in Table 9. Full details will be provided in the SAP.

Table 10 Secondary endpoint analyses

Endpoint	Statistical Analysis Methods
Secondary: Time to first moderate/severe exacerbation	Analysis Method Time to first moderate/severe exacerbation will be analyzed using a Cox's proportional hazards model with covariates of smoking status (current vs previous smoker), number of exacerbations in the previous year, baseline disease severity (as %predicted post-bronchodilator FEV1) and geographic region. Missing data due to study withdrawal will be considered censored at random (non-informative censoring). Supplementary Analysis A supplementary analysis may be conducted including a novel prognostic 'super-covariate' score to the analysis model. Full details will be provided in the SAP.
Change from baseline in SGRQ total score at Week 52	Analysis Method Change from baseline in SGRQ total score will be analyzed using a repeated measures mixed model with covariates of smoking status (current vs previous smoker), geographic region, baseline total score, visit and interaction terms of visit by baseline and visit by treatment group. Missing data due to study withdrawal will be considered MAR. Supplementary Analysis A supplementary analysis may be conducted including a novel prognostic 'super-covariate' score to the analysis model. Full details will be provided in the SAP.
Change from baseline in E-RS: COPD total score at Week 52	Analysis Method Change from baseline in E-RS: COPD total score will be analyzed using a repeated measures mixed model with covariates of smoking status (current vs previous smoker), geographic region baseline total score, visit and interaction terms of visit by baseline and visit by treatment group. Missing data due to study withdrawal will be considered MAR. Supplementary Analysis A supplementary analysis may be conducted including a novel prognostic 'super-covariate' score to the analysis model. Full details will be provided in the SAP.

9.3.1.3. Secondary analyses for the pre-specified pooled analysis across Studies 222714 and 222725 (this study)

The same set of ICEs will be addressed using the same strategies as for the primary estimand in Table 9.

Table 11 Secondary analyses for the pre-specified pooled analysis

Endpoint	Statistical Analysis Methods
Annualized rate of moderate/severe exacerbations requiring ED visit or hospitalization using pooled data from study 222714 and 222725	Analysis Method The annualized rate of moderate/severe exacerbations requiring ED visit or hospitalization will be analyzed using a negative binomial model with covariates of study, smoking status (current vs previous smoker), number of exacerbations in the previous year, baseline disease severity (as %predicted post-bronchodilator FEV1) and geographic region and $\log_e$(time in study) as an offset. Missing data due to study withdrawal will be considered missing at random (MAR). Supplementary Analysis A supplementary analysis may be conducted including a novel prognostic 'super-covariate' score to the analysis model. Full details will be provided in the SAP.
Annualized rate of severe exacerbations using pooled data from study 222714 and 222725	Analysis Method The annualized rate of severe exacerbations will be analyzed using a negative binomial model with covariates of study, smoking status (current vs previous smoker), number of exacerbations in the previous year, baseline disease severity (as %predicted post-bronchodilator FEV1) and geographic region and $\log_e$(time in study) as an offset. Missing data due to study withdrawal will be considered MAR. Supplementary Analysis A supplementary analysis may be conducted including a novel prognostic 'super-covariate' score to the analysis model. Full details will be provided in the SAP.

9.3.1.4. Exploratory endpoint analyses

Full details of the analyses of all exploratory endpoints will be described in the SAP.

9.4. Interim analyses

A single unblinded interim analysis for futility is planned. The analysis will be performed by a SDAC in conjunction with an IDMC to maintain study integrity. The futility analysis will not increase the type-I error rate. Full details of the timing, operating characteristics and futility decision criteria will be provided in an IDMC charter and SAP.

A late stage interim analysis to stop the study early for efficacy may be conducted with full details included in an amendment to the protocol and/or SAP, as well as within the IDMC charter. The overall type-I error rate for the study will be maintained at 5% (two-sided).

9.5. Sample size determination

The sample size for the study has been estimated to provide sufficient power to conclude superiority of depemokimab relative to placebo for the primary endpoint. Approximately 960 participants will be randomized into the study under a 2:1 randomization ratio; 640 participants will be randomized to depemokimab and 320 participants to placebo.

With an assumed true annualized rate of moderate/severe exacerbations in the placebo arm of 1.2, an assumption of an average follow up across participants of 1.72 years and an assumed true treatment reduction in the annualized exacerbation rate with depemokimab compared with placebo of 21%, a sample size of 960 (2:1 randomization; 640 depemokimab, 320 placebo) would provide 90% power to detect a statistically significant reduction between treatment arms at the two-sided 5% level of significance (one-sided 2.5%). The estimate of 0.6 used for the dispersion parameter is similar to that seen in a post-hoc subgroup analysis of the integrated METREX and METREO studies examining participants with a screening BEC of ≥300 cells/µL. The minimal detectable effect for this design is a 13.2% reduction in the annualized exacerbation rate.

Blinded sample size re-evaluation will be carried out prior to randomizing the last participant to assess whether, based on the overall annualized rate of moderate/severe exacerbations and the level of dispersion seen within the available data, the initial planned sample size of 960 randomized participants would continue to provide sufficient power/assurance for this study. The blinded sample size re-estimation will follow the method described in [Friede, 2010]. A negative binomial distribution will be fitted to the blinded exacerbations from the available data with participant follow-up time as an offset, and estimates obtained for the overall blinded exacerbation rate and the dispersion (shape) parameter. These estimates will be used to determine the sample size that would be required to maintain sufficient power/assurance. The study sample size may be increased if required, to a potential maximum of 1400 participants.

The sample size was determined using [PASS, 2020].

9.5.1. Sample size sensitivity

The sample size estimate of 960 was based on a 2:1 randomization, an assumed true annualized rate of moderate/severe exacerbations in the placebo arm of 1.2, an assumption of an average follow up across participants of 1.72 years and an assumed true reduction of 21% in this annualized rate for participants treated with depemokimab+SoC compared with participants treated with placebo+SoC. Changes in these assumptions will impact the power of the study. Table 12 illustrates the effect on the power of the study based on 960 participants (randomized 2:1 depemokimab:placebo) and a dispersion parameter k=0.6.

Table 12 Effect on power of changes to underlying assumptions to annualized rate in placebo arm and rate reduction with depemokimab

%reduction in annualized exacerbation rate with Depemokimab	Annualized Exacerbation Rate in placebo arm (Average follow up: 1.72 years)			Average follow up (Annualized Exacerbation Rate in placebo arm: 1.2)		
	1.1	1.2	1.3	1.65	1.72	1.80
	Study Power					
19%	81.2%	82.8%	84.1%	82.0%	82.8%	83.5%
21%	88.8%	90.0%	91.0%	89.5%	90.0%	90.6%
23%	94.0%	94.8%	95.5%	94.4%	94.8%	95.2%
25%	97.1%	97.6%	98.0%	97.4%	97.6%	97.8%

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 and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to 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.
- By default, collected samples for the study will be stored for a maximum of 20 years, unless the local regulations have a different retention period. 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 informed consent was obtained before the participant was enrolled in the study and the date the 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 copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining samples for optional further research related and not related to this study. The investigator or authorized designee will explain to each participant the objectives of the further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

In case of unexpected pregnancy, participant must be informed that PI such as date of birth and 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

Recruitment will be competitive. Recruitment will be performed by the investigators at the participating sites. The Sponsor will not participate in recruitment of participants to the study. In addition, study will be published in public databases such as ClinicalTrials.gov.

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 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, that their data will be used as described in the informed consent.
- The participant 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, third parties working on behalf of GSK, and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- 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

- An Independent Data Monitoring Committee (IDMC) comprised of clinical experts external to GSK will review unblinded data at defined time-points during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional time-points for review may be added.
- Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request.
- An independent external adjudication committee for all SAE reports and all potential MACE (CV death, non-fatal MI, non-fatal stroke, and heart failure) will be utilized in this study to ensure external objective medical review of these events in a blinded fashion
- In addition to the IDMC, the GSK SRT will review blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study.
- 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 randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

- G**SK** 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 Report 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.

- When source data are sent for external assessment or adjudication (e.g., endpoint adjudication committee; expert reader), source data are stored by the external body for 15 years from the issue of the final CSR, unless the local regulations have a different retention period.

10.1.9. Source documents

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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/eDiaries or entered in the eCRF/eDiaries that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgement.
- 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.
- Source data are shared with third parties contracted by GSK for external assessment or adjudication (e.g., endpoint adjudication committee). The non-exhaustive list of source data shared may include, discharge summaries, imaging reports, scans, videos, pathology reports, biological specimens, ECG reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the external assessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third-party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

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 13 will be performed by the central laboratory.
- To maintain the blind, the following data for post-randomization samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- 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 13 Protocol-required safety laboratory tests

Laboratory tests	Parameters	
Hematology[1]	• Platelet count	
	• RBC count	
	• RBC indices	– Mean corpuscular volume – Mean corpuscular hemoglobin – %Reticulocytes
	• WBC count with differential: (post-dose results blinded as described in footnote 1)	– Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
	• Hemoglobin	
	• Hematocrit	
Clinical chemistry[2]	• Blood urea nitrogen/Urea • Potassium • Creatinine* • Sodium • Calcium • Glucose • Creatine phosphokinase	– AST/SGOT – ALT/SGPT – Alkaline phosphatase[3] – Total bilirubin – Direct bilirubin – Total protein
Routine urinalysis	Not Applicable	
Pregnancy testing	• Highly sensitive (serum or urine) hCG pregnancy test (as needed for WOCBP)[4]	
Other screening tests	• Follicle stimulating hormone and estradiol (as needed in WONCBP only) • All study-required laboratory tests will be performed by a central laboratory, with the exception of parasite screening: which will be performed at a local laboratory.	

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; eGFR = Estimated glomerular filtration rate; hCG = Human chorionic gonadotropin; IEC = Independent 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 nonchildbearing potential.

1. To maintain the treatment blind, the following data for post-randomization samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.
2. 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).
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

*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 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 NOT 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 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 and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant 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.

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, AESI, 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, SAEs, AESIs, pregnancies or any other events of interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a 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/SAE/AESI/pregnancy 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 during the study***: AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until it is resolved until 9 weeks after EOS visit week or until the participant is lost to follow-up.
- If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology**.**

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 paper pregnancy follow-up report/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 post-study 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 and pregnancy information after removal of write access to the participant's eCRF

When additional SAE 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 post-study 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 in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study 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 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 Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to depemokimab or COPD with an eosinophilic phenotype and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to depemokimab or COPD eosinophilic phenotype and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to depemokimab or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on depemokimab or COPD with an eosinophilic phenotype and related diseases continues but no longer than 20 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver safety requirements and guidelines

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

Table 14 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 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.	• 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 pharmacokinetic (PK) analysis, obtained within a week of meeting increased liver monitoring criteria[5] • CPK and LDH, GGT, GLDH, and serum albumin. • Fractionate bilirubin, if total bilirubin ≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. • 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.

Liver event study intervention stopping criteria	
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.	If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above: • 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.

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

Table 15 Liver event increased monitoring criteria

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 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.

10.7. Appendix 7: 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.

10.7.1. 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.

10.7.2. 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).

10.7.3. Definition of device deficiency

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

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

10.7.4.1. 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 GSK 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.

10.7.4.2. Assessment of intensity

See Section 10.3.5.2.

10.7.4.3. Assessment of causality

See Section 10.3.5.3.

10.7.4.4. 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.

10.7.5. 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 medical monitor by telephone.
- If the site during the course of the study or post-study 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 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.

10.7.6. Reporting of SADEs

SADE Reporting to GSK

- Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must 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.

10.7.7. 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.

10.8. Appendix 8: Country-specific requirements

10.8.1. Other countries

In countries where medical records systems automatically associate the term “asthma” with use of inhaled corticosteroids, the Investigator should ensure and attest that these participants do not have asthma, and that COPD is the cause of the lung disease in the source documentation.

10.9. Appendix 9: 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., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.10. Appendix 10: Exploratory endpoint analyses

Full details of the analyses of all exploratory endpoints of particular interest are outlined in Table 16 and will be described in the SAP.

Table 16 Other exploratory objectives and endpoints

Objectives	Endpoints
Other Exploratory Endpoints	
• To evaluate depemokimab 100 mg SC compared with placebo on additional patient reported outcome efficacy measures	• Change from baseline in SGRQ total score at Week 26, Week 78, and Week 104 • SGRQ total score responders (≥4-unit reduction in SGRQ total score from baseline) at Week 26, Week 52, Week 78, and Week 104 • Change from baseline in E-RS: COPD total score at Week 26 • Change from baseline in E-RS: COPD Breathlessness subscale, Cough and Sputum and Chest Symptoms subscale score at Week 26 and Week 52 • E-RS: COPD total score responders (≥2 unit reduction from baseline) at Week 26, Week 52 • E-RS: COPD Breathlessness subscale score responders (≥1 unit reduction from baseline), Cough and Sputum subscale score responders (≥0.7 unit reduction from baseline), and Chest Symptoms subscale score responders (≥0.7 unit reduction from baseline) at Week 26, Week 52,
• To evaluate depemokimab 100 mg SC compared with placebo additional efficacy and other endpoints	• Annualized rate of moderate/ severe exacerbation requiring systemic steroids • Percentage of rescue medication free days • Percentage of nights with no awakenings due to COPD symptoms • Mean number of occasions of rescue medication use/day
• To evaluate depemokimab 100 mg SC compared with placebo on daily symptoms as measured by EXACT	• Days with high symptom variability (defined by a 5-point increase in EXACT from the previous day) • Exacerbation-like events (defined by a 12-point increase in EXACT above baseline for at least two consecutive days or 9-point increase for at least three consecutive days • Symptom recovery and time to recovery after a moderate or severe COPD exacerbation as defined by a 9-point improvement in EXACT

Table 17 Exploratory objectives and endpoints for pre-specified pooled analysis across Studies 222714 and 222725 (this study)

Objectives	Endpoints
Other/Exploratory: Pre-specified pooled analysis across studies 222714 and 222725 (this study)	

• To evaluate the impact of depemokimab compared with placebo on severe COPD exacerbations	• Time to first exacerbation requiring ED visit or hospitalization
	• Time to first severe exacerbation
	In patients who experience a severe COPD exacerbation following randomization:
	  • Proportion of patients who are re-hospitalized or die within 30- and 90-days following discharge
	  • Proportion of patients who have a moderate or severe exacerbation within 30- and 90-days following discharge
	  • Time to next moderate or severe exacerbation

10.11. Appendix 11: Protocol amendment history

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

Amendment 1 (18 April 2025)

Overall rationale for the current Amendment:

In the original protocol, it was stated that partipants would be monitored for 1 hour post administration of study intervention. In Protocol Amendment 1, this was changed to a minimum of 2 hours to be in accordance with the IB. Additional changes have been made to reduce the burden to the participants and for clarification of study procedures.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
1.3.1. Schedule of activities 2.3.1. Risk Assessment 6.5. Study intervention compliance	Updated post-dose monitoring time from 1 hour to a minimum of 2 hours.	This change was made to be in accordance with the Investigator's Brochure.
1.3.1 Schedule of activities	Visit 7 and Visit 15 have been changed from in-clinic visits to remote visits. Clinical chemistry and hematology sample collection have been removed from these visits. Physical examination, vital signs and immunogenicity have been removed from Visit 15.	These changes were made to reduce the burden to participants.
4.2 Scientific rationale for study design	Under Primary efficacy endpoint, the definition of moderate/severe exacerbations was updated	The definition was updated to align with the definition in Section 8.2.1.
4.4 End-of-study definition	"Follow-up" was added to the definition for End of Study	To clarify that the End of Study definition includes the Follow-up visit/call, as specified in the Schedule of Activities
8.3.4. Clinical safety laboratory tests	Removed duplicate text related to the reporting of clinically significant values for any of the tests that do not return to normal.	To remove duplicated text.
8.3.6 Medical problems	"Concomitant medications" has been removed.	Concomitant medications will not be recorded by the participant in the medical problems and healthcare utilization worksheet.
8.10 Medical resource	LTOT has been removed	LTOT is not being collected in the healthcare utilization form.

Section # and title	Description of change	Brief rationale
utilization and health economics		
Global	Correction of grammar, formatting, or spelling	To correct minor errors and improve readability.

11. REFERENCES

Agustí A, Edwards LD, Rennard SI, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One. 2012;7(5):e37483. doi: 10.1371/journal.pone.0037483. Epub 2012 May 18.

American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005;171(8):912-30.

Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biological clusters and their biomarkers. Am J Respir Crit Care Med. 2011;184:662–71.

Bafadhel M, Pavord I, Russell R. Eosinophils in COPD: just another biomarker? Lancet Respir Med. 2017;5:747–59.

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

Barnes P, Burney P, Silverman E, et al. Chronic Obstructive pulmonary disease. Nat Rev Dis Primers. 2015;1:15076.

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

Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023;389 (3):205-14.

Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. N Engl J Med. 2024;390(24):2274-83.

Bischoff SC, Brunner T, De Weck AL, et al; Interleukin 5 modifies histamine release and leukotriene generation by human basophils in response to diverse agonists. J Exp Med. 1990;172 (6):1577–82.

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

Boudewijn IM, Faiz A, Steiling K, et al. Nasal gene expression differentiates COPD from controls and overlaps bronchial gene expression. Respir Res. 2017;18(1):213.

Bowerman C, Bhakta NR, Brazzale D, et al. A Race-neutral Approach to the Interpretation of Lung Function Measurements. Am J Respir Crit Care Med. 2023;207(6):768-77.

Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.

Bretz F, Maurer W, Xi D. Replicability, Reproducibility, and Multiplicity in Drug Development. CHANCE. 2019;32(4):4–11.

Brightling CE, McKenna S, Hargadon B, et al. Sputum eosinophilia and the short-term response to inhaled mometasone in chronic obstructive pulmonary disease. Thorax. 2005;60(3):193-8.

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

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

Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated BECs: results from two multicentre, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3(5):355-66.

Celli B, Fabbri L, Criner G, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for its Revision. Am J Respir Crit Care Med. 2022;206(11):1317-25.

Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191(7):758-66.

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

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

Dahl M, Tybjaerg-Hansen A, Vestbo J, et al. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(6):1008-11.

Dahl M, Vestbo J, Lange P, et al. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175(3):250-5.

Depemokimab Investigator's Brochure (IB).(GSK Document Number RPS-CLIN-132006) Effective 25-Nov-2024.

Donohue JF, Herje N, Crater G, et al. Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study. Int J Chron Obstruct Pulmon Dis. 2014;9:745-51.

Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602-15.

Evaluating Respiratory Symptoms (E-RS™) in COPD (E-RS™: COPD), User Manual (version 7.0) June 2023 Website: EXACT PROgram – Evidera.

Faiz A, Imkamp K, van der Wiel E, et al. Identifying a nasal gene expression signature associated with hyperinflation and treatment response in severe COPD. Sci Rep. 2020;10(1):17415.

Fawcett LK. Turgutoglu N, Allam KM, et al. Comparing Cytology Brushes for Optimal Human Nasal Epithelial Cell Collection: Implications for Airway Disease Diagnosis and Research. Pers. Med. 2023;13(5):864.

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

Friede T, Schmidli H. Blinded Sample Size Reestimation with Negative Binomial Counts in Superiority and Non-inferiority Trials. Methods Inf Med. 2010;49(6):618-24.

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

Global Initiative for Chronic Obstructive Lung Disease 25 GOLD Report. Available from: https://goldcopd.org/2025-gold-report/

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88.

GSK Study Report 2019N411063. A randomized double-blind (sponsor open), placebo controlled, single ascending dose, first time in human study in participants with mild to moderate asthma to assess safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of GSK3511294 administered subcutaneously. 2019.

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

Halpin DM, Miravitlles M, Metzdorf N, et al. Impact and prevention of severe exacerbations of COPD: a review of the evidence. International Journal of COPD. 2017:12 2891–2908.

Hamizan A, Alvarado R, Rimmer J, et al. Nasal mucosal brushing as a diagnostic method for allergic rhinitis. Allergy Asthma Proc. 2019;40(3):167-72.

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

Jackson DJ, Wechsler ME, Jackson DJ. SWIFT-1 and SWIFT-2 Investigators; SWIFT-1 Investigators; SWIFT-2 Investigators. Twice-Yearly Depemokimab in Severe Asthma with an Eosinophilic Phenotype. N Engl J Med. 2024;391(24):2337-49.

Jones P, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test (CAT) Eur Respir J. 2009;34:648–54.

Jones P, Harding G, Wiklund I, et al. Tests of the Responsiveness of the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) Following Acute Exacerbation and Pulmonary Rehabilitation. Chest. 2012;142:134-40.

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

Khurana S, Brusselle GG, Bel EH, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX Study. Clin Ther. 2019;41(10):2041-56.e5.

Leidy NK, Wilcox TK, Jones PW, et al. EXACT-PRO Study Group. Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO) measure. Value Health. 2010;13(8):965-75.

Leidy NK, Wilcox TK, Jones PW, et al. Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. Am J Respir Crit Care Med. 2011;183:323-9.

Leidy NK, Sexton CC, Jones PW, et al. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. Thorax. 2014;69(5):424-30.

Lommatzsch M, Speer T, Herr C, et al. IgE is associated with exacerbations and lung function decline in COPD. Respir Res. 2022;23(1):1.

Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, Phase IIIb study. Clin Ther. 2016;38(9):2058-70.e1.

Mackay AJ, Donaldson GC, Patel ARC, et al. Detection and severity grading of COPD exacerbations using the exacerbations of chronic pulmonary disease tool (EXACT) European Respiratory Journal. 2014;43(3):735-44.

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

Maspero J, Adir Y, Al-Ahmad M, et al. Type 2 inflammation in asthma and other airway diseases. ERJ Open Res. 2022;8(3):00576-2021.

Meguro M, Barley EA, Spencer S, et al. Development and validation of an improved COPD-Specific Version of the St. George Respiratory Questionnaire. Chest. 2007;132:456-63.

Miller MR, Hankinson J, Odencrantz J. Standardisation of spirometry. Eur Respir J. 2005;26:319-88.

Mosler K, Coraux C, Fragaki K, et al. Feasibility of nasal epithelial brushing for the study of airway epithelial functions in CF infants. Journal of Cystic Fibrosis. 2008;7(1):44-53.

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

Ochi H, De Jesus NH, Hsieh FH, et al. IL-4 and -5 prime human mast cells for different profiles of IgE-dependent cytokine production. Proc Natl Acad Sci U S A. 2000;97(19):10509-13.

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

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

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

Pavord I, Chanez P, Criner G, et al. Mepolizumab for eosinophilic Chronic Obstructive Pulmunory Disease. NEJM. 2017;377:1613-27.

Pertzov B, Unterman A, Shtraichman O, et al. Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma. J Asthma. 2019. DOI:10.1080/02770903.2019.1658208. Epub 2019 Sep 3.

Perera PN, Armstrong EP, Sherrill DL, et al. Acute exacerbations of COPD in the United States: inpatient burden and predictors of costs and mortality. COPD. 2012;9(2):131–41.

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

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

Rhatigan K, Hirons B, Kesavan H, et al. Patient Global Impression of Severity Scale in Chronic Cough: Validation and Formulation of Symptom Severity Categories. J Allergy Clin Immunol Pract. 2023;11(12):3706-12.e1. doi: 10.1016/j.jaip.2023.08.046. Epub 2023 Sep 9.

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

Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. Int J Chron Obstruct Pulmon Dis. 2006;1:39–47.

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

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

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

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

Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S73-80.

Toy E, Gallagher K, Stanley EL, et al. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. COPD. 2010;7(3):214-28.

van Nijnatten J, Faiz A, Timens W, et al. A bronchial gene signature specific for severe COPD that is retained in the nose. ERJ Open Res. 2023;9(6):00354-2023.

Vogelmeier C, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary Am J Respir Crit Care Med. 2017;195:557–82.

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

Signature Page for 222725 TMF-22390960 v1.0

Reason for signing: Approved	Name: Jeff Min Role: Approver Date of signature: 05-Aug-2025 13:44:25 GMT+0000

Signature Page for TMF-22390960 v1.0