TITLE PAGE

Protocol Title: A randomised, double-blind, parallel group Phase III study to assess the efficacy and safety of 100 mg SC depemokimab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) – ANCHOR-2 (depemokimAb iN CHrOnic Rhinosinusitis)

Protocol Number: 218079/Amendment 5

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Brief Title: Efficacy and safety of subcutaneous depemokimab in patients with chronic rhinosinusitis with nasal polyps

Study Phase: Phase 3

Sponsor Name and Legal Registered Address:	GSK Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 5	26 Jun 2024	TMF-19486952
Amendment 4	12 March 2024	TMF-18821671
Amendment 3	17 October 2023	TMF-16242633
Amendment 2	26 October 2022	TMF-15028297
Protocol Clarification Letter	8 July 2022	TMF-14822401
Protocol Clarification Letter	29 April 2022	TMF-14646867
Amendment 1	09 February 2022	TMF-14448864
Protocol Clarification Letter	07 January 2022	TMF-14395957
Original Protocol	24 November2021	TMF-13978226

Amendment 5 (26 Jun 2024)

Overall rationale for the current Amendment: The protocol has been amended to update the primary and secondary estimand strategy to handle the initiation of medications that may modulate the disease course of CRSwNP intercurrent event with a composite strategy in alignment with FDA guidelines [FDA, 2023]. The previously defined primary estimand, which handled this intercurrent event with a treatment policy strategy, becomes a supplementary estimand to the primary estimand for the co-primary endpoints and to the secondary estimand for the pooled secondary endpoints related to nasal surgery. The pooled secondary endpoints related to nasal surgery have an additional supplementary estimand to handle the initiation of medication that may modulate the disease course of CRSwNP with a hypothetical strategy to reflect global differences in availability of biologics for CRSwNP. Additionally, the definition of non-continuous endpoints has been expanded to refer to the presence or absence of intercurrent events being handled with a composite strategy in alignment with the estimand framework.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Section 1.1. Synopsis, Section 3.2. Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)	Non-continuous (binary and time-to-event) endpoints including Other efficacy endpoints and Pooled Secondary and Other efficacy endpoints have been expanded to refer to the presence or absence of intercurrent events being handled with a composite strategy.	To reflect the composite strategy in the endpoint definition, in alignment with the estimand framework.
Section 1.1. Synopsis, Section 3.1. Objectives and Endpoints and Section 8.2.6.1. Sino-Nasal Outcome Test (SNOT-22)	The SNOT-22 responder definition has been corrected to require a decrease in score of "≥8.9" instead of ">8.9".	To align with the published clinically meaningful difference.

Section # and title	Description of change	Brief rationale
Questionnaire		
Section 1.1. Synopsis, Section 3.2. Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)	The asthma control objectives have been corrected to describe the asthma population with an ACQ-5 score of >0.75 as having "partially or not well controlled" asthma instead of "uncontrolled" asthma.	To more accurately describe the asthma population in alignment with published interpretations of the ACQ-5 score.
Section 1.1. Synopsis and Section 3.2 Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)	Additional pooled other endpoint: Number of courses of antibiotics to treat sinus-related infection up to Week 52	To capture the results of these data as an endpoint.
Section 1.3. Schedule of Activities (SoA)	The recall period for the PGIS has been corrected from "the last week" to "the last 4 weeks".	To align the recall period as described in Section 8.2.6.2.
Section 2.2. Introduction	Replaced references to Clinical Study Reports with the published articles.	To cite published data.
Section 3.3. Primary Estimands, Section 3.4. Secondary Estimands and Section 3.5. Secondary Estimands for Prespecified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)	The primary estimand has been updated to handle the initiation of medications that may modulate the disease course of CRSwNP intercurrent event with a composite strategy, in which participants who experience the intercurrent event are considered to have an unfavorable outcome.	To align with FDA guidelines on developing drugs for treatment of CRSwNP.
Section 3.3. Primary Estimands	The previously defined primary estimand, in which all changes in background medication or start of a prohibited medication (including those medications that may modulate the disease course of CRSwNP) to be handled with a treatment policy strategy, becomes a supplementary estimand to the primary estimand for the co-primary endpoints.	To align with FDA guidelines on developing drugs for treatment of CRSwNP.
Section 3.5 Secondary Estimands for Pre-specified Pooled Analysis Across Studies	The estimand strategy has been updated to handle the initiation of medications that may modulate the disease course of CRSwNP intercurrent event with a composite strategy, in which participants who experience the	To align with FDA guidelines on developing drugs for treatment of CRSwNP.

Section # and title	Description of change	Brief rationale
	intercurrent event are considered to have an unfavorable outcome. The previously defined primary estimand, in which all changes in background medication or start of a prohibited medication (including those medications that may modulate the disease course of CRSwNP) to be handled with a treatment policy strategy, becomes a supplementary estimand to the primary estimand for the pooled surgery endpoints. And additional supplemental estimand was added to handle the initiation of medications that may modulate the disease course of CRSwNP with a hypothetical strategy.	To reflect global differences in availability of biologics for CRSwNP
Section 9.3.1. Co-Primary and Key Secondary Endpoint(s) Analyses	Addition of a tipping point sensitivity analysis for the coprimary endpoints.	To explore the impact of missing data.
Section 9.5 Sample Size Determination	Updates to power calculations.	To account for updated estimand strategy.
All sections	Other minor editorial corrections.	NA

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LIST OF ABBREVIATIONS AND TRADEMARKS

Abbreviations

Abbreviation	Definition
ACQ-5	Asthma Control Test
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Antineutrophil cytoplasmic antibodies
AUC	Area under the curve
CA	Competent authority
CF	Cystic fibrosis
Cmax	Maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyps
CS(s)	Corticosteroid(s)
CT	Computerised tomography
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECRS	Eosinophilic chronic rhinosinusitis
eDiary	Electronic diary

Abbreviation	Definition
EGPA	Eosinophilic granulomatosis with polyangiitis
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ESS	Endoscopic sinus surgery
EW	Early withdrawal
FPFV	First-participant-first-visit
FTIH	First-time-in-human
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyl transferase
HES	Hypereosinophilic Syndrome
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICS/ETN	Inhaled corticosteroids exhalation through nose
ICSR	Individual Case Safety Reports
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
INCS	Intranasal corticosteroid
INR	International normalised ratio
IRT	Interactive response technology
IV	Intravenous
JESREC	Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis

Abbreviation	Definition
LMK	Lund Mackay
LTRA	Leukotriene receptor antagonist
mAb(s)	Monoclonal antibody(ies)
MCID	Minimal clinically important difference
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MPO	Myeloperoxidase
NAb	Neutralising antibodies
NP	Nasal polyps
OC	Osteomeatal complex
OCS	Oral corticosteroid
PCS	Physical component summary
PD	Pharmacodynamic
PFS	Pre-filled safety syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic
PR3	Anti-proteinase 3
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous

Abbreviation	Definition
SCS	Systemic corticosteroids
SDAC	Statistical Data Analysis Centre
SF-36	Short Form (36) Health Survey
SGRQ	St. George's Respiratory Questionnaire
SNOT-22	Sino-nasal Outcome Test
SoA	Schedule of activities
SoC	Standard of care
SRM	Study reference manual
SSD	Safety syringe device
TB	Tuberculosis
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US	The United States
VAS	Visual analogue scale
VRS	Verbal response scale
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

Terms

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

Term	Definition
Background treatment	Type of medicinal product administered to each of the clinical trial participants, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety and efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
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.
Caregiver	A ‘caregiver’ is someone who • lives in the close surroundings of a participant and has a continuous caring role or • has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.

Term	Definition
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
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).
Decentralized Trial Platform	A digital engagement technology allowing for the remote delivery and access to trials for participants, sites, and sponsors.
Direct-from-Participant Shipments	Home pickup of collected biological specimens, or pickup and return of unused/partially used/expired trial materials for return to investigator site.
Direct-to-Participant Shipments	Shipping of Investigational Product, lab kits, devices, etc., to the participant's residence under secure and controlled conditions.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.

Term	Definition
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Home Healthcare Services	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
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.

Term	Definition
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Medicinal products used to assess endpoints	A product given to the participant in a Clinical Trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
NIMP/ AxMP	A NIMP or AxMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
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 (product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.

Term	Definition
Pharmacogenomics	The ICH E15 Guidance for Industry defines pharmacogenomics as the "Study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of pharmacogenomics, 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 pharmacogenomics.
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.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	This term refers to the visit conducted in the place other than the study site.

Term	Definition
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.
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).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study completion date	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).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. 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.

Term	Definition
Subcohort	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule, etc.) at the time of enrollment.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Telemedicine	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.

TRADEMARK INFORMATION

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A randomised, double-blind, parallel group Phase III study to assess the efficacy and safety of 100 mg SC depemokimab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) – ANCHOR-2 (depemokimAb iN CHrOnic Rhinosinusitis)

Brief Title: Efficacy and safety of subcutaneous depemokimab in patients with chronic rhinosinusitis with nasal polyps

Rationale:

Interleukin-5 (IL-5) is the predominant cytokine in nasal polyps (NP) associated with tissue eosinophilia. IL-5 is increased in NP tissue of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) compared with that in healthy controls and correlates with the degree of tissue eosinophilia. Reduction in eosinophils has been identified as a therapeutic strategy for numerous disorders.

Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorization for asthma with an eosinophilic phenotype, including three 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 health-related quality of life (HRQoL) in patients with asthma with an eosinophilic phenotype.

The recently completed Phase III study of mepolizumab in adults with CRSwNP (SYNAPSE, study 205687) demonstrated the efficacy of mepolizumab 100 mg SC by showing statistically significant and clinically meaningful improvement in the co-primary endpoints of total endoscopic nasal polyp score and symptoms of nasal obstruction associated with chronic rhinosinusitis (CRS) compared with placebo when administered every 4 weeks for up to 52 weeks in addition to standard of care (SoC) therapy. Nucala has been recently approved for the treatment of CRSwNP in a few countries including the United States and the EU.

Depemokimab (GSK3511294) is an immunoglobulin G (IgG)-1 allotype three antibody with increased serum half-life. It blocks IL-5 binding to the IL-5 receptor complex, causing a reduction in the circulating population of eosinophils. The extended pharmacokinetic (PK) and pharmacology characteristics of depemokimab have been achieved by reducing clearance and increasing affinity for IL-5. This will potentially enable a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab.

Depemokimab is anticipated to confer a similar efficacy and benefit: risk profile as other IL-5 targeting mAbs, while being administered with a dosing interval of up to 6 months. As such, depemokimab may offer the convenience of an improved dosing schedule.

This study is to assess the efficacy and safety, over a 52-week treatment period of depemokimab 100 mg SC +SoC given once every 26 weeks as add-on maintenance to participants with CRSwNP.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the efficacy of depemokimab 100mg SC + SoC compared to placebo + SoC at Week 52 in participants with a diagnosis of CRSwNP	**Co-primary endpoints:** a) Change from baseline in total endoscopic NP score at Week 52 (centrally read) b) Change from baseline in mean nasal obstruction score (verbal response scale [VRS]) from Week 49 through to Week 52
Secondary	
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in terms of symptom scores for rhinorrhoea (runny nose) and loss of smell	• Change from baseline in mean symptom score for rhinorrhoea (runny nose) (VRS) from Week 49 through to Week 52 • Change from baseline in mean symptom score for loss of smell (VRS) from Week 49 through to Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in terms of the Lund Mackay CT score	• Change from baseline in Lund Mackay CT score at Week 52
To evaluate the impact on quality of life of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in patients with a diagnosis of CRSwNP	• Change from baseline in SNOT-22 total score at Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC prior to Week 26 in participants with a diagnosis of CRSwNP	• Change from baseline in mean nasal obstruction score (VRS) from Week 21 through to Week 24 • Change from baseline in total endoscopic NP score at Week 26

Objectives	Endpoints
Other	
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on individual NP symptoms	• Change from baseline in mean overall symptom (VAS) score from Week 49 through to Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Achieving a one point or greater decrease from baseline in NP Score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Change from baseline in mean individual symptom (VRS) score for facial pain from Week 49 through to Week 52 • Change from baseline in mean individual symptom (VRS) score for mucus in throat from Week 49 through to Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on composite symptom endpoints	• Change from baseline in the mean nasal polyps symptoms composite score (combining VRS scores for nasal obstruction, rhinorrhoea (runny nose), loss of smell, and mucus in throat) from Week 49 through to Week 52 • Change from baseline in mean CRS symptoms and facial pain composite score (combining VRS scores for nasal obstruction, rhinorrhoea (runny nose), loss of smell, and facial pain) from Week 49 through to Week 52 • Achieving a meaningful decrease from baseline in their mean individual symptoms VRS and composite VRS from Week 49 through to Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP.
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on health-related quality of life	• Achieving an 8.9 point or greater decrease from baseline in SNOT-22 total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP. • Achieving a 28 point or greater decrease

Objectives	Endpoints
	from baseline in SNOT-22 total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP. • Change from baseline in SF-36 Mental Component Summary (MCS) score, Physical Component Summary (PCS) score and eight domains at Week 52 • Change from baseline in WPAI-GH scores at Week 52
Safety	
To evaluate the safety and tolerability of depemokimab 100 mg SC + SoC every 26 weeks, compared to placebo + SoC in patients with a diagnosis of CRSwNP	• Incidence of Adverse events (AEs)/ Serious adverse events (SAEs) • Change from baseline in vital signs (heart rate, systolic and diastolic blood pressure, body temperature) at discrete timepoints during the 52-week period • Change from baseline in ECG values at discrete timepoints during the 52-week period • Change from baseline in laboratory parameters (including haematological and clinical chemistry parameters) and hepatobiliary laboratory abnormalities at discrete timepoints during the 52-week period • Incidence of immunogenicity as measured by the presence of antidrug antibody (ADA) and neutralising antibodies (NAb) to depemokimab
Pharmacokinetics and Pharmacodynamics	
To evaluate the pharmacokinetics and pharmacodynamics of depemokimab 100 mg SC + SoC in participants with a diagnosis of CRSwNP	• Depemokimab plasma concentration at measured timepoints during the 52-week period • Ratio to baseline in absolute blood eosinophil count at measured timepoints during the 52-week period.

Objectives and Endpoints for Pre-Specified Pooled Analysis Across Studies 218079 (this study) and 217095 (replicate study)

Objectives	Endpoints
Secondary: Pre-specified pooled analysis across studies 218079 (this study) and 217095 (replicate study)	
To evaluate the impact of depemokimab 100 mg SC + SoC compared to placebo + SoC on the requirement for nasal surgery (actual or planned) at Week 52 in patients with a diagnosis of CRSwNP	• Time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52 • Time to first nasal surgery (actual) or disease-modulating medication for CRSwNP up to Week 52
To evaluate the impact on use of systemic corticosteroids of depemokimab 100 mg SC + SoC compared to placebo + SoC up to Week 52 in patients with a diagnosis of CRSwNP	• Requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery (actual) during the Week 52 treatment period
To evaluate the impact on asthma control of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in the sub-group of participants with partially or not well-controlled (ACQ-5 Score >0.75) asthma and a diagnosis of CRSwNP	• Change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 52
Other: Pre-specified pooled analysis across studies 218079 (this study) and 217095 (replicate study)	
To evaluate the impact of depemokimab 100 mg SC + SoC compared to placebo + SoC on nasal surgery and oral corticosteroid (OCS) use in patients with a diagnosis of CRSwNP	• Time to first nasal surgery (actual) or course of systemic CS or disease-modulating medication for CRSwNP up to Week 52 • Time to first nasal surgery (actual or entry on waiting list) or course of systemic CS or disease-modulating medication for CRSwNP up to Week 52

Objectives	Endpoints
To evaluate the impact on nasal surgery (actual or reduced need for) of depemokimab 100 mg SC + SoC compared to placebo + SoC in patients with a diagnosis of CRSwNP	• Participants no longer having a need for nasal surgery, defined as meeting all of the following: – NP score <5 at Week 52 (centrally read) – Mean overall VAS symptom score ≤7 during Week 49 to Week 52 – No surgery during the treatment period up to Week 52 – No use of disease-modulating medication for CRSwNP up to Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on systemic steroid or antibiotic use as part of SoC in patients with a diagnosis of CRSwNP	• Number of courses of systemic steroid therapy for CRSwNP up to Week 52 • Number of courses of systemic steroid therapy, regardless of indication, up to Week 52 • Total systemic steroid exposure (mg of prednisolone equivalent) regardless of diagnosis up to Week 52 • Time to first course of systemic CS for CRSwNP up to Week 52 • Number of courses of antibiotics to treat sinus-related infection up to Week 52
To evaluate the effect of depemokimab 100 mg SC + SoC compared to placebo + SoC on asthma control in the subgroup of participants with partially or not well-controlled (ACQ-5 Score >0.75) asthma and a reduction in exacerbation frequency in all participants with comorbid asthma	The following asthma related endpoints will be assessed: • Achieving a meaningful decrease from baseline in ACQ-5 score of 0.5 points or greater at 52 weeks without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Number of clinically significant asthma exacerbations defined as worsening of asthma requiring systemic corticosteroids (intravenous [IV] or oral steroid) for at least 3 days or a single intramuscular (IM) corticosteroid dose and/or ED visit and/or hospitalization for asthma up to Week 52

Overall Design:

- This is a randomized, double-blind, placebo-controlled, parallel group, Phase III study of depemokimab + SoC in adults with CRSwNP. The objective of the study is to evaluate the efficacy and safety of depemokimab 100 mg, administered SC by the site staff, via a pre-filled safety syringe device (SSD) every 6 months + SoC for 52 weeks. Efficacy of depemokimab will be assessed using co-primary endpoints of change from baseline in total endoscopic NP score at Week 52 and change from baseline in mean nasal obstruction VRS (verbal response scale) score from Week 49 through to Week 52. Nasal surgery will be assessed from a pre-specified pooled analysis of study 218079 (this study) and study 217095.
- The study population will consist of adult participants (≥18 years of age) with CRSwNP. In addition, participants must have an endoscopic NP score of at least 5 out of a maximum score of 8, with a minimum score of 2 in each nasal cavity. Participants must also have a prior treatment with systemic corticosteroids (SCS) anytime within the past 2 years; and/or have a medical contraindication/intolerance to SCS; and/or had a documented history of prior surgery for NP at the Screening Visit.
- The study will include an approximate 4-week run-in period followed by randomization to a 52-week treatment period. Randomization will be stratified based on occurrence of previous surgery for nasal polyps and country. Participants will be randomized in a 1:1 ratio into one of the two treatment groups, receiving 100 mg of depemokimab SC + SoC or placebo + SoC for a total of 2 doses (26 weeks apart).
- Throughout the entire study, participants will be on the SoC for CRSwNP. Depending on local practice[1], SoC can include intranasal corticosteroids (INCS), saline nasal douching, occasional short courses of systemic corticosteroids (except during the run-in period), and/or antibiotics. With the exception of participants in Japan, participants should take INCS throughout the study.
- Participants in this study who use inhaled corticosteroids exhalation through nose (ICS/ETN) method of administration for their asthma and NP disease are required to maintain this method throughout the study period.

[1] Note: Use of INCS is mandatory for all participants except for those in Japan (INCS is not part of current SoC for CRSwNP in Japan). In Japan, participants not on INCS at screening will be permitted to start INCS, if required for symptom management. In Japan, once participants are on INCS, then they should remain on INCS for the remainder of the study.

Number of Participants:

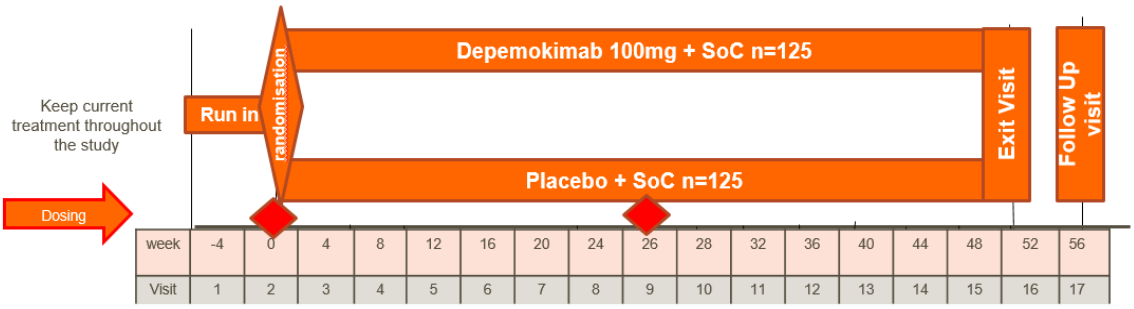
Approximately 417 participants will be screened to ensure 250 randomly assigned 1:1 to depemokimab 100 mg SC + SoC or placebo + SoC (approximately 125 participants per treatment group).

Data Monitoring/ Other Committee: Yes (see Appendix 1 in Section 10.1 for details).

An Independent Data Monitoring Committee (IDMC) will be utilized in this study to ensure external objective review of the safety data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (Section 10.1 - Appendix 1).

1.2. Schema

Figure 1 Study Schematic



1.3. Schedule of Activities (SoA)

The Schedule of Activities (SoA) for this study are provided in Table 1. Study visits will include:

- In-clinic visits (with a marker of "a" in Table 1)
- Telemedicine visits (with a marker of "b"), where permitted by local regulations
- Optional home nursing visits (with a marker of "c"), where permitted by local regulations

Refer to study reference manual (SRM) for further details.

Table 1 Schedule of Activities Table

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
Eligibility Assessments																			
Informed Consent	X																		To be signed before any study procedures. Can occur at a separate visit, prior to Screening, if preferred.
Optional Genetic Informed Consent	X																		Not applicable for China. Informed consent for optional genetics sample must be obtained before collecting a sample.
Optional Biomarker Informed Consent	X																		Not applicable for China. Informed consent for optional exploratory biomarkers must be obtained before collecting a sample.
Inclusion and exclusion criteria	X																		
Demography	X																		
Medical history; Past and current medical conditions	X																		Medical history includes past and current medical conditions for the preceding 12 months including cardiovascular medical history as well as family history of premature cardiovascular disease, CRSwNP disease, CRSwNP/eosinophilic chronic

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			rhinosinusitis (ECRS) and asthma therapy, substance usage, smoking history, asthma and exacerbation history, and concomitant medications for the preceding 12 months.
History of NP surgery	X																		
History of systemic CS use including for CRSwNP	X																		
Randomization & Study Intervention																			
Review of randomization criteria		X																	
Randomization		X																	Randomization Day is Day 1
Study Intervention Administration		X							X										A minimum of 2 hours observation post-injection (at randomization and at Week 26; V9).
Device deficiencies review		X							X										
Safety Assessments																			
Physical exam	X	X							X							X	X		Height to be measured at Screening (V1) only. Weight does not need to be collected at V9. At V2 and V9, physical examination to be performed prior to dosing.
Vital signs	X	X		X			X		X	X			X		X	X	X		Temperature, systolic and diastolic blood pressure and heart rate.

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
12-lead ECG	X	X	X						X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of V2 and V9 where 12-lead ECG machine read values should be used.
SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any SAEs assessed as related to study procedures or related to a GSK product will be recorded from the time a participant consents to participate in the study.
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review (including INCS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessment																			
Assessment of endoscopic NP score	X	X			X		X		X		X		X		X	X	X		For V2, the nasal endoscopy assessment may be performed up to 7 days prior to the clinic visit. Nasal endoscopy must occur prior to randomization. For all other visits the nasal endoscopy assessment must not exceed the protocol defined windows of ±7 days from the nominal

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			study visit.
CT Scan	X															X	X		CT scan is mandatory unless not approved by local ethics committee or institutional review board. The first CT scan must be performed prior to randomization and should be the last assessment performed, where possible. If the first CT scan cannot be performed as the last assessment before randomization, the subject should have completed their screening visit and all screening lab results, the central NP score and ECG central over-read results should be assessed by the PI before a CT scan is conducted. The second CT scan should be performed at V16 or EW visit (up to 14 days prior to the nominal study visit). Note: If a participant is permanently discontinued both from the study intervention and from the

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			study, and the second dose of study intervention was not received, decision on performing CT scan during EW visit at Week 26 will be made by the investigator in consultation with the Medical Monitor. Please refer to Pregnancy test (WOCBP only)
Assessment of Actual NP Surgery or planned NP Surgery		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Wherever possible (and when optional consent provided for exploratory biomarkers), the removed tissue from a nasal surgery will be collected and stored. Not applicable for China.
Assessment of systemic CS and antibiotics dose and duration including for CRSwNP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
Patient-Reported Outcomes																			
Dispensing and Training of the eDiary	X																		
eDiary Compliance Check		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary Collection																X	X		
Individual symptom scores (including nasal obstruction, rhinorrhea [runny nose], loss of smell, facial pain, and mucus in throat) (VRS)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Performed using eDiary. eDiary will be completed by participants in the morning between Screening Visit (V1) and V16.
Overall symptoms score (VAS)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Performed using eDiary. eDiary will be completed by participants in the morning between Screening Visit (V1) and V16.
Nasal obstruction score (VAS)[f]	X	X						X								X	X		Performed using eDiary.
SNOT-22[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Performed using eDiary.
PGIS[f]		X	X	X	X			X					X			X	X		Performed using eDiary. The PGIS will ask the patient to rate the severity of their nasal polyps symptoms over the last 4 weeks.
PGIC[f]			X	X	X			X					X			X	X		Performed using eDiary. The PGIC will ask the patient to rate the change in their nasal symptoms since the start of trial medication.
ACQ-5[f]		X		X		X		X	X		X		X		X	X	X		**For asthmatic participants**

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			only. Performed using eDiary.
Review for asthma exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**For asthmatic participants only**. An asthma exacerbation is defined as worsening of asthma requiring systemic corticosteroids (IV or oral steroid) for at least 3 days or a single IM CS dose and/or emergency department visit, or hospitalization.
SF-36[f]		X		X					X				X			X	X		Performed using eDiary.
WPAI-GH[f]		X		X					X				X			X	X		Performed using eDiary.
Laboratory Assessments																			
Parasitic screening	X																		Parasitic screening is only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months. Please refer to SRM for full list of high-risk countries. Sites should use local laboratories. If sites wish to use central laboratories, they should note that the central test is stool microscopy for ova and parasites. For details of the organisms detected by this test

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			refer to the parasitic screening section of the SRM.
Clinical chemistry (including liver chemistry)	X	X	X	X	X		X		X	X			X			X	X		
Urinalysis[h]	X	X							X				X			X	X		Urinalysis to be performed at local laboratories using dipstick test. If results are abnormal (blood or protein is abnormal [evidence of microalbuminuria or hematuria of ≥1+]) a second urine sample should be taken and sent to central laboratory.
Hematology	X	X	X	X	X		X		X	X	X		X		X	X	X		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, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at V2 and V9.
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	For WOCBP, a serum

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			pregnancy test should be done at Screening Visit, at V16, and EW Visit. Highly sensitive urine pregnancy tests should be done for all other time points. Urine pregnancy test should also be performed within 24 hours prior to any CT scan and results assessed prior to the CT scan. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. Participants who withdraw early from the study should have a urine pregnancy test 4 weeks after the EW Visit.
PK samples		X	X	X	X		X		X	X	X		X			X	X		Must be performed pre-dose at V2 and V9. PK samples at Week 52 (Visit 16/EW Visit) will be collected for approximately 200 participants; sites will be notified once 200 samples have been collected.
IL-5 samples		X	X		X				X				X			X	X		Must be performed pre-dose

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			at V2 and V9.
Complement C3 and C4 sample		X			X				X				X			X	X		
Total IgE sample		X																	
Anti-MPO antibody, anti-PR3 antibody, ANA including anti-dsDNA Ab		X																	Collected baseline (pre-dose) serum sample will be stored and may be tested for ANCA, (anti-MPO antibody, anti-PR3 antibody) and ANA including anti-dsDNA Ab, if necessary (Section 8.6.3)
Immunogenicity		X	X	X	X				X				X			X	X		Must be performed pre-dose at V2 and V9.
Optional Samples [g, h]																			
Optional Genetics sample		X																	Genetics sample can be collected at V2 or at any visit during the Treatment Period. Not applicable for China.
Optional Exploratory Blood Biomarker samples		X			X				X							X			Must be performed pre-dose at V2 and V9. Not applicable for China. A whole blood sample for transcriptomics (Section 8.6.4.2) is collected at V2 and V16 only.
Collect NP surgery samples – Optional		X																	Wherever possible, the removed tissue from a nasal surgery will be collected and stored. Not applicable for

Procedure	Screening (Visit 1)[a, d]	Treatment Period															Withdraw/Follow Up		Notes
		Week															EW Visit	Follow-up	
		0	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	30/56	
		Visit (±7 days)																	
		2[a]	3[a]	4[c]	5[a]	6[b]	7[a]	8[b]	9[a]	10[a]	11[a]	12[b]	13[a]	14[b]	15[a]	16[a]	a, e	b, e	
																			China.
Optional Nasal Biopsy sample																X			Only in participating countries and sites.

Abbreviations: Ab, antibody; ACQ, asthma control questionnaire; AE, adverse event; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CV, cardiovascular, CRSwNP, chronic rhinosinusitis with nasal polyps; dsDNA, double stranded Deoxyribonucleic acid; ECG, electrocardiogram; eDiary, electronic diary; EW, early withdrawal; INCS, intranasal corticosteroids; NP, nasal polyps; MPO, myeloperoxidase; PGIS, patient global impression of severity; PGIC, patient global impression of change; PI: Principal Investigator; PK, pharmacokinetic; PR3, proteinase 3; SAE, serious adverse event; SF-36, 36 item short form health survey; SNOT-22, 22-item sinonasal outcomes test; SRM, study reference manual; VAS, visual analogue scale; VRS, verbal response scale; WPAI-GH, workers productivity and activity impairment – general health; WOCBP, women of childbearing potential; V, Visit.

a. In-clinic visit
b. Telemedicine visit
c. Optional home nursing visit (Week 8; V4 only)
d. Screening window should be 28 days ± 7 days i.e., maximum of 35 days from Day 1 and minimum of 21 days
e. If a participant withdraws from the study, then the EW Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments, concomitant medication review and pregnancy testing (i.e., at Week 30 or 56).
f. All questionnaires should be performed before any other assessments on each particular visit.
g. Informed consent for optional genetics sample or optional exploratory biomarker samples (blood surgery or nasal biopsy) must be obtained before collecting any samples.
h. **China only**: Optional samples (genetics, exploratory biomarkers, surgery and nasal biopsy samples) will not be collected from participants in China. Urine dipstick will not be performed in China, all urine sample will instead be sent for central laboratory urinalysis. Investigators should be aware of the time needed for central laboratories to return results, and should perform appropriate local investigations if any urgent result is required.

2. INTRODUCTION

2.1. Study Rationale

Depemokimab is a humanised mAb (IgG1, kappa) antagonist of IL-5 with an extended pharmacology. It blocks IL-5 binding to the IL-5 receptor complex, causing a reduction in the circulating population of eosinophils. Treatment with anti-IL-5 mAbs such as mepolizumab, administered every 4 weeks, is well tolerated and is approved as an add-on maintenance treatment in patients with severe eosinophilic asthma.

The recently completed Phase III study of mepolizumab in adults with CRSwNP (SYNAPSE, study 205687) demonstrated the efficacy of mepolizumab 100 mg SC by showing statistically significant and clinically meaningful improvement in the co-primary endpoints of total endoscopic nasal polyp score and symptoms of nasal obstruction associated with NP compared with placebo when administered every 4 weeks for up to 52 weeks in addition to SoC therapy [Han, 2021].

Depemokimab is anticipated to confer a similar efficacy and benefit: risk profile as other IL-5 targeting monoclonal antibodies, while being administered with a dosing interval of up to 6 months. As such, depemokimab may offer the convenience of an improved dosing schedule.

This study is to assess the efficacy and safety, over a 52-week treatment period of depemokimab 100 mg SC + SoC given once every 26 weeks as add-on maintenance therapy to participants with CRSwNP.

2.2. Background

Background on CRSwNP / eosinophilic chronic rhinosinusitis (ECRS)

Nasal polyposis (NP) is a chronic inflammatory disease of the nasal passage linings and/or sinuses leading to soft tissue growth in the upper nasal cavity. The resultant swellings which can grow in both nostrils (bilateral), greatly impact a patient's health-related quality of life through increases in nasal obstruction, loss of smell, facial pain, facial pressure and nasal discharge. The persistence of these symptoms due to NP leads to CRS. The condition is therefore also described as CRS with NP (CRSwNP). The European Position Paper on Rhinosinusitis and NP [Fokkens, 2020] defines the severity of disease using a total severity visual analogue scale (VAS) in which a patient is asked to indicate on a 10 cm VAS how troublesome they consider their symptoms. An overall VAS symptom score of 0-3 is defined as mild disease, >3-7 as moderate and >7-10 as severe [Lim, 2007; Fokkens, 2020]. Symptoms are invariably accompanied with findings of inflammation of the nasal mucosa and the presence of a polyp seen through nasal endoscopy or positive imaging findings, for example using computerized tomography (CT). The aetiology of CRSwNP is currently unknown.

The current SoC for CRSwNP is treatment with saline washes, INCS and, for severe symptoms, when short term relief is required, intermittent courses of systemic corticosteroids [Fokkens, 2020]. Antibiotic courses may also be required for intercurrent sinus infection, which often complicates severe NP. Although many patients with

CRSwNP can be adequately controlled with simple medical care (INCS and oral corticosteroid [OCS], occasional nasal douching and antibiotic courses) [Alobid, 2012; Newton, 2008], progression to surgery as a result of severe symptoms and disruption to quality of life is common. Surgery, when ultimately indicated, involves the removal of the polyp tissue and diseased mucosa, restoring aeration of the nasal passage and sinuses. Over 250,000 NP surgeries are performed in the US annually [Bhattacharyya, 2010]. However, polyps have a strong tendency to recur, often requiring repeat surgery [Levine, 1990; Larsen, 1997; Rucci, 2003; Wynn, 2004; Jankowski, 2006; Brescia, 2015; DeConde, 2017; Loftus, 2020] with a timescale that can vary from a few months to years. Data suggests patients with NP associated with tissue eosinophilia constitute the majority of those who have a recurrence after surgery [Brescia, 2015]. Repeat (revision) surgery is associated with diminishing success and a higher potential for adverse effects [Bhattacharyya, 2004; Chu, 1997], hence alternative treatment options are needed for this patient group.

While the recurrence of bilateral NP despite surgery is common and known to be associated with the IL-5/eosinophilic pathway in adults, this is less so for children [Jones, 1999; Fokkens, 2020]. The number of eosinophils and cells expressing messenger RNA for IL-4, IL-5 and IL-10 is higher in patients with CRS excluding cystic fibrosis (CF) versus those with CF and controls [Fokkens, 2020]. Anetrochoanal polyps are also another form of NP more common in children that are usually unilateral and associated with low eosinophil tissue levels [Fokkens, 2020].

CRSwNP in Japan and China

In Japan, CRS is recognized as a common chronic disease [Tokunaga, 2015]. In recent years, cases of CRSwNP associated with eosinophilic infiltration have increased in Japan due to westernization of eating habits and environments [Tokunaga, 2015]. Patients are diagnosed as ECRS using the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) scoring system based on the presence of bilateral NP, CT findings, and eosinophilia in peripheral blood. This scoring system provides a criterion to diagnose and classify ECRS without the use of biopsy or operational specimens. A patient is diagnosed as having ECRS if the JESREC score is 11 out of 17 points or higher. Patients with ECRS (JESREC score ≥11) are further classified into three groups according to blood eosinophilia, ethmoid-dominant shadow in CT, and comorbidity (bronchial asthma, AI, NSAIDs intolerance). These groups were significantly correlated with the rate of NP recurrence and refractory disease [Tokunaga, 2015].

Similarly, CRS is among the most prevalent chronic diseases in China with an estimated prevalence of 8.0% [Shi, 2015]. A recent report found that the proportion of eosinophilic CRSwNP patients significantly increased over 11 years [Wang, 2019]. Although there are no established diagnosis criteria for eosinophilic CRSwNP in China so far, these patients differ significantly from non-eosinophilic patients in clinical characteristics and treatment outcomes: they have higher risk of having comorbid allergic rhinitis and asthma, are frequently associated with extensive sinus disease, and have higher polyp recurrence rate after surgery. Hence, precision medicine on inflammatory endotypes by verification and mapping of the eosinophilic disease are of great importance to optimize care pathways in Asia.

Standard of care (SoC) for ECRS is systemic corticosteroids in Japan and there is a trend to use orally inhaled corticosteroids exhalation through nose (ICS/ETN) method of administration for the management of NP for patients with both ECRS and concomitant asthma disease [Kobayashi, 2018]. Although longer term effects on nasal polyp disease are yet to be fully evaluated, the short term effects of ICS/ETN on NP size can be significant. Of note, in Japan INCS is not licensed for ECRS.

2.2.1. The Role of Anti IL5 Therapy in CRSwNP

IL-5 is the predominant cytokine in NP associated with tissue eosinophilia, promoting the activation and prolonged survival of eosinophils [Bachert, 1997; Bachert, 1998]. IL-5 is increased in NP tissue compared with that in healthy controls, and correlates with the degree of tissue eosinophilia, strongly suggesting a rationale for anti-IL-5 therapy in this condition [Bachert, 1997].

Inhibition of IL-5 will remove a key eosinophil growth factor, and given the short circulating half-life of eosinophils, it will result in a rapid reduction in the circulating population. Reduction in eosinophils has been identified as a therapeutic strategy for numerous disorders, with mAbs targeting IL-5, such as mepolizumab, currently approved for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA), CRSwNP, and hypereosinophilic syndrome (HES) and in development for other indications [Legrand, 2015].

The current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype. Mepolizumab 100 mg SC (every 4 weeks) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. The safety profile of mepolizumab is favourable.

The recently completed Phase III study of mepolizumab in CRSwNP (SYNAPSE, study 205687) demonstrated the efficacy of mepolizumab 100 mg SC by showing statistically significant and clinically meaningful improvement in the co-primary endpoints of total endoscopic nasal polyp score and symptoms of nasal obstruction associated with CRS compared with placebo when administered every 4 weeks for up to 52 weeks in addition to SoC therapy [Han, 2021].

2.2.1.1. Depemokimab (GSK3511294) Long-Acting IL-5

Depemokimab is an extended pharmacology humanised mAb. It inhibits IL-5 signalling by blocking human IL-5 binding to the IL-5 receptor complex, which is expressed on the eosinophil cell surface. Treatment with anti-IL-5 monoclonal antibodies such as mepolizumab, administered every 4 weeks, is well tolerated and is approved as an add-on maintenance treatment in patients with severe eosinophilic asthma, EGPA, HES, and CRSwNP. Depemokimab is anticipated to confer a similar efficacy and benefit: risk profile as other IL-5 targeting monoclonal antibodies, while being administered with a longer dosing interval.

Depemokimab demonstrated an approximately 29-fold increase in IL-5 potency compared to mepolizumab in a cell-based in vitro assay and approximately 2-fold reduction in clearance in a single-dose pharmacokinetic (PK)/pharmacodynamic (PD) study in cynomolgus monkeys. Consistent with the in vitro data, in cynomolgus monkeys, depemokimab demonstrated approximately 30-fold greater IL-5 binding affinity compared with mepolizumab, as evaluated by the serum total IL-5 profile and duration of blood eosinophil suppression. The reversal to 50% of the maximal inhibition of blood eosinophils was observed at around Day 169 for depemokimab (1 mg/kg) and at Day 29 for mepolizumab (1 mg/kg).

The safety profile of depemokimab (10 and 100 mg/kg doses) has been evaluated in a 4-week single-dose and a 26-week repeat dose toxicity (2 doses 3 months apart given at Day 1 and Week 14) studies, administered by the subcutaneous route to cynomolgus monkeys. Depemokimab binding assessed by immunohistochemistry did not demonstrate specific positive staining in any of the tissues examined with the staining restricted to the positive control material (IL-5 coated coupled beads), suggesting little likelihood for nonpharmacological effects.

As a long-acting anti-IL-5 mAb, depemokimab is anticipated to provide the same clinical benefit with a similar safety profile compared with mepolizumab and others in its class and with the added benefit of an extended duration of action requiring less frequent SC dosing (once every 6 months). As such, depemokimab may offer the convenience of an improved dosing schedule.

Depemokimab in the clinic:

GSK has completed a single ascending dose first-time-in-human (FTIH) study (Study 205722) to investigate the safety, tolerability, immunogenicity, PK and PD of depemokimab administered subcutaneously in participants with mild- to -moderate asthma. Eligible participants had a screening blood eosinophil level of ≥200 cells/μL for relevance to the target population and facilitate investigation of the blood eosinophil profile following single doses of depemokimab. The study 205722 showed depemokimab to be well tolerated in adult participants with mild/moderate asthma who received a single SC dose of depemokimab up to 300 mg [Singh, 2022].

A detailed description of the chemistry, pharmacology and safety of depemokimab is provided in the current Investigator's Brochure (IB) [GSK3511294 Clinical Investigator's Brochure].

2.3. Benefit/Risk Assessment

The benefit-risk of depemokimab in this trial is favourable. Summaries of findings from nonclinical studies conducted with depemokimab and completed FTIH study 205722, as well as more detailed information about the known and expected benefits and risks and reasonably expected AEs of depemokimab can be found in the current IB [GSK3511294 Clinical Investigator's Brochure] or later

The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Depemokimab (GSK3511294)		
Allergic reactions including anaphylaxis	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 8 in Section 10.8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with depemokimab in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity SMQ with preferred term of rash verbatim "localised rash both bends of arms", 82 days post 30 mg SC dose of depemokimab. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of serious adverse events (SAEs) by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. • Use of criteria of Joint National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8 in Section 10.8). • Use of standardized CRFs to collect relevant data on systemic reactions. • Participants will be monitored in the clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at randomization and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals. • Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.
Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in one female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal	• 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).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with depemokimab in FTIH study 205722 in participants with mild to moderate asthma (36 participants received depemokimab; 12 participants received placebo).	• Daily monitoring of SAEs will be done by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies will be performed by a GSK safety review team. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a relevant medical expert (member of the IDMC). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.4). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1.1).
Immunogenicity, anti-drug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and neutralising antibodies (NAb), which have the potential to modulate PK or PD, or to produce adverse reactions. • In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the depemokimab 30 mg dose group (5 participants), which was also the group with the highest total serum IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the depemokimab plasma concentration-time and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants. Neutralizing antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.8).
Local injection site reactions.	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • In the depemokimab FTIH study 205722, injection site reactions were reported by one (3%) participant who	• 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. • Use of standardized CRFs to collect relevant data on local injection site reactions.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	received depemokimab and one (8%) participant who received placebo.	• The IDMC will review unblinded safety data at regular intervals.
QTc prolongation	• Four out of six monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the depemokimab FTIH study (205722), no treatment effect for ECG parameters including corrected QT interval (QTcF) was observed across the depemokimab treatment groups (n=36). No participants met QTcF protocol specified criteria (QTcF >500 msec or increase from baseline >60 msec, or uncorrected QT >600 msec) that would require additional monitoring. • Analysis of the relationship between depemokimab plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study did not reveal any clinically or statistically significant trends of concern with increasing depemokimab dose up to 300 mg. The predicted increase in mean QTcF change from baseline with depemokimab plasma concentrations point estimates remained below 10 msec [FDA, 2005] up to concentrations of 100 ug/mL, with a 95% lower CI consistent with zero change from baseline (i.e. the 95% lower bound of the CI is below zero) [GSK Document Number 2020N457410_00].	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.3.3. • Participants with QTc prolongation on screening will be excluded (criterion 30, Section 5.2). • Participants with clinically significant cardiac abnormalities that are uncontrolled with standard treatment are excluded (criterion 18, Section 5.2). • Participants who meet QT stopping criteria as specified in Section 7.1.3 will not receive another dose of study intervention. • The IDMC will review unblinded safety data at regular intervals.
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	• Participants who are pregnant, breastfeeding, or plan to become pregnant at screening are excluded (criterion 28, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1.1). • 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 testes [Setchell, 1975;Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	dose and until 30 weeks after the last administered dose as described in Section 10.4.2.
Study Procedures		
Potential risk for injury with phlebotomy	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).
Exposure of subjects to ionising radiation from Sinus CT	• Two sinus CT scans are included at baseline (as a last assessment prior to randomization, where possible) and at Visit 16, or Early Withdrawal, if appropriate (see Section 8.2.3). • The total effective radiation dose from the two sinus CT procedures is estimated to be 2mSv per study (i.e., 1mSv per scan). • The average annual global background radiation dose is 2.4mSv and therefore the total estimated dose from study procedures is less than 1-years of background radiation. The additional risk of developing a fatal malignancy as a result of this radiation exposure is around 1 in 10000.	• The minimum number of CT procedures will be performed to achieve study objectives (with approximately 52 weeks spacing between procedures). • The first CT scan must be performed prior to randomization and should be the last assessment performed, where possible. If the first CT scan cannot be performed as the last assessment before randomization, the subject should have completed their screening visit and all screening lab results, the central NP score and ECG central over-read results should be assessed by the Principal Investigator (PI) before a CT scan is conducted. The second CT scan should be performed at V16 or EW visit (up to 14 days prior to the nominal study visit). Note: If a participant is permanently discontinued both from the study intervention and from the study, and the second dose of study intervention was not received, decision on performing CT scan during EW visit at Week 26 will be made by the investigator in consultation with the Medical Monitor • Please refer to Section 8.3.5 for Pregnancy testing requirements (WOCBP only)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Application of an increased minimum age for inclusion in the study was considered to further mitigate the risks. However, such a restriction is impracticable in this population and might also result in the study sample being skewed and unrepresentative. Therefore, given the moderate radiation dose, a minimum age for inclusion of 18 years is considered justifiable. • Participants who have been exposed to ionising radiation in excess of 10mSv above background over the previous three-year period as a result of occupational exposure or previous participation in research studies are excluded (criterion 22, Section 5.2). • Participants are asked about any occupational exposure or previous participation in research studies at screening so that dose estimates can be obtained, where necessary.
Exposure of foetus to ionising radiation from Sinus CT	• As the study procedure is a sinus CT, the abdomen is out of the field of view and in the event of an undetected pregnancy the foetal radiation dose will be limited to scatter and hence very small. Nevertheless, steps are required to avoid accidental exposure of pregnant subjects.	• WOCBP will be required to have a negative highly sensitive urine pregnancy test within the 24 hours before each CT scan. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant will be excluded from participation if the serum pregnancy result at screening is positive.

2.3.2. Benefit Assessment

Current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype.

Mepolizumab 100 mg SC (every 4 weeks) has been approved for the treatment of severe asthma with an eosinophilic phenotype and CRSwNP and mepolizumab 300 mg SC (every 4 weeks) has been approved for eosinophilic granulomatosis with polyangiitis (EPGA) and HES in several different countries. The benefit: risk profile of mepolizumab is favourable. Considering a precedented mechanism of action and demonstrated efficacy of mepolizumab in patients with CRSwNP along with good tolerability and a favourable safety profile, as well as clinical safety results from the completed FTIH study 205722 with depemokimab, proposed depemokimab CRSwNP therapy is expected to deliver an efficacy and safety profile similar to mepolizumab, with the added benefit of an extended duration of action requiring less frequent SC dosing (once every 6 months). As such, depemokimab may offer the convenience of an improved dosing schedule.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures being implemented to minimize risk to participants in this study, the potential risks of participating in this study are justified by the anticipated benefits that may be afforded to participants with CRSwNP. Therefore, the Sponsor considers that the investigation of the efficacy and safety of depemokimab is justified in this study with a positive benefit: risk ratio.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of depemokimab 100mg SC + SoC compared to placebo + SoC at Week 52 in participants with a diagnosis of CRSwNP	**Co-primary endpoints:** • Change from baseline in total endoscopic NP score at Week 52 (centrally read) • Change from baseline in mean nasal obstruction score (verbal response scale [VRS]) from Week 49 through to Week 52
Secondary	
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in terms of symptom scores for rhinorrhoea (runny nose)	• Change from baseline in mean symptom score for rhinorrhoea (runny nose) (VRS) from Week 49 through to Week 52 • Change from baseline in mean symptom score for loss of smell (VRS) from

Objectives	Endpoints
and loss of smell	Week 49 through to Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in terms of the Lund Mackay CT score	• Change from baseline in Lund Mackay CT score at Week 52
To evaluate the impact on quality of life of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in patients with a diagnosis of CRSwNP	• Change from baseline in SNOT-22 total score at Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC prior to Week 26 in participants with a diagnosis of CRSwNP	• Change from baseline in mean nasal obstruction score (VRS) from Week 21 through to Week 24 • Change from baseline in total endoscopic NP score at Week 26
Other	
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on individual NP symptoms	• Change from baseline in mean overall symptom (VAS) score from Week 49 through to Week 52 • Achieving a one point or greater decrease from baseline in NP Score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Change from baseline in mean individual symptom (VRS) score for facial pain from Week 49 through to Week 52 • Change from baseline in mean individual symptom (VRS) score for mucus in throat from Week 49 through to Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on composite symptom endpoints	• Change from baseline in the mean nasal polyps symptoms composite score (combining VRS scores for nasal obstruction, rhinorrhoea (runny nose), loss of smell, and mucus in throat) from Week 49 through to Week 52 • Change from baseline in mean CRS symptoms and facial pain composite score

Objectives	Endpoints
	(combining VRS scores for nasal obstruction, rhinorrhoea (runny nose), loss of smell, and facial pain) from Week 49 through to Week 52 • Achieving a meaningful decrease from baseline in their mean individual symptoms VRS and composite VRS from Week 49 through to Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on health-related quality of life	• Achieving an 8.9-point or greater decrease from baseline in SNOT-22 total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Achieving a 28 point or greater decrease from baseline in SNOT-22 total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Change from baseline in SF-36 Mental Component Summary (MCS) score, Physical Component Summary (PCS) score and eight domains at Week 52 • Change from baseline in WPAI-GH scores at Week 52
Safety	
To evaluate the safety and tolerability of depemokimab 100 mg SC + SoC every 26 weeks, compared to placebo + SoC in patients with a diagnosis of CRSwNP	• Incidence of AEs/ Serious adverse events (SAEs) • Change from baseline in vital signs (heart rate, systolic and diastolic blood pressure, body temperature) at discrete timepoints during the 52-week period • Change from baseline in ECG values at discrete timepoints during the 52-week period • Change from baseline in laboratory parameters (including haematological and clinical chemistry parameters) and hepatobiliary laboratory abnormalities at

Objectives	Endpoints
	discrete timepoints during the 52-week period • Incidence of immunogenicity as measured by the presence of ADA and neutralising antibodies (NAb) to depemokimab
Pharmacokinetics and Pharmacodynamics	
To evaluate the pharmacokinetics and pharmacodynamics of depemokimab 100 mg SC + SoC in participants with a diagnosis of CRSwNP	• Depemokimab plasma concentration at measured timepoints during the 52-week period • Ratio to baseline in absolute blood eosinophil count at measured timepoints during the 52-week period.

3.2. Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)

Objectives	Endpoints
Secondary: Pre-specified pooled analysis across studies 218079 (this study) and 217095 (replicate study)	
To evaluate the impact of depemokimab 100 mg SC + SoC compared to placebo + SoC on the requirement for nasal surgery (actual or planned) at Week 52 in patients with a diagnosis of CRSwNP	• Time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52 • Time to first nasal surgery (actual) or disease-modulating medication for CRSwNP up to Week 52
To evaluate the impact on use of systemic corticosteroids of depemokimab 100 mg SC + SoC compared to placebo + SoC up to Week 52 in patients with a diagnosis of CRSwNP	• Requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery (actual) during the Week 52 treatment period
To evaluate the impact on asthma control of depemokimab 100 mg SC + SoC compared to placebo + SoC at Week 52 in the sub-group of participants with partially or not well-controlled (ACQ-5 Score >0.75) asthma and a diagnosis of CRSwNP	• Change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 52

Objectives	Endpoints
Other: Pre-specified pooled analysis across studies 218079 (this study) and 217095 (replicate study)	
To evaluate the impact of depemokimab 100 mg SC + SoC compared to placebo + SoC on nasal surgery and OCS use in patients with a diagnosis of CRSwNP	• Time to first nasal surgery (actual) or course of systemic CS or disease-modulating medication for CRSwNP up to Week 52 • Time to first nasal surgery (actual or entry on waiting list) or course of systemic CS or disease-modulating medication for CRSwNP up to Week 52
To evaluate the impact on nasal surgery (actual or reduced need for) of depemokimab 100 mg SC + SoC compared to placebo + SoC in patients with a diagnosis of CRSwNP	• Participants no longer having a need for nasal surgery, defined as meeting all of the following: – NP score <5 at Week 52 (centrally read) – Mean overall VAS symptom score ≤7 during Week 49 to Week 52 – No surgery during the treatment period up to Week 52 – No use of disease-modulating medication for CRSwNP up to Week 52
To evaluate the efficacy of depemokimab 100 mg SC + SoC compared to placebo + SoC on systemic steroid or antibiotic use as part of SoC in patients with a diagnosis of CRSwNP	• Number of courses of systemic steroid therapy for CRSwNP up to Week 52 • Number of courses of systemic steroid therapy, regardless of indication, up to Week 52 • Total systemic steroid exposure (mg of prednisolone equivalent) regardless of diagnosis up to Week 52 • Time to first course of systemic CS for CRSwNP up to Week 52 • Number of courses of antibiotics to treat sinus-related infection up to Week 52
To evaluate the effect of depemokimab 100 mg SC + SoC compared to placebo + SoC on asthma control in the subgroup of participants with partially or not	The following asthma related endpoints will be assessed: • Achieving a meaningful decrease from baseline in ACQ-5 score of 0.5 points or

Objectives	Endpoints
well-controlled (ACQ5 Score >0.75) asthma and a reduction in exacerbation frequency in all participants with co-morbid asthma	greater at 52 weeks without first having nasal surgery (actual) or disease-modulating medication for CRSwNP • Number of clinically significant asthma exacerbations defined as worsening of asthma requiring systemic corticosteroids (intravenous [IV] or oral steroid) for at least 3 days or a single intramuscular (IM) corticosteroid dose and/or ED visit and/or hospitalization for asthma up to Week 52

3.3. Primary Estimands

The primary estimands are defined as follows:

Treatment Comparison: depemokimab 100 mg SC + SoC compared to placebo + SoC

Population: Participants with a diagnosis of CRSwNP / ECRS

Co-primary variables/endpoints:

- Change from baseline in total endoscopic NP score at Week 52 (centrally read)
- Change from baseline in mean nasal obstruction score (verbal response scale [VRS]) from Week 49 through to Week 52

Summary measure: Difference in means between treatment groups - depemokimab 100 mg SC + SoC versus placebo + SoC

Main Intercurrent events (ICE) anticipated:

- Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery (ESS)) – to be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who undergo surgery will be assigned the worst possible value of the relevant score for all assessments following surgery (i.e., the worst value that it is possible to select on the given scale).
- Premature discontinuation of study treatment – to be handled using a treatment policy strategy
- Initiation of a medication that may modulate the disease course of CRSwNP by reduction of blood eosinophils or type II inflammation to be handled using a composite strategy by incorporating the occurrence of the event into the definition of the endpoint. Medications that may modulate the disease course to be selected either based on published evidence or mechanism of action, and to include the initiation of some biologics, chronic SCS and INCS. Specifically, participants who start a medication that may modulate the disease course of CRSwNP will be assigned the

worst possible value of the relevant score for all assessments following the start of the medication (i.e., the worst value that is possible to select on the given scale).

  - All other changes in background medication or start of a prohibited medication – to be handled using a treatment policy strategy

- COVID-19 related events – to be handled using a treatment policy strategy
- Course(s) of systemic CS for any reason – to be handled using a treatment policy strategy

Supplementary estimand strategy for co-primary endpoints: In addition, the intercurrent event for all changes in background medication or start of medication that may modulate the disease course of CRSwNP to be handled under the treatment policy strategy will be considered as a supplementary estimand to the primary estimand.

3.4. Secondary Estimands

The secondary estimands are defined as follows:

Treatment Comparison: As for primary estimand

Population: As for primary estimand

Variables/endpoints:

- Change from baseline in mean symptom score for rhinorrhea (runny nose) (VRS) from Week 49 through to Week 52
- Change from baseline in mean symptom score for loss of smell (VRS) from Week 49 through to Week 52
- Change from baseline in Lund Mackay CT score at Week 52
- Change from baseline in SNOT-22 total score at Week 52
- Change from baseline in mean nasal obstruction score (VRS) from Week 21 through to Week 24
- Change from baseline in total endoscopic NP score at Week 26

Summary measure: As for primary estimand

Main Intercurrent events (ICE) anticipated: As for primary estimand

3.5. Secondary Estimands for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095

3.5.1. Secondary estimand for surgery endpoints

The secondary estimand for time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication up to Week 52 and for time to first nasal surgery (actual) or disease-modulating medication up to Week 52 is defined as follows:

Treatment Comparison: depemokimab 100 mg SC + SoC compared to placebo + SoC

Population: participants with a diagnosis of CRSwNP / ECRS

Variable/endpoint:

- Time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52
- Time to first nasal surgery (actual) or disease-modulating medication for CRSwNP up to Week 52

Summary measure: Hazard ratio between treatment groups - depemokimab 100 mg SC + SoC versus placebo + SoC

Main Intercurrent events (ICE) anticipated:

- Premature discontinuation of study treatment – to be handled using a treatment policy strategy
- Initiation of a medication that may modulate the disease course of CRSwNP by reduction of blood eosinophils or type II inflammation to be handled using a composite strategy by incorporating the occurrence of the event into the definition of the endpoint. Medications that may modulate the disease course to be selected either based on published evidence or mechanism of action, and to include the initiation of some biologics, chronic SCS and INCS. Specifically, participants who start a medication that may modulate the disease course of CRSwNP will be counted as requiring surgery at the time the medication was started.
    - All other changes in background medication or start of a prohibited medication – to be handled using a treatment policy strategy
- COVID-19 related events – to be handled using a treatment policy strategy
- Course(s) of systemic CS for any reason – to be handled using a treatment policy strategy

Supplementary estimand strategy for pooled secondary endpoints related to nasal surgery:

- **Supplementary estimand 1**: In addition, the intercurrent event for all changes in background medication or start of medication (including those medications that may modulate the disease course of CRSwNP) to be handled under the treatment policy strategy will be considered as a supplementary estimand to the primary estimand.
- **Supplementary estimand 2**: In addition, the intercurrent event for initiation of a medication that may modulate the disease course of CRSwNP by reduction of blood eosinophils or type II inflammation to be handled under the hypothetical strategy. Medications that may modulate the disease course to be selected either based on published evidence or mechanism of action, and to include the initiation of some biologics, chronic SCS and INCS.
    - All other changes in background medication or start of a prohibited medication to be handled using a treatment policy strategy

3.5.2. Secondary estimand for systemic steroids endpoint

The secondary estimand for requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery (actual) during the Week 52 treatment period is defined as follows:

Treatment Comparison: depemokimab 100 mg SC + SoC compared to placebo + SoC

Population: participants with a diagnosis of CRSwNP / ECRS

Variable/endpoint:

- Requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery (actual) during the Week 52 treatment period

Summary measure: Odds ratio between treatment groups - depemokimab 100 mg SC + SoC versus placebo + SoC

Main Intercurrent events (ICE) anticipated:

- Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and ESS) – to be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who undergo surgery will be counted as requiring systemic corticosteroids during the Week 52 treatment period.
- Premature discontinuation of study treatment – to be handled using a treatment policy strategy
- Initiation of a medication that may modulate the disease course of CRSwNP by reduction of blood eosinophils or type II inflammation to be handled using a composite strategy by incorporating the occurrence of the event into the definition of the endpoint. Medications that may modulate the disease course to be selected either based on published evidence or mechanism of action, and to include the initiation of some biologics, chronic SCS and INCS. Specifically, participants who start a medication that may modulate the disease course of CRSwNP will be counted as requiring corticosteroids during the 52-week treatment period.
    - All other changes in background medication or start of a prohibited medication – to be handled using a treatment policy strategy
- COVID-19 related events – to be handled using a treatment policy strategy
- Course(s) of systemic CS for any reason – to be handled using a treatment policy strategy

3.5.3. Secondary estimand for ACQ-5

The secondary estimand for change from baseline in ACQ-5 score at Week 52 is defined as follows:

Treatment Comparison: depemokimab 100 mg SC + SoC compared to placebo + SoC

Population: Participants with a diagnosis of CRSwNP / ECRS and partially or not well-controlled asthma with an ACQ-5 score >0.75 at baseline

Variable/endpoint:

- Change from baseline in ACQ-5 score at Week 52

Summary measure: Difference in means between treatment groups - depemokimab 100 mg SC + SoC versus placebo + SoC

Main Intercurrent events (ICE) anticipated:

- Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery (ESS)) – to be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who undergo surgery will be assigned a score of 6, the worst possible value of ACQ-5 for all assessments following surgery.
- Premature discontinuation of study treatment – to be handled using a treatment policy strategy
- Initiation of a medication that may modulate the disease course of CRSwNP by reduction of blood eosinophils or type II inflammation to be handled using a composite strategy by incorporating the occurrence of the event into the definition of the endpoint. Medications that may modulate the disease course to be selected either based on published evidence or mechanism of action, and to include the initiation of some biologics, chronic SCS and INCS. Specifically, participants who start a medication that may modulate the disease course of CRSwNP will be assigned the worst possible value of the relevant score for all assessments following the start of the medication (i.e., the worst value that is possible to select on the given scale).
    - All other changes in background medication or start of a prohibited medication – to be handled using a treatment policy strategy
- COVID-19 related events – to be handled using a treatment policy strategy
- Course(s) of systemic CS for any reason – to be handled using a treatment policy strategy

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel group, Phase III study of depemokimab 100 mg + SoC in approximately 250 adults with CRSwNP. The objective of the study is to evaluate the efficacy and safety of depemokimab 100 mg, administered SC by the site staff, via a pre-filled safety syringe device every 6 months + SoC for 52 weeks. Efficacy of depemokimab will be assessed using co-primary endpoints of change from baseline in total endoscopic NP score at Week 52 and change from baseline in mean nasal obstruction VRS score from Week 49 through to Week 52. Nasal surgery will be assessed from a pre-specified pooled analysis of study 218079 (this study) and study 217095.

The study population will consist of adult participants (≥18 years of age) with CRSwNP. In addition, participants must have an endoscopic NP score of at least 5 out of a maximum score of 8, with a minimum score of 2 in each nasal cavity. Participants must also have a prior treatment with SCS anytime within the past 2 years; and/or have a medical contraindication/intolerance to SCS; and/or had a documented history of prior surgery for NP at the Screening Visit.

The study will include a 4-week run-in period followed by randomization to a 52-week treatment period as a double-blind, placebo-controlled phase. The total study duration will be approximately 56 weeks. Randomization will be stratified based on occurrence of previous surgery for nasal polyps and country. Participants will be randomized in a 1:1 ratio into one of the two treatment groups, receiving 100 mg of depemokimab SC or placebo (both in addition to SoC) for a total of two doses (26 weeks apart).

Throughout the entire study, participants will be on the SoC for CRSwNP. Depending on local practice*, SoC can include INCS, saline nasal douching, occasional short courses of systemic corticosteroids (except during the run-in period), and/or antibiotics. With the exception of participants in Japan, participants should take INCS throughout the study.

There is a trend, especially in Japan, to use orally ICS/ETN method of administration for the management of NP for participants with both ECRS and concomitant asthma disease [Kobayashi, 2018]. Although longer term effects on CRSwNP disease are yet to be fully evaluated, the short-term effects of ICS/ETN on NP size can be significant. Therefore, participants in this study who use ICS/ETN method of administration for their asthma and NP disease are required to maintain this method throughout the study period.

(*Note: Use of INCS is mandatory for all participants, except for those in Japan [INCS is not part of current SoC for CRSwNP in Japan]. In Japan, participants not on INCS at screening will be permitted to start INCS, if required for symptom management. In Japan, once participants are on INCS, then they should remain on INCS for the remainder of the study.)

4.2. Scientific Rationale for Study Design

Current data from mepolizumab pre-clinical and clinical development indicate the ability of mepolizumab to inhibit IL-5 leading to consistent reduction in blood eosinophils, with demonstration of clinical benefit in the treatment of conditions associated with eosinophilic inflammation. Data from Phase II and Phase III studies of mepolizumab in CRSwNP have shown efficacy in both NP score and symptoms as well as impact on the need for surgery.

In addition, data from the Phase III asthma programme with mepolizumab demonstrate, compared with placebo, a reduction in asthma exacerbations, improvements in asthma control and quality of life (as measured by the Asthma Control Test (5-item) [ACQ-5] and St. George's Respiratory Questionnaire [SGRQ], respectively), improvements in lung function and a reduction in oral corticosteroid (OCS) use in those participants on chronic OCS treatment. No new safety issues were identified in the Study 205687 (SYNAPSE study) in addition to those already identified in the severe asthma studies. Since depemokimab targets the same IL-5 epitope as mepolizumab, it therefore follows that establishing the same reduction in blood eosinophils as mepolizumab, via the same IL-5 neutralization is expected to generate similar clinical efficacy in the CRSwNP patient population selected for this study. Safety in depemokimab is expected to be similar to that of mepolizumab.

4.2.1. Participant Input into Design

Sixteen CRSwNP patients who met the proposed Inclusion Criteria provided input into the study design: 4 from the United States, 4 from Argentina, 3 from Germany and 5 from the United Kingdom.

Insights were gained via a 25-minute online qualitative survey.

The questions included in the survey were centred around:

1. Understanding patient’s motivations for participating
2. Study Assessments and Procedures
3. Retention and ongoing support required

In line with the feedback received there will be clear explanations for all study specific procedures provided in the informed consent form (ICF), suggested recruitment and retention techniques will be explored and flexibility/support with visit scheduling (e.g., telemedicine visits and concierge services) will be implemented where allowed by local regulations.

4.3. Justification for Dose

Using model-informed drug development (MIDD) principles, GSK has identified that the dose and dosing frequency of depemokimab that matches phase 3 mepolizumab-like blood eosinophil pharmacology (seen in SYNAPSE) for the entire length of treatment, in the CRSwNP population, is 100 mg SC administered every 26 weeks. Further analysis

shows that there will be limited additional benefit, in term of eosinophil reduction, beyond this dose [GSK Document Number 2021N475816_00].

The depemokimab 100 mg SC every 26 weeks dosing regimen is further supported by the Bayesian dose-time exposure-response analysis [GSK Document Number 2019N418119_00] focussed on asthma and utilized to select a dose of 100 mg SC every 26 weeks for the Phase III trials (206713 and 213744). The clinical pharmacology of mepolizumab was similar in participants with nasal polyps and severe asthma, and the same is anticipated to be valid for depemokimab.

Since depemokimab targets the same IL-5 epitope as mepolizumab, it therefore follows that establishing the same reduction in blood eosinophils as mepolizumab, via the same IL-5 neutralization is expected to generate similar clinical efficacy in the CRSwNP patient population selected for this study. Furthermore, given the precedented safety profile of IL-5 neutralization is comparable to placebo, it also follows that targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of depemokimab.

The proposed 100 mg SC dose is 3 times lower than the highest dose tested in the Phase 1 study 205722 (300 mg SC) and approximately 70 times lower than the no observed adverse effect level dose (NOAEL). The safety margins are detailed in Table 2 for i) a typical 70 kg individual, ii) a 66.7 kg individual (average male body weight in adult Japanese [Statistics of Japan, 2021]), iii) a 53.2 kg individual (average female body weight in adult Japanese [Statistics of Japan, 2021]) and iv) a 29 kg individual (lowest body weight in adult Japanese [Statistics of Japan, 2021]). Based on the wide safety margins described above, the favourable safety profile in the Phase 1 study 205722, including at the 300 mg dose and the large clinical and real-world experience with compounds targeting IL5/IL5R, the proposed dose is anticipated to be safe and adequate.

Table 2 Predicted Exposure for Depemokimab 100 mg SC Q26W Versus Measured Exposure in Phase 1 study 205722 and Measured Exposure with the NOAEL Dose (100 mg/kg, highest dose tested in the 26 weeks study in cynomolgus monkeys)

Body Weight (kg)	Predicted Ph3 exposure[1]	Measured in Ph1[2]	Ratio (measured in Ph1 to predicted Ph3)	Measured NOAEL[3]	Ratio (measured NOAEL to predicted Ph3)
AUC (ug*day/mL)					
70.0	754.3 (678.8-838.4)	1873.7 (1439.3, 2439.1)	2.5x	46666.7 (37416.7-53750.0)	61.9x
66.7	782.5 (704.0-869.8)		2.4x		59.6x
53.3	926.9 (833.5-1030.6)		2.0x		50.3x
29.0	1463.7 (1315.4-		1.3x		31.9x

Body Weight (kg)	Predicted Ph3 exposure[1]	Measured in Ph1[2]	Ratio (measured in Ph1 to predicted Ph3)	Measured NOAEL[3]	Ratio (measured NOAEL to predicted Ph3)
	1628.6)				
C_{max} (ug/mL)					
70.0	11.6 (10.4-12.8)	28.6 (22.5-36.4)	2.5x	1390 (1090-1610)	119.8x
66.7	12.1 (10.9-13.4)		2.4x		114.9x
53.3	15.0 (13.6-16.7)		1.9x		92.7x
29.0	27.2 (24.4-30.3)		1.1x		51.1x

1 Geometric mean (95%CI of predicted geometric mean), predicted after second dose at week 26 using the popPK model developed on Ph1, including typical value of parameter estimates and their uncertainty

2 Geometric mean (95%CI) of 300mg dose, determined via NCA. AUC refers to $AUC_{(0\text{-inf})}$

3 Mean (range), gender averaged of 100 mg/kg dose, highest dose tested in cynomolgous monkeys. C_{max} and AUC measured after second dose at week 14.

The potential impact of ethnic differences on depemokimab exposure, pharmacology, efficacy and safety is considered low based on the evidence accumulated with mepolizumab and with monoclonal antibodies targeting soluble ligands.

Mepolizumab PK showed no apparent ethnic differences, and neither race, nor ethnicity, nor country was identified as a covariate of mepolizumab exposure in the population PK meta-analysis of 13 mepolizumab studies across various eosinophilic conditions. Consistent with those pharmacokinetic observations, the efficacy, safety and pharmacodynamics of mepolizumab at the dose used for severe eosinophilic asthma have been profiled in participants of North East Asian ancestry and confirmed to be of low ethnic sensitivity [GSK Document Number 2020N460984_00].

Depemokimab is catabolised by proteolytic enzymes, not restricted to hepatic tissue and does not undergo target-mediated clearance, similarly to mepolizumab and other therapeutic monoclonal antibodies. Inter-ethnic differences are not anticipated in the clearance of depemokimab via these ubiquitous proteolytic enzymes. These observations are consistent with other therapeutic monoclonal antibodies for which only small inter-ethnic differences in pharmacokinetics between East Asian and White/Caucasian populations have been reported, mostly attributed to the well-established population differences in body weight [Chiba, 2014; Matsushima, 2015; Ogasawara, 2019].

Based on this evidence, the same benefit/ risk is expected for depemokimab for all participants administered the same dosing regimen, and no clinically significant effect of body weight (in the range of body weight included in this trial) and ethnicity is anticipated. Thus, no dose adjustment is recommended.

Depemokimab's potential for drug-drug interaction is deemed low in light of its elimination pathways. In addition, there is no in vivo evidence that neutralisation of IL-5 alters expression of cytochrome P450s or transporters [GSK3511294 Clinical Investigator's Brochure].

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in Table 1 for the last participant in the trial globally, whichever is earlier.

A participant is considered to have completed study treatment dosing if he/she receives study treatment at Visit 9 (Week 26). A participant is considered to have completed the study if he/she has completed the visit at Week 52, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

Participants with CRSwNP as per inclusion exclusion criteria will be enrolled into the study. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

In order to confirm eligibility, the investigator must review each participant's medical records prior to a participant entering the run-in period. To be randomized into the study, participants will be required to meet the additional randomization criteria (see Section 5.3). Participants are eligible to be included in the study only if all of the following criteria apply at screening:

AGE
4. 18 years of age and older inclusive, at the time of signing the informed consent.
CRSwNP / ECRS DIAGNOSIS
2. Endoscopic bilateral NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) assessed by the investigator (see Clario Video Guideline) 3. Participants who have had at least one of the following at Visit 1: – previous nasal surgery for the removal of NP, – have used at least three consecutive days of systemic corticosteroids in the previous 2 years for the treatment of NP, – medically unsuitable or intolerant to systemic corticosteroid.

4. Participants (except for those in Japan) must be on daily treatment with INCS (including intranasal liquid steroid wash/douching) for at least the 8 weeks immediately prior to screening.
5. Participants presenting with **severe NP** symptoms defined as symptoms of nasal congestion/blockade/obstruction with moderate or severe severity and loss of smell or rhinorrhoea (runny nose) based on clinical assessment by the investigator.
6. Presence of symptoms of chronic rhinosinusitis as described by at least 2 different symptoms for at least 12 weeks prior to Visit 1, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), plus
   - facial pain/pressure

   and/or
   - reduction or loss of smell

GENDER

7. Male or eligible female participants:

Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Appendix 4

OR

  - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4, from at least 14 days prior to the first dose of study intervention until at least 30 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. Additional requirements for pregnancy testing are located in the SoA (Section 1.3).
- Contraceptive use by WOCBP should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

INFORMED CONSENT
8. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this study protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. As a result of medical interview, physical examination, or screening investigation the physician responsible considers the participant unfit for the study
2. Cystic fibrosis
3. Antrochoanal polyps
4. Nasal cavity tumor (malignant or benign)
5. Fungal rhinosinusitis
6. Severe nasal septal deviation occluding one nostril preventing full assessment of nasal polyps in both nostrils
7. Participants who had a sino-nasal or sinus surgery changing the lateral wall structure of the nose making impossible the evaluation of nasal polyp score
8. Acute sinusitis or upper respiratory tract infection (URTI) at screening or in 2 weeks prior to screening
9. Ongoing rhinitis medicamentosa (rebound or chemical induced rhinitis)
10. Participants who have had an asthma exacerbation requiring admission to hospital within 4 weeks of Screening
11. Participants who have undergone any intranasal and/or sinus surgery (for example polypectomy, balloon dilatation or nasal stent insertion) within 6 months prior to Visit 1; nasal biopsy prior to Visit 1 for diagnostic purposes only is excepted.
12. Participants where NP surgery is contraindicated in the opinion of the Investigator
13. **Eosinophilic Diseases:** Participants with other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) EGPA (formerly known as Churg-Strauss Syndrome) or Eosinophilic Esophagitis
14. **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1
15. **Immunodeficiency:** A known immunodeficiency (e.g., human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids (CSs) taken as therapy for asthma
16. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (NOTE: Participants that had localised carcinoma of the skin which was resected for cure will not be excluded).

17. **Liver Disease:**
    - Alanine aminotransferase (ALT) >2x ULN
    - Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
    - Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice. NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) are acceptable if participant otherwise meets entry criteria.
18. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
19. **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.
20. **Hypersensitivity:** Participants with allergy/intolerance to the excipients of depemokimab in Section 6.1, a monoclonal antibody, or biologic.
21. **COVID-19:** Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection must be excluded. Participants with known COVID-19 positive contacts within the past 14 days must be excluded for at least 14 days following the exposure during which the participant should remain symptom-free. Reported smell/ taste complications from COVID-19 must be used as exclusion.
22. Participants that have been exposed to ionising radiation in excess of 10mSv above background over the previous 3-year period as a result of occupational exposure or previous participation in research studies. NOTE: Clinically justified therapeutic or diagnostic exposures are not included in this cumulative calculation.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

23. **Previous participation:** Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.
24. **Investigational Medications (Biologics or non-biologics):** Participants currently enrolled in another clinical study OR participants who have received treatment with an investigational drug within the specified washout periods (refer to Section 6.8.2) prior to Visit 1 (this also includes investigational formulations of marketed products).

PRIOR/CONCOMITANT THERAPY
25. **Monoclonal antibodies targeting IL-5/5R:** Participants who have received mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), or benralizumab (Fasenra) within 12 months prior to Visit 1. 26. **Other mAbs in the treatment of asthma or CRSwNP**: Participants who have received omalizumab (Xolair) or dupilumab (Dupixent) within 130 days prior to Visit 1. 27. **Other mAbs not used for the treatment of asthma or CRSwNP:** Participants who have received any mAb within 5 half-lives of Visit 1 (with the exception of mAbs for the treatment of COVID-19, which are permitted, unless experimental) For a full list of prohibited medication see Section 6.8.2
PREGNANCY:
28. Women who are pregnant or lactating or are planning on becoming pregnant during the study. Requirements for pregnancy testing are provided in Section 8.3.5.
OTHER DISEASES/ABNORMALITIES:
29. Any participant who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g., cancer). In addition, any participant who has any other condition (e.g., neurological condition) that is likely to affect respiratory function should not be included in the study.
DIAGNOSTIC ASSESSMENTS:
30. **ECG Assessment**: QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block in the 12-lead ECG central over-read from Screening Visit 1. See Section 8.3.3 for further ECG guidance.
DRUG OR ALCOHOL ABUSE:
31. A known or suspected history of alcohol or drug abuse within 2 years prior to Screening (Visit 1) that in the opinion of the investigator would prevent the participant from completing the study procedures.
ADHERENCE:
32. Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.
AFFILIATION WITH INVESTIGATOR SITE:
33. Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.

INABILITY TO READ:
34. In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete a questionnaire.

5.3. Randomization Criteria

Those participants who meet the randomization criteria below will be randomized into the study until the target of approximately 250 randomized participants is reached.

In rare instances and following consultation with the Medical Monitor a participant can be rescreened. Rescreened participants are required to sign a new ICF.

At the end of the run-in period, study participants must fulfill the following additional criteria in order to be randomized to study treatment:

1. Endoscopic bilateral NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) taken at Visit 1 as assessed at central laboratory
2. Mean nasal obstruction VRS of 2 or greater over the last 7 days preceding Visit 2 (excluding Visit 2) (from electronic diary [eDiary])
3. eDiary compliance for at least 4 out of the last 7 days preceding Visit 2 (excluding Visit 2).
4. Not had any NP surgery between Visit 1 and Visit 2 and not on a waiting list for NP surgery at the time of randomization.
5. Laboratory abnormality: No evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
6. Liver Chemistry Tests: obtained at Visit 1:
   - ALT ≤ 2x upper limit of normal (ULN)
   - Bilirubin ≤ 1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
7. ECG: QTcF < 450 msec, or QTcF < 480 msec for participants with Bundle Branch Block, in the 12-lead ECG machine-read at Randomization Visit 2. No evidence of a clinically significant abnormality in the central over-read of the 12-lead ECG conducted at Screening Visit 1 that would impact the participant's participation during the study, based on the evaluation of the Investigator. See Section 8.3.3 for further ECG guidance.
8. **Asthma Exacerbation:** No asthma exacerbations during run-in period. An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids for at least 3 days and/or overnight stay at emergency department visit, or hospitalization.

9. **Maintenance Therapy:** No new systemic corticosteroids for CRSwNP have been started during the run-in period.
10. If the participant has an URTI or cold during run-in, then run-in should be extended to have the Visit 2, 2 weeks post the resolution of the cold but no greater than a total of 6 weeks from Visit 1. Participants with colds that are not resolved within the 4th week of the nominal run-in period (28 days after screening) will be ineligible for randomization as they would have exceeded the 6 weeks period.

5.4. Lifestyle Considerations

Not applicable for this study.

5.5. Screen/Run-in Failures

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

For the purposes of this study, screening failures will be sub-divided as follows:

- Participants will be assigned a study number at the time of signing the informed consent.
- Those participants that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period will be designated as screen failures.
- Those participants that enter the run-in period, but are not randomized, will be designated as run-in failures.

Rescreening of participants will be permitted, however, advanced approval to proceed with rescreening the participant must be obtained from the Medical Monitor (for contact details, see study reference manual [SRM]). Rescreened participants should sign a new ICF and should be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Randomization / Initiation of Study Intervention Administration

Initiation of the study intervention administration could be temporarily delayed at Week 0 (Visit 2) and Week 26 (Visit 9), such as due to parasitic infection (see Section 7.1.4). A delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

The term 'study intervention' is used throughout the protocol to describe any combination of products received by the participant as per the protocol design. Study intervention may therefore refer to the individual study treatments or the combination of those study treatments.

Depemokimab is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Depemokimab Injection, 100 mg/mL, drug product is supplied as a sterile, preservative-free aqueous solution of purified mAb in a Type I glass syringe. The drug product and syringe will be assembled in a single use, disposable pre-filled syringe (PFS) to enable delivery of the drug product. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, disodium edetate, water for injection and polysorbate 80.

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

Description of depemokimab and placebo is provided in Table 3.

Table 3 Description of Depemokimab and Placebo

Arm Name	Depemokimab 100 mg	Placebo
Intervention Name	Depemokimab 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloridesolution in single use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)	Placebo once every 26 weeks(Week 0 and Week 26)
Route of Administration	SC injection	SC injection
Use	IMP	Placebo
Non-IMP	NA	NA
Authorized AxMP/Unauthorized AxMP	NA	NA
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging andLabelling	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 willbe labelled as required per country requirement.

Abbreviations: PFS, Pre-filled safety syringe; IMP, Investigational Medicinal Product; N/A, not applicable

GSK will provide or reimburse the sites for SoC such as INCS and courses of OCS.

6.1.1. Medical Devices

Depemokimab Injection, 100 mg/mL, is supplied as a sterile, preservative-free aqueous solution in a 3 mL Type I untreated borosilicate clear glass vial with a 13 mm fluorinated-polymer coated grey bromobutyl rubber stopper and a 13 mm aluminium overall seal with a plastic flip-off cap, or in a 1 mL long Type I glass siliconized barrel with a 29G thin wall stainless steel needle sealed with rubber plugger stopper. The prefilled syringe is assembled in an SSD.

6.1.2. Treatment Assignment

Participants eligible to enter the study will be assigned to treatment randomly via an interactive response technology (IRT) system. The randomization schedule will be generated using the GSK validated randomization software RAMOS NG. Randomization will be stratified based on occurrence of previous surgery for nasal polyps. A separate randomization list will be developed for each country. Participants will be assigned to study treatment 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.

6.2. Preparation, Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention are provided in the SRM.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study intervention. A MSDS describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

The recommended storage condition is 2 - 8°C, protected from light. The expiry date, where required, is stated on the product label.

Depemokimab Injection, 100 mg/mL (PFS SSD), should not be administered concomitantly with other drugs in the same syringe or administration assembly.

For subcutaneous administration, Depemokimab Injection, 100 mg/mL (PFS SSD) and matching placebo in-use instructions are provided in the SRM.

6.3. Measures to Minimize Bias: Randomization and Blinding

A participant may continue in the study if that participant's treatment assignment is unblinded by the investigator or treating physician, but will not receive the second dose of study intervention at Week 26 (if not already received). The primary reason for discontinuation from study intervention (the event or condition which led to the unblinding) will be recorded in the eCRF. Every effort should be made to ensure the data of the participant are collected when possible.

The RAMOS NG will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason for the unblinding must be recorded in the source documentation and case report form (CRF), as applicable.

To maintain the blind, data on IL-5 levels and 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, prior to the unblinding of the study.

GSK's Pharma Safety staff may unblind 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.3.1. 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 reassignment of subject identification numbers) PK and PKPD unblinded datasets, including baseline demographic characteristics.

6.4. Study Intervention Compliance

- Participants will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- Participants will be monitored for a minimum of 2 hours (both at randomization and at Week 26) after study intervention administrations in the clinic. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, 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 patient to another facility for additional care if appropriate.
- Administration will be documented in the source documents and reported in the eCRF.

6.5. Dose Modification

Not applicable for this study.

6.6. 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.

6.7. 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, single SC doses of depemokimab up to 300 mg were well tolerated in adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

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

- Contact the Medical Monitor immediately.
- Treat the participant with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of depemokimab.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose of depemokimab/placebo (either at randomization [Day 1] or Visit 9 [Week 26]).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.8. Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements, and vaccine) that the participant is receiving 12 months prior to enrolment, or receives during the study, must be recorded along with:

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

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

Initiation or changes in the dosing regimen of allergen immunotherapy from screening to end of the study are not allowed.

With the exception of participants in Japan, daily INCS treatment is an inclusion criterion, and participants should continue INCS treatment throughout the study. Participants in Japan who are not on INCS at screening are permitted to start INCS while on study, if required for symptom management.

Initiation or changes in the dosing regimen of leukotriene receptor antagonist from screening to end of the study are allowed, if required for symptom management.

6.8.1. Permitted CRSwNP and Asthma Medications

The following medications may be used for all participants:

1. Short courses of systemic corticosteroids (for example of systemic corticosteroids for treatment of CRSwNP) are permitted prior to Screening and after Randomization, but not during the Run-in period. Although the use of rescue medications such as systemic CS is allowable during the treatment phase of the study (Visit 2 and onwards); the date and time of rescue medication administration as well as the name

and dosage regimen (dose and duration) of the rescue medication must be recorded in the eCRF for NP as well as for other comorbidities.

2. Throughout the study, asthmatic participants are to be maintained on their baseline SoC asthma treatment.
3. Courses of antibiotics and saline nasal douches are permitted at any time. For antibiotic treatment for CRSwNP / ECRS, the type, dose and duration must also be recorded in the eCRF.
4. INCS are allowed with no interruption throughout the study duration. **If a participant in Japan is not on INCS prior to screening, the participant is permitted to start INCS during the study, if required for symptom management**. Once on INCS, the participant should remain on INCS for the remainder of the study.

6.8.2. Prohibited Medications

The following medications are not allowed prior to screening (Visit 1), according to the following schedule, or during the study (Table 4):

Table 4 Prohibited medications

Prohibited Medication	Time Period Prior to Screening Visit
Investigational products (non-biologic)	30 days or 5 half-lives whichever is longer
Investigational products (biologic)	3 months or 5 half-lives whichever is longer
Omalizumab [Xolair]	130 days
Dupilumab [Dupixent]	130 days
Mepolizumab [Nucala], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra]	12 months
Other monoclonal antibodies (other than for the treatment of COVID-19, see Section 6.8.3)	5 half-lives
Immunosuppressive medications such as those listed below (not all inclusive)	
Chronic systemic corticosteroids including oral, intramuscular, long-acting depot	1 month
Methotrexate, cyclosporin, Azathioprine	1 month
Oral gold	3 months
Chemotherapy used for conditions other than asthma	12 months
Insertion of any non-drug or drug eluting nasal stents such as Propel stents	6 months
Direct steroid injections into CRSwNP / ECRS	6 months

6.8.3. COVID-19 Vaccines and treatments

Participants can be vaccinated against SARS-CoV-2 infection using authorized COVID-19 vaccines in line with local/national guidelines for COVID-19 vaccines.

Experimental COVID-19 vaccines are not permitted.

Any COVID-19 treatment (including monoclonal antibodies) approved by local government (in line with local/national guidelines) is permitted.

Experimental COVID-19 treatments are not permitted.

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

Refer to the SRM for further details.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

At the point of informed consent prior to screening, participants will be requested to provide permission and agree to be contacted even after study withdrawal/study intervention discontinuation to collect information relating to any surgical intervention to the NP. Every effort will be made to have all participants attend study visits up to Week 52 even if they discontinue study treatment in order to capture NP scores, symptom score, any subsequent surgical procedures or entry into a waiting list for NP surgery.

7.1. Discontinuation of Study Intervention

A participant may discontinue from study intervention at any time at his/her own request, or at the discretion of the investigator. If study treatment is permanently discontinued (for any reason), the participants are encouraged to remain in the study until the completion of the Week 52 Visit assessments (Table 1; refer to the SRM for further details). If this not possible, the investigator should encourage the participant to participate in as much of the study as they are willing (or able) to.

The participant's NP surgical status will be tracked for the duration of the study. The participants are also allowed to have nasal surgery during the study without discontinuation from study intervention.

All participants will be followed up for the study duration. As a minimum the participants should agree to be contacted by telephone to enquire regarding any safety assessments and any NP surgery events. The primary reason for discontinuation of study intervention (and sub-reason, if applicable) will be recorded in the eCRF. If for any reason, the participant later chooses to withdraw from the study, a Withdraw from Study Visit (see Section 7.2) should be conducted according to Table 1.

7.1.1. Specified Study Intervention Discontinuation Criteria

A participant must be discontinued from study intervention if any of the following stopping criteria are met:

- Liver Chemistry: Meets any of the protocol defined liver chemistry stopping criteria (see Section 7.1.2 and Appendix 6)
- QTc: Meets any of the protocol defined QTc stopping criteria (see Section 7.1.3)
- Pregnancy: Positive pregnancy test (see Section 8.4.5 and Appendix 4)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 8 in Section 10.8).
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.4).
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant by the investigator or treating physician (see Section 6.3).

7.1.2. Liver Chemistry Stopping Criteria

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

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

- a participant meets one of the conditions outlined in Figure 2 and Figure 3

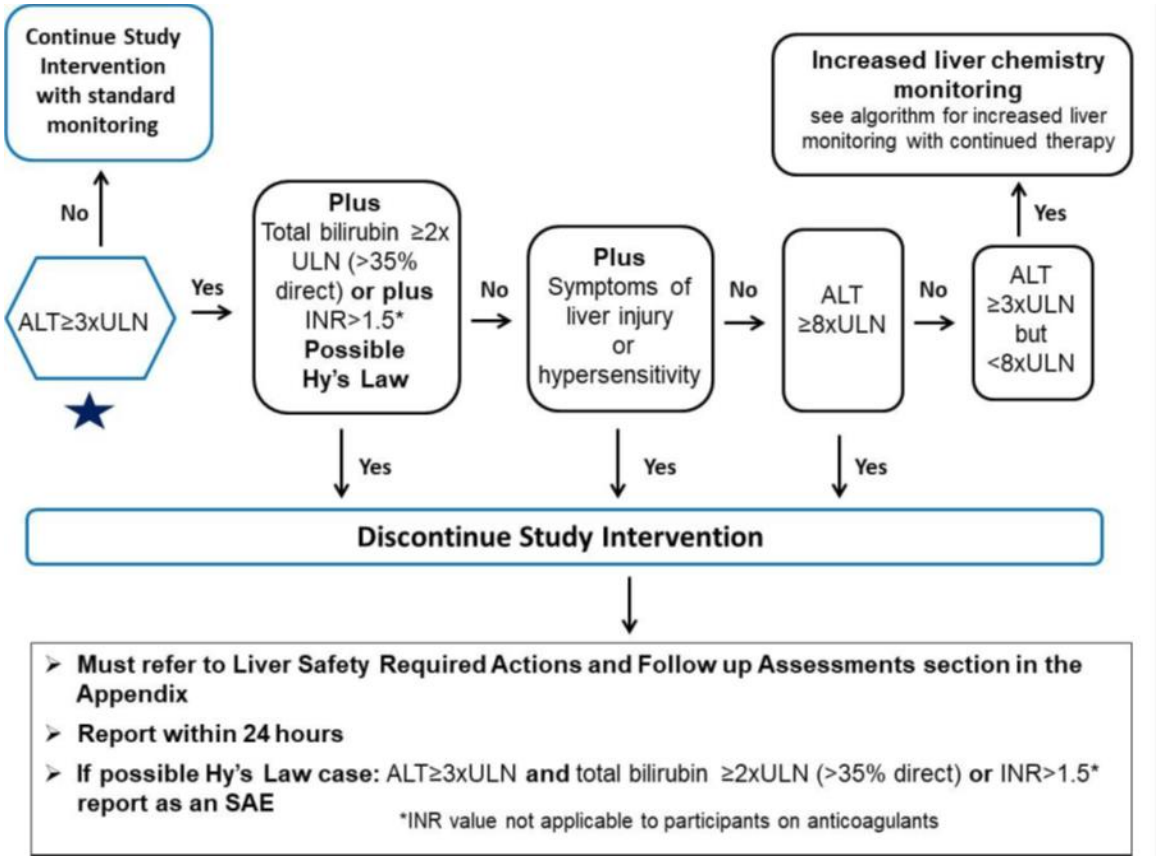
OR

- 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.

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

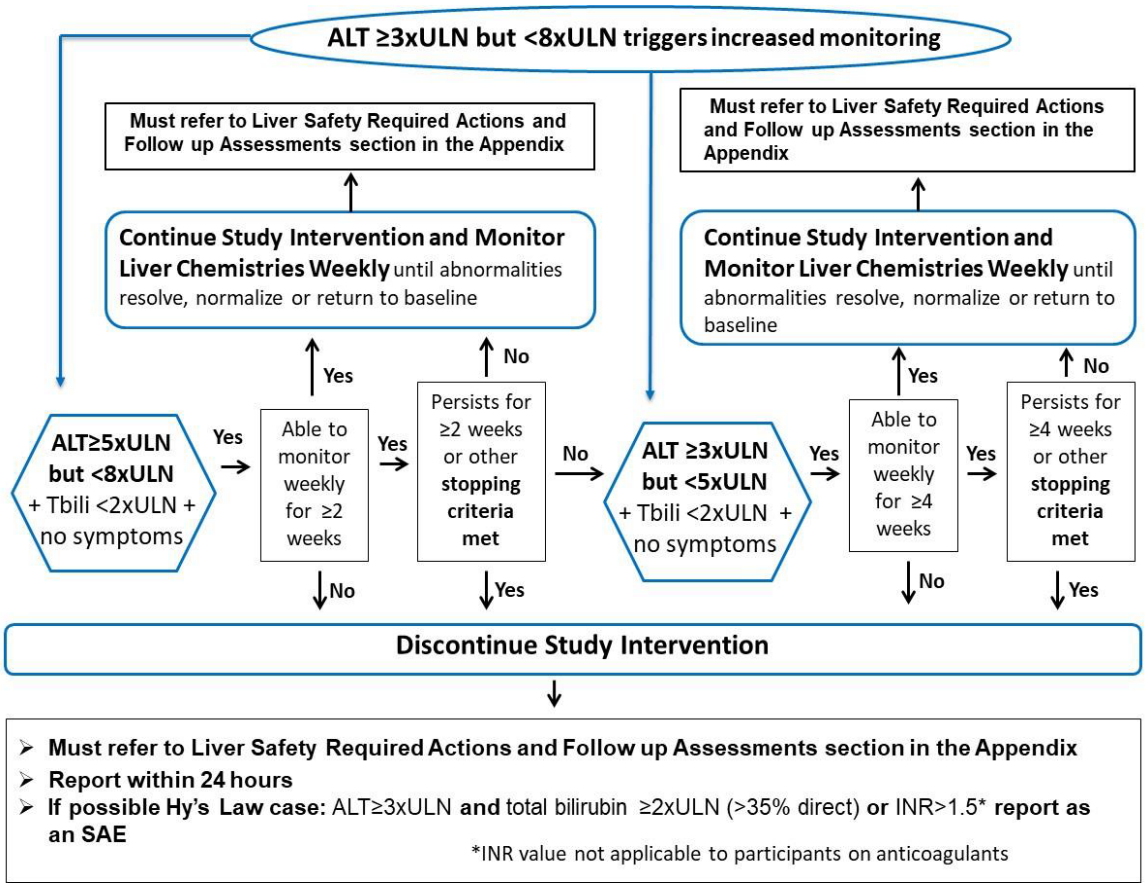
Details of liver chemistry stopping criteria, required actions, and follow-up assessments after liver stopping or monitoring event are given in Appendix 6.

Figure 2 Liver Chemistry Stopping Criteria Algorithm



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

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



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

7.1.3. QTc Stopping Criteria

The QT interval corrected for heart rate by Fredericia's formula (QTcF) must be used for each individual participant to determine eligibility for the study and discontinuation from study treatment. This formula may not be changed or substituted for the duration of the study.

For this study, the following QTc stopping criteria will apply:

- QTcF >500 msec or uncorrected QT >600 msec
- Change from baseline: QTcF >60msec
- For participants with bundle branch block, follow the criteria listed below:
  - QTcF >500 msec (if baseline QTcF <450 msec)
  - QTcF ≥530 msec (if baseline QTcF 450-480 msec)

The QTcF value from the 12-lead ECG central over-read at randomization visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study.

- After randomization 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 9 (Week 26) where 12-lead ECG machine read values should be used.

7.1.4. Temporary Discontinuation

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

For example, if a participant becomes infected (parasitic infection) during the study treatment period before receiving the second dose of study intervention and does not respond to antihelminth treatment, a delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

7.1.5. COVID-19 Testing

Participants that test positive for COVID-19 do not have to discontinue study intervention. Participants are encouraged to remain in the study and be followed up per study schedule as participants well-being allows. Every effort should be made by the Investigator/site staff to keep the participant in the study until their nominal 52 weeks post randomization date.

- COVID-19 tests during the study may be performed, as determined by the investigator or local guidelines.
- All positive COVID-19 tests should be reported on the relevant eCRFs and the AE/SAE eCRFs, as appropriate.
- Positive tests should be reported to the appropriate local government authorities, per local regulations.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorized representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.

Participants who prematurely withdraw from the study should attend:

- Early Withdrawal (EW) Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) AND
- Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy assessments.

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

Participants who are prematurely withdrawn from study should be encouraged to complete their eDiary up until their EW Visit.

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.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls/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.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status information of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented along with other relevant study information. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

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

given as medically required. If possible, PK, ADA, C3, and C4 samples may be taken at the time of the event along with 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

(*Note: 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 GSK Medical Monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.

Unscheduled PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [ANA], antineutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [PR3] antibody), may also be conducted using the frozen baseline serum samples (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.6.3). Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Table 1.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in Table 1, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedure met the protocol specified criteria and was performed within the time frame defined in the SoA (Section 1.3).
- Following randomization, laboratory results that could unblind the participant's intervention assignment will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- When permitted by local regulations, all effort will be made so that whenever possible the study visits will be home nursing visits (when a study nurse will visit the participant at home instead of the participant having to go to the site) or telemedicine (virtual visit, typically video or voice call). Please follow Table 1 for information on the optional home nursing visits or telemedicine visits.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data including year of birth, sex, race, and ethnicity in the participant's eCRF, where permitted by local regulations.

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 pre-existing conditions of interest per the eCRF, prior to study start.

8.2. Efficacy Assessments

8.2.1. Endoscopic NP Score

Endoscopic NP score will be assessed at study visits as described in Table 1. This score is graded based on NP size and recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status.

Endoscopic NP score will be performed at the site by trained health care professional (usually ENT surgeon). All image recordings of endoscopies will be sent to an independent reviewer at Clario, the central lab for blinded NP scoring. There is potential for the site score to differ from the central score. In such cases, the output from the central labs is considered final and will be utilized for patient eligibility and for the analysis of this endpoint (for additional details refer to the Clario Video Guideline).

For Visit 2, the nasal endoscopy assessment may be performed up to 7 days prior to the clinic visit but must occur prior to randomization. For all other visits the nasal endoscopy assessment must not exceed the protocol defined windows of ±7 days from the nominal study visit.

8.2.2. Symptoms

Clario will provide the eDiary for administering electronic Patient-Reported Outcome (ePRO) on the study.

8.2.2.1. Individual Symptoms Verbal Response Scale (VRS)

All VRS symptom scores will be administered using the eDiary and will be collected daily in the morning from screening to the end of the Treatment Period.

Every day, the participant will be asked to indicate on a VRS, the severity of 4 nasal polyposis symptoms at their worst over the last 24 hours (one VRS for each symptom):

1. nasal obstruction; 2. rhinorrhoea (runny nose); 3. loss of smell; 4. facial pain; 5. mucus in the throat.

A 4-point Likert scale will be used, with appropriate verbal response options of no symptoms, mild symptoms, moderate symptoms, and severe symptoms. Participants will be instructed on how to use the scale prior to use.

Please refer to the SRM for further details on the phrasing of these questions and response options.

8.2.2.2. Overall Visual Analogue Scale (VAS) Symptoms Score

The overall symptoms VAS to be used in the study will be administered using the eDiary and will be collected daily in the morning from screening to the end of the treatment period.

Every day, the participant will be asked to indicate on a VAS, the overall severity of nasal polyposis symptoms at their worst over the last 24 hours.

The left-hand side of the scale (0) represents "None" and the right-hand side of the scale (100) represents "As bad as you can imagine". The participant selects a point on the line that represents their current experience on the continuum. The eDiary will be suitably pixilated to allow the selection of all integers from 0 to 100. Participants will be instructed on how to use the scale prior to use. The final VAS scores that are reported will be derived from the electronically captured score by dividing each score by 10 and will range between 0 and 10.

8.2.2.3. Nasal Obstruction Symptoms VAS

A Nasal Obstruction VAS score will be administered using the eDiary at key timepoints to facilitate understanding and interpretation of the Nasal Obstruction VRS (see Table 1).

Through run-in, baseline and 4 weeks prior to Week 24 (i.e., from Week 21 through to Week 24) and Week 52 (i.e., from Week 49 through to Week 52) the participant will be asked to indicate on a VAS the Nasal Obstruction symptoms at their worst.

8.2.3. Computed Tomography (CT) Scan

CT scan is mandatory unless not approved by local ethics committee or institutional review board. The first CT scan must be performed prior to randomization and should be the last assessment performed, where possible. If the first CT scan cannot be performed as the last assessment before randomization, the subject should have completed their screening visit, and all screening lab results, the central NP score and ECG central over-read results should be assessed by the PI before a CT scan is conducted. The second CT scan should be performed at V16 or EW visit (up to 14 days prior to the nominal study visit). Note: If a participant is permanently discontinued both from the study intervention and from the study, and the second dose of study intervention was not received, decision on performing CT scan during Early Withdrawal visit at Week 26 will be made by the investigator in consultation with the Medical Monitor.

The Lund Mackay (LMK) CT scoring system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal complex (OC) is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side. This scoring system has been validated in several studies.

All image recordings of CT scans will be sent to an independent reviewer at Clario for centralized blinded data assessment and central reading for LMK scoring will be used for analysis.

For participants in whom the OC is missing (because of a previous surgery) the reader should consider the location of the former OC and provide a scoring (as if the OC was there).

Detailed information on the CT assessment will be available in a separate operational manual provided to the sites. CT scans central reading for LMK scoring will be used in the statistical analysis.

8.2.4. NP Surgery

At each visit, it will be recorded whether the participant is on a waiting list for NP surgery and whether the participant has received confirmed documented surgery. As an endpoint, for the purpose of this study, NP surgery is defined as any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (polypectomy/ESS). Dilatation of the air passages in the nasal cavity (e.g., balloon sinuplasty) will not be included in this endpoint. Procedures occurring on the same date will be considered as part of the same surgery event.

Wherever possible the removed tissue from a nasal surgery will be collected and stored. Detailed processing and storage instructions are provided in the laboratory manual.

8.2.5. Corticosteroid Medication

The dose and duration of courses of systemic steroids (for NP and for any other reason) will be recorded in the eCRF. The dose and duration of the course of systemic CS will be according to the participants SoC for systemic CS use for its NP condition.

For the purpose of this study courses of systemic corticosteroids separated by less than 7 days will be considered to be one continuous course.

8.2.6. Health-Related Quality of Life (HRQoL) Assessments

Participants should complete all questionnaires in a quiet location, free from distraction, prior to the completion of other study procedures. All questionnaires will be completed on an electronic handheld device provided by Clario. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. During training participants should be instructed to select the single response option for each question that most closely reflects their health over the time period indicated for each questionnaire. Participants will not be able to skip or miss questions.

8.2.6.1. Sino-Nasal Outcome Test (SNOT-22) Questionnaire

SNOT-22 is a 22-item measure of disease specific HRQoL. It will be completed by the participant at study visits according to Table 1 on the eDiary.

The SNOT-22 has been shown to be a reliable outcome measure for successful septal surgery [Buckland, 2003]. It is also recommended as a suitable questionnaire in CRS management [Morley, 2006] and its routine use is recommended as a tool to evaluate outcomes in NP [Browne, 2006].

Participants will be asked to rate the severity of their condition on each of the 22 items over the previous 2 weeks using a 6-point rating scale of 0-5 including: 0 = Not present/no problem; 1 = Very mild problem; 2 = Mild or slight problem; 3 = Moderate problem; 4 = Severe problem; 5 = Problem as “bad as it can be”. The total score range for the SNOT-22 is 0-110, where higher scores indicate greater disease impact. Psychometric analyses of data from the 205687 study (SYNAPSE) indicate that a decrease of 28 points or greater is a clinically meaningful within participant change [Han, 2021]. The

previously published minimum clinically important difference (MCID) of a difference of ≥8.9 will also be reported [Hopkins, 2009]. In addition to the overall score, the SNOT-22 provides two summary scores of symptoms and impacts and 6 domain scores of nasal symptoms, ear and facial symptoms, non-nasal symptoms, fatigue, impact on sleep and emotional.

8.2.6.2. Patient Global Impression of Change and Severity of Nasal Polyp Symptoms

Two single item patient global impression scales will be completed by participants to assess change and severity of nasal polyps symptoms, according to Table 1. Both items will have a 5-point Likert response scale. The primary objective of these scales is to provide anchors for subsequent in trial psychometric analyses.

- The Patient Global Impression of Change (PGIC) will ask the patient to rate the change in their nasal polyps symptoms since the start of trial medication.
- The Patient Global Impression of Severity (PGIS) will ask the patient to rate the severity of their nasal polyps symptoms over the last 4 weeks.

8.2.7. For Asthmatic Participants Only:

8.2.7.1. Asthma Control Questionnaire (ACQ-5)

The ACQ-5 is a 5-item questionnaire, which has been developed as a measure of patients' asthma control that can be quickly and easily completed [Juniper, 1999; Juniper, 2005]. The questions are designed to be self-completed by the participant. The 5 questions enquire about the frequency and/or severity of asthma symptoms over the previous week (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall period is the past week.

ACQ-5 will be assessed during the study according to Table 1.

8.2.7.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by:

- Worsening of asthma which requires use of systemic CSs* and/or hospitalization and/or Emergency Department visit.

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

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

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

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

The time period for collection of exacerbation information in the eCRF will be from the start of study intervention until the Exit Visit or Follow-up Visit if applicable.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Where possible, these should be aligned with SoC.

8.3.1. Physical Examinations

- A physical examination will include, at a minimum, assessments of the skin, eyes, cardiovascular (CV), respiratory, gastrointestinal and neurological systems. Height (screening only) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illness.

8.3.2. Vital Signs

- Temperature, systolic and diastolic blood pressure and heart rate will be assessed.
- Blood pressure and heart rate measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.

8.3.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in Table 1 using an ECG machine, provided by GSK via Clario the designated central laboratory, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The QTcF formula must be used for each individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled.
- If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the participant should be screened/ randomized/ discontinued from the study intervention (but not from the study). Refer to Section 5.2 and Section 5.3 for exclusion and randomization criteria related to ECG assessment, and Section 7.1.3 for QTc stopping criteria.

- ECG measurements will be made after the participant has rested in the supine position for 5 minutes and should be obtained after the vital signs assessments. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method (for additional details refer to the Vendor Manual).
- Paper ECG traces are required to be maintained at the site with other source documents.
  - For further details please refer to the SRM.

8.3.4. Clinical Safety Laboratory Tests

- Q2 Solutions is the central laboratory service provider for this study.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the central laboratory manual and the SoA. The timing and frequency are provided in Table 1.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study until the Exit Visit (or Follow-up visit/call if applicable) should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- 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

- Pregnancy testing entry criteria are provided in Section 5.1.
- Serum pregnancy test should be conducted for all WOCBP at Screening Visit, at Week 52 Visit, and at Early Withdrawal Visit. In addition, urine pregnancy tests should be performed at the timepoints specified in Table 1, including at the Follow-up Visit/call (if applicable).
- To mitigate risk of exposure of foetus to ionising radiation from Sinus CT, highly sensitive urine pregnancy test should also be performed within 24 hours prior to the CT scan and results to be assessed prior to CT scan.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required and the result assessed prior to the CT scan.
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last administered dose of study intervention:
  - Participants should have a urine pregnancy test at the Follow-up Visit/call (Week 56). A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
  - Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the 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.

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

The definitions of an AE and SAE can be found in Appendix 3.

The definitions of device-related safety events, adverse device effects (ADEs) and serious adverse device effects (SADEs) can be found in Appendix 7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

The investigator or their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

- All SAEs will be collected from the start of intervention (Day 1) until the follow-up visit at the timepoints specified in Table 1. However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- All AEs will be collected from the start of intervention (Day 1) until the follow-up visit at the timepoints specified in Table 1.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- 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, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs and procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

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 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

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

8.4.5. Pregnancy

- Investigator will collect pregnancy information on any female participants, who becomes pregnant while participating in this study.
- Details of all pregnancies in female participants will be collected from the start of study intervention and until 30 weeks after the last administered dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit to GSK within 24 hours of learning of the female participant's 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.
- 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 and Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will immediately discontinue study medication.

8.4.6. Cardiovascular and Death Events

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

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the eCRF within 1 week of receipt of a CV event data query prompting its completion.

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

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Not applicable for this study.

8.4.8. Adverse Events of Special Interest

Adverse events of special interest (AESI) include:

- Allergic reactions including anaphylaxis

Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 8).

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

See Section 2.3.1 for additional details.

8.4.9. Medical Device Deficiencies

Medical devices are being provided for use in this study. 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 sites use 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 Appendix 7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 3.

8.4.9.1. 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 device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- Medical device deficiencies and any associated AE/SAEs for associated person (i.e., spouse, caregiver, site staff) will be collected. The associated person will be provided with a safety reporting information and authorization letter.
- The method of documenting medical device deficiencies is provided in Appendix 7.

8.4.9.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.
- 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.

8.4.9.3. Prompt Reporting of Medical 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 device deficiency.
- The medical device deficiency report form will be sent to the sponsor electronically. If this primary method is unavailable, then alternative method should be utilized (notification by telephone with a copy of the SAE paper data collection, see Appendix 7 for details).
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.9.4. 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

To characterize the PK in patients with CRSwNP, blood samples for analysis of depemokimab plasma concentration will be obtained at visits specified in Table 1. Samples obtained at Visit 2 (Day 1) and at Visit 9 (Week 26) should be drawn prior to dosing. Samples at Visit 16 / EW Visit (Week 52) will be collected for approximately 200 participants. No requirement to fast prior to sample being taken. The date and exact time of collection for each sample will be documented in the eCRF.

Details for collection, processing, storage, and shipping procedures are provided in the laboratory manual. PK samples will be analysed using an appropriately validated assay method under the supervision of the sponsor. Study 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/Biomarkers

Collection, processing, storage and shipping procedures for biomarker and PD samples are provided in the laboratory manual.

8.6.1. Blood Eosinophil Counts

In order to investigate the PD effects of depemokimab, blood eosinophil counts will be measured as part of the standard haematological assessments according to Table 1. (Section 1.3). For haematology 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, sites will be sent total white blood counts throughout the study.

8.6.2. Total IL-5 Levels

To characterize the binding of depemokimab to IL-5 in patients with CRSwNP, blood samples will be collected for measurement of total serum IL-5 levels at the visits specified in Table 1. Total IL-5 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.

8.6.3. Complement, IgE and Inflammatory Biomarkers

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

A baseline serum sample will be collected at Visit 2 and stored. If necessary, this sample may be analysed for the presence of ANCA (using anti-MPO antibody and anti-PR3 antibody tests), and ANA, including anti-dsDNA antibodies.

After dosing, repeat of these analytes as well as additional biomarkers (as determined by clinical presentation) may be considered on an ad-hoc basis should there be clinical concerns regarding an immune-mediated AE (see Section 7.4).

8.6.4. Exploratory Biomarkers

Participation in exploratory biomarker research is optional. Participants who do not wish to participate in the exploratory biomarker research may still participate in the study.

China only: Exploratory biomarker samples will not be collected from participants from China.

With the participant's consent, surgically removed polyp tissues, nasal fluid and blood samples collected during this study may be used for the purposes of measuring novel biomarkers to identify factors that may influence the disease under treatment, and/or medically related conditions, as well as the biological and clinical responses to depemokimab. If relevant, this approach will be extended to include the identification of biomarkers associated with AEs.

GSK may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with participants consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of CRSwNP or related diseases, the development of related or new treatments or research methods.

8.6.4.1. Serum: Soluble Marker Analysis

Serum samples will be collected to explore changes in levels of soluble markers in response to depemokimab and may be used to identify novel candidate biomarkers of the biological responses associated with disease.

8.6.4.2. Whole Blood: Gene Expression Analysis (Transcriptomics)

Whole blood will be collected into PaxGene RNA tubes and transcriptomic analysis may be conducted using RNA Sequencing technology, facilitating the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for a blood sample. The same samples may also be used to confirm findings by application of alternative technologies.

8.6.4.3. Nasal Samples

8.6.4.3.1. Surgical

Whenever possible, surgical samples from participants undergoing surgery while on the study will be collected for the purposes of measuring PD biomarkers to understand the biological and clinical responses to depemokimab. The surgical samples may be analysed

histologically for immune cell infiltration and transcriptional analysis may be performed to evaluate the changes in gene profiles that may correlate with biological and clinical responses to depemokimab. These samples may also be used to advance our understanding of disease pathogenesis as well as patient heterogeneity and may also be used for assay validation purposes. Instructions for the collection and handling of biological samples will be described in the laboratory manual.

8.6.4.3.2. Nasal Biopsy

Nasal biopsy samples will be collected from participants who consent to this optional procedure at Visit 16 (Week 52) in participating countries and sites. Nasal biopsy samples will be collected during endoscopy for the purposes of measuring biomarkers to better understand the biological responses to depemokimab within the tissue and the relationship to clinical responses. Instructions for the collection and handling of biological samples will be described in the laboratory manual.

8.7. Genetics

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

Up to 6 mL blood sample for deoxyribonucleic acid (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.

Please see Appendix 5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in laboratory manual.

8.8. Immunogenicity Assessments

Antibodies to depemokimab will be evaluated in serum samples collected from participants according to Table 1. Additionally, serum samples should also be collected at the Exit Visit, or the final in-clinic visit for participants who withdraw early from the study. Processing, storage and shipping procedures are provided in the laboratory manual.

In the immunogenicity assessment for depemokimab under supervision by GSK, a tiered analyses approach will use a validated binding ADA assay (screening, confirmation and titration assays) and a validated neutralising antibody (NAb) assay. If necessary, further immune response characterisation may be performed as needed. Intervention information that would unblind the participant's intervention assignment will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.9. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are evaluated in this study by means of the Short Form-36 (SF-36) and the Work Productivity and Activity Impairment Questionnaire (WPAI) questionnaires.

8.9.1. Short Form-36 (SF-36) Questionnaire (Version 2)

SF-36 will be performed by the participants at study visits described in Table 1.

SF-36 is one of the most widely used generic questionnaires. It consists of 36 self-administered questions that cover 8 health domains: physical functioning, role physical, bodily pain, and general health, vitality, role emotional, social functioning, and mental health with a recall of 4 weeks. Scale scores range from 0 to 100 and higher scores indicate better QoL. In addition, the PCS and the MCS scores can be derived following the original authors' recommendations [Ware, 1994].

Radenne [Radenne, 1999], demonstrated a high internal validity and reliability in patients with NP and reported that NP impaired QoL in all SF-36 domains. Khan [Khan, 2019] also found that patients with CRSwNP had significantly lower mean SF-36 PCS and MCS scores than the general population, demonstrating that CRSwNP negatively affects HRQoL.

Alobid [Alobid, 2005] showed that a significant improvement was observed in all domains of SF-36 after medical and surgical treatment. Both mental and physical health reached population levels. Combined steroid treatment and ESS had similar long-term outcomes on QoL. Radenne [Radenne, 1999] showed that steroids and ESS improved the symptoms and the QoL in patients with NP especially in body pain, general health, vitality, social functioning, and mental health domains with no significant differences between both treatment regimes.

8.9.2. Work Productivity and Activity Impairment Questionnaire (WPAI)

WPAI will be assessed by the participant at study visits described in Table 1.

The WPAI questionnaire is an instrument to measure impairments in both paid work and unpaid work [Reilly, 2002]. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome, ankylosing spondylitis and Crohn's disease [Reilly, 2004; Reilly, 2010; Reilly, 2008]. In addition, the WPAI questionnaire has been used to compare work impairments between treatment groups in clinical studies and trials or between participants with different disease severity levels [Reilly, 2004; Reilly, 2010; Reilly, 2008; Revicki, 2007; Pearce, 2006; Chen, 2008].

The WPAI-GH consists of six questions: 1 = currently employed; 2 = hours missed due to health problems; 3 = hours missed other reasons; 4 = hours actually worked; 5 = degree health affected productivity while working (using a 0 to 10 VAS); 6 = degree health affected productivity in regular unpaid activities (VAS) [Reilly, 1993]. The recall

period for the questions 2 to 6 is 7 days. Four main outcomes can be generated from the WPAI: 1) percent work time missed due to health for those who were currently employed; 2) percent impairment while working due to health for those who were currently employed and actually worked in the past seven days; 3) percent overall work impairment due to health for those who were currently employed; 4) percent activity impairment due to health for all respondents [Reilly, 2002]. For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to health will be equal to the percent work time missed due to health.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study is designed to test the inequality of depemokimab 100 mg SC vs. placebo (both in addition to SoC) in both co-primary endpoints of total endoscopic NP score at Week 52 and mean nasal obstruction VRS symptom score from Week 49 through to Week 52. Each co-primary endpoint will be tested at the two-sided 5% alpha level, both tests are required to be significant to achieve the primary objective of this study.

Demonstration of efficacy for each of these tests will be based on a hypothesis testing approach, whereby the null hypothesis is that there is no difference between treatment groups for the endpoint of interest and the alternative hypothesis is that there is a difference between treatment groups.

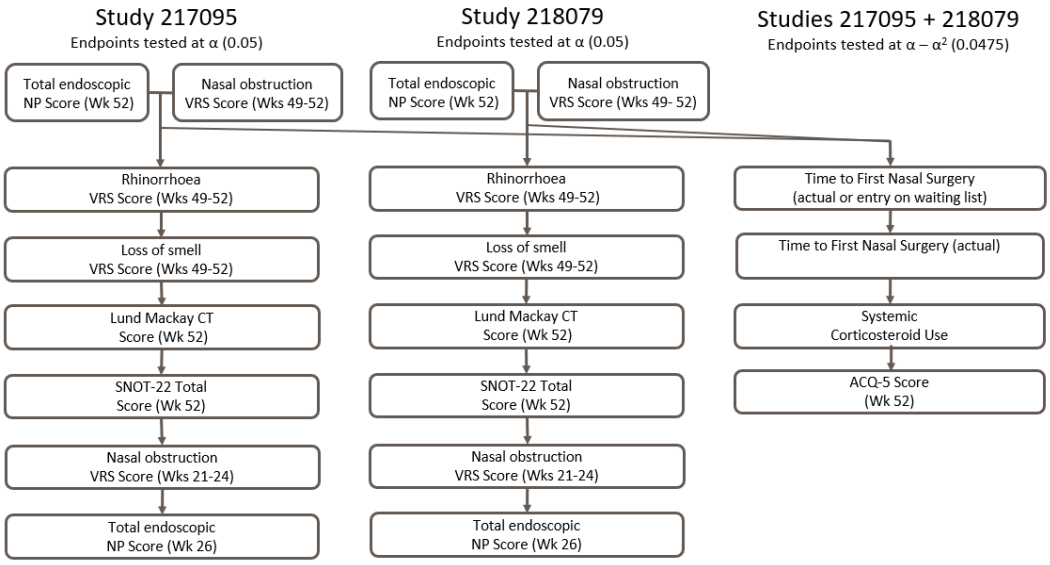
9.1.1. Multiplicity Adjustment

Hypotheses to be tested will be structured as shown in Figure 4. The co-primary endpoints will be tested first and if these comparisons are both significant at the two-sided 5% level, testing will continue within the study according to the testing procedure detailed in Figure 4. 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 this study (218079) and study 217095 is planned for the secondary endpoints of time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP, time to first nasal surgery (actual) or disease-modulating medication for CRSwNP, proportion of participants requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery (actual), and ACQ-5 Score. This pooled analysis will be carried out after both studies have completed and only if statistical significance is achieved for both co-primary endpoints within both studies. Endpoints in the pooled analyses will be tested in a hierarchical manner at a significance level of $\alpha - \alpha^2$ (4.75%) [Bretz, 2019]. The time to first nasal surgery (actual) or disease-modulating medication for CRSwNP will only be tested if statistical significance is achieved for time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP. The proportion of participants requiring nasal surgery (actual) or at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP will only be tested if statistical significance is achieved for both time to first nasal surgery

(actual or entry on waiting list) or disease-modulating medication for CRSwNP and time to first nasal surgery (actual) or disease-modulating medication for CRSwNP. Similarly, the ACQ-5 Score will only be tested if statistical significance is achieved for time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP, time to first nasal surgery (actual) or disease modulating medication for CRSwNP, and proportion of participants requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery (actual).

Figure 4 Conceptualisation of Statistical Testing Strategy Across Studies 218079 and 217095



Note: Endpoint names in Figure 4 are abbreviated. Refer to Section 3 for full nomenclature of endpoints.

The treatment comparisons defined as part of the multiple testing strategy will be limited to the specified key comparisons shown in Figure 4. Other pairwise comparisons will be performed but will not form part of the multiple testing strategy. Analyses of other efficacy measures are nested under the secondary efficacy measures and no multiplicity adjustment is planned for these other efficacy endpoints.

If significance is achieved for both of the co-primary efficacy endpoints within this study, then the secondary endpoints within the study will be tested in a closed-testing manner using the pre-defined hierarchy. If significance is also achieved for each of the secondary efficacy endpoints within the study, then all other efficacy endpoints for the study will be tested without multiplicity adjustment.

If significance is achieved for both of the co-primary efficacy endpoints in both this study (218079) and study 217095, then the 4 secondary endpoints that are pre-specified to be a pooled analysis across both studies will be tested in a closed testing manner according to the pre-defined hierarchy. If significance is achieved at the $\alpha - \alpha^2$ (4.75%) level for all 4 of these endpoints, then all of the other efficacy endpoints that are pre-specified to be a pooled analysis across both studies will also be tested at the $\alpha - \alpha^2$ (4.75%) significance level without any multiplicity adjustment.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened	All participants screened and for whom a record exists on the study database.
Screened-China	All participants screened and for whom a record exists on the study database from China.
Screened-Japan	All participants screened and for whom a record exists on the study database from Japan.
Randomised	All randomised participants
Full Analysis Set (FAS)	All randomised participants who take at least 1 dose of study treatment excluding participants from sites 255403 and 255387[a]. Participants will be analysed according to the treatment they are allocated at randomisation.
FAS-China	All participants in the FAS population who are enrolled from China.
FAS-Japan	All participants in the FAS population who are enrolled from Japan and are of Japanese heritage only.
FAS-Modified	All participants in the FAS population plus randomised participants from sites 255403 and 255387[a] who receive at least one dose of study treatment.
Safety	All randomised participants who take at least 1 dose of study treatment excluding participants from sites 255403 and 255387[a]. Participants will be analysed according to the treatment they are allocated at randomisation, unless the participant receives a different treatment to randomized active treatment at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual treatment they received.
Safety-China	All participants in the Safety population who are enrolled from China.
Safety-Japan	All participants in the Safety population who are enrolled from Japan and are of Japanese heritage only.
Safety-Modified	All participants in the safety population plus randomised participants from sites 255403 and 255387[a] who receive at least 1 dose of study treatment Participants will be analysed according to the treatment they are allocated at randomisation, unless the participant receives a different treatment to randomized active treatment at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual treatment they received.
PK	All participants in the FAS population for whom at least one pharmacokinetic sample was obtained, analysed and was measurable, including imputed values that were below the limit of quantification. Participants will be analysed according to the treatment they received.

a. The Japan Ministry of Health, Labour and Welfare (MHLW) confirmed GCP violations in several studies involving Medipharma, a Japanese Site Management Organisation (SMO). Medipharma provided site management services to sites 255403 and 255387in Study 218079.

9.3. Statistical Analyses

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

9.3.1. Co-Primary and Key Secondary Endpoint(s) Analyses

The treatment comparison of depemokimab 100 mg SC + SoC vs. placebo + SoC is of interest for the co-primary and secondary endpoints. Multiplicity arising from the multiple secondary endpoints will be controlled as detailed in Section 9.1.1.

Endpoint	Statistical Analysis Methods
Co-Primaries	The comparison of depemokimab 100 mg SC + SoC with placebo + SoC will be expressed as a difference in means in change from baseline values presented with corresponding 95% confidence intervals, the p-value for the difference in means between treatment groups and will be based on a mixed model repeated measures (MMRM) analysis with covariates of treatment group, baseline score, baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline score and visit by treatment group. Off-treatment data from participants who withdrew early from interventional product and continued in the study will be included in the analyses, missing data will be assumed to be missing at random (MAR). A sensitivity analysis using MMRM with multiple imputation will be performed for each co-primary endpoint to assess the potential impact of choices for handling missing data in the primary analysis. For the sensitivity analysis, participants with missing data at Week 52 who had taken their Week 26 dose of interventional product (and therefore considered on-treatment at Week 52) will have missing data imputed under the assumption of MAR. Participants with missing data at Week 52 who had not taken their Week 26 dose of interventional product (and therefore considered off-treatment at Week 52) will have missing data imputed using a jump to reference (J2R) approach. Implementation of the J2R method assumes that for participants in the experimental treatment group (Depemokimab) with missing data, their imputed mean response is that of the reference treatment group (Placebo). An additional tipping point sensitivity analysis will explore the impact of missing data by using differing assumptions for each of the co-primary endpoints. Assumptions about missing values on the experimental treatment arm and placebo arm will vary independently, and will include scenarios where participants with missing data in the experimental treatment arm have worse outcomes than participants with missing data in the placebo arm. This analysis will allow for determination of 'tipping point(s)' of the values for missing data that would cause a change in the statistical significance of the result of the treatment comparison. The deltas (small numerical shifts in the values of missing data) investigated will cover a range that this is plausible for the respective endpoint under the MAR assumption and will be investigated on final data to ensure it supports a tipping point range. Subgroup analyses for each of the co-primary endpoints will be performed for age, gender, race, region and baseline blood eosinophil category. Full details of all analyses will be provided in the statistical analysis plan.
Secondary	The pooled analysis of time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP and time to first nasal surgery (actual) or disease-modulating medication for CRSwNP will be analysed using Cox's proportional hazards model allowing for covariates of treatment group, baseline total endoscopic nasal polyps score, baseline nasal obstruction score (VRS), baseline blood eosinophil count, region, study and previous surgery for

Endpoint	Statistical Analysis Methods
	nasal polyps. Missing values will be considered censored at random. Summaries and graphs of Kaplan-Meier estimates of the proportion of participants requiring surgery over time will be provided. Change from baseline in mean rhinorrhoea (runny nose) score, mean loss of smell score, Lund Mackay CT score and SNOT-22 total score will be analysed in a similar manner to the co-primary endpoints. The pooled analysis of proportion of participants requiring at least 1 course of systemic corticosteroids or disease-modulating medication for CRSwNP or nasal surgery(acutal) will be analysed using a logistic regression model with covariates for treatment group, number of courses of systemic corticosteroids in 12 months prior to screening (0, 1, >1 as ordinal), baseline blood eosinophil count, baseline total endoscopic nasal polyps score, baseline nasal obstruction score (VRS), region, study and previous surgery for nasal polyps. The pooled analysis of ACQ-5 will be based on MMRM with MAR assumption for missing data with covariates for treatment group, baseline score, baseline blood eosinophil count, region, previous surgery for nasal polyps, study, visit and interaction terms for visit by baseline score and visit by treatment group.

9.3.2. Safety Analysis

All safety analyses will be performed on the Safety Population.

AEs will be coded using the MedDRA coding dictionary and summarised by preferred term and treatment. Separate summaries will be provided for all AEs, drug-related AEs, SAEs and for AEs leading to permanent discontinuation of study intervention or withdrawal from the study.

Immunogenicity data, ECG, vital signs, and laboratory data will be summarised descriptively.

Further details will be given in the statistical analysis plan.

9.3.3. Pharmacokinetic Analysis

All randomized participants will be sampled for plasma depemokimab levels. Assessment of depemokimab concentration will be performed at the timepoints indicated in Table 1.

Results will be presented using appropriate graphic and tabular summaries. Plasma depemokimab concentration data obtained from this study, and other studies with depemokimab, will be used in a population PK analysis, which will be reported separately. Potential effects of covariates on depemokimab PK including, but not limited to, demographic, disease characteristics and baseline eosinophil count, ethnicity and geographic region, and anti-drug-antibodies will be evaluated. Derived PK parameters will include clearance and AUC.

9.3.4. Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Analysis

All randomized participants will be sampled for blood eosinophil count at the timepoints indicated in Table 1.

Results will be presented using appropriate graphic and tabular summaries.

Plasma depemokimab concentration and blood eosinophil count data obtained from this study, and other studies with depemokimab, will be used in a population PKPD analysis, which will be reported separately. Potential effects of covariates including, but not limited to, demographic and disease characteristics, ethnicity and geographic region, and baseline eosinophil count will be evaluated. Derived PKPD parameters will include maximum eosinophils suppression.

9.4. Interim Analysis

A safety IDMC is being implemented for the study, the IDMC charter is available on request and will detail the schedule for any planned interim safety analyses and the analysis plan for the IDMC review. Members of the IDMC and the independent Statistical Data Analysis Centre (SDAC) responsible for preparing results for the IDMC will have access to unblinded randomization codes and any interim safety results.

Blinded interim data will be used to facilitate validation, including estimation of meaningful score changes, of the patient-reported outcomes (e.g., VRS) included in this trial. No assessment of efficacy or safety will be included in this validation assessment.

The study statistician, investigators, and GSK personnel involved in monitoring of the study will not have access to randomized treatment codes until the study completes as planned or is terminated.

No other interim analysis is planned, however if recruitment is significantly slower than anticipated GSK may conduct a single unblinded interim analysis to assess futility. Any unblinded interim analysis for futility will be performed by an SDAC in conjunction with an IDMC to maintain study integrity. In the case where a futility interim will be implemented, full details of the timing and stopping boundary will be included in a statistical analysis plan and updated IDMC charter, and these will be submitted to regulatory agencies as appropriate prior to any futility analysis being performed.

9.5. Sample Size Determination

The sample size for this study is based on the co-primary efficacy endpoints of total endoscopic nasal polyps score at Week 52 and mean nasal obstruction VRS symptoms score from Week 49 through to Week 52, and a pre-specified pooled analysis of data from study 218079 (this study) and study 217095 for the key secondary endpoint of time to nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP.

Approximately 250 participants will be randomized in this study in a ratio of 1:1 giving 125 randomised participants per arm. This sample size allows for up to 5% of randomized participants to be non-evaluable, providing a minimum of 118 evaluable participants per arm in the analyses of primary and secondary endpoints.

For the co-primary efficacy endpoint of total endoscopic nasal polyps score at Week 52, the study has >99% power assuming a true population difference of -1.10 between depemokimab and placebo. This assumes a standard deviation of 1.665 with significance declared at the two-sided 5% significance level. The smallest observed effect which is predicted to result in a statistically significant difference between depemokimab 100 mg SC + SoC and placebo + SoC is a treatment difference of –0.42.

For the co-primary efficacy endpoint of mean nasal obstruction VRS score during Weeks 49-52, the study has >99% power assuming a true population difference of -0.70 between depemokimab and placebo. This assumes a standard deviation of 0.84 with significance declared at the two-sided 5% significance level. The smallest observed effect which is predicted to result in a statistically significant difference between depemokimab 100 mg SC + SoC and placebo + SoC is a treatment difference of –0.21.

The overall power for both co-primary endpoints is >99%.

The planned number of patients recruited within this study is not sufficient to adequately assess whether depemokimab significantly reduces the risk of nasal surgery compared to placebo. A pre-specified pooled analysis of data from this study (217095) and study 218079 is planned for the endpoint of time to first surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP. The proportion of participants in the pooled placebo group expected to require surgery or disease-modulating medication for CRSwNP is 23%. Assuming a true population hazard ratio of 0.38 (62% reduction in risk of required surgery) this pooled analysis has >90% power to observe statistical significance at the 2-sided 4.75% level. In the pooled analysis, the smallest observed effect which is predicted to result in a statistically significant difference between depemokimab 100 mg SC + SoC and placebo + SoC is a hazard ratio of 0.64 (36% reduction in risk of surgery).

The overall power for both co-primary endpoints and the pre-specified pooled analysis of time to first surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP using data from this study (217095) and study 218079 is >90%.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide 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 his/her representative will explain the nature of the study, including the risk and benefit, to the participant or their LAR and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their LAR 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 protect requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their LAR. Participants who are rescreened are required to sign a new ICF.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.
- GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about depemokimab or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have depemokimab approved for medical use or approved for payment coverage.
- The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. 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. A separate signature will be required to document a participant's agreement to allow any participant data or samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

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, the study will be published in public databases such as ClinicalTrials.gov.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. 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 his/her 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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other 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 and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- 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 IDMC comprised of clinical experts external to GSK will review unblinded data at defined timepoints during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional timepoints for review may be added.

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

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

10.1.7. 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 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the 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.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make 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.
- Requests for access may be made through www.clinicalstudydatarequest.com.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF 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 eCRF.
- 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 data documents.
- Quality tolerance limits (QTLs) will be pre-defined in the Integrated Quality Risk Management Plan (IQRMP) to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the Data Management Plan.
- 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 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a different retention period. 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.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for 25 years.

10.1.9. Source Documents

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

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and site start and closure

First Act of Recruitment

The start of study is defined as first subject first visit (FSFV) 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.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Appendix Table 1 will be performed by the central laboratory Q2 Solutions.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- 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 laboratory safety report.

Appendix Table 1 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Haematology[1]	Platelet Count	*RBC Indices:*	*WBC count with Differential:* *(post-dose results blinded asdescribed in footnote 1)*	
	RBC Count	MCV	WBC	
	Haemoglobin	MCH	Neutrophils	
	Haematocrit	%Reticulocytes	Lymphocytes	
			Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[2]	BUN	Potassium	AST(SGOT)	Total and directbilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase[3]	Albumin
		Magnesium	GGT	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones by dipstick Microscopic examination and UACR (if blood or protein is abnormal[evidence of microalbuminuria or haematuria of ≥1+]) UACR will require a separate urine sample to be sent to central laboratory for analysis.			
Pregnancy testing	Highly sensitive serum pregnancy test at Screening Visit 1, Exit Visit and at Early Withdrawal Visit; highly sensitive urine pregnancy tests for other assessments at time points specified in Table 1, and additionally within 24 hours prior to CT scan (as needed for WOCBP) [4]			
Other Tests	FSH (if required to confirm postmenopausal status, see Section 10.4) Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories. If sites wish to use central laboratories, they should note that the central test is stool microscopy for ova and parasites. For details of the organisms detected by this test refer to the parasitic screening section of the SRM. Total IgE Complement (C3 and C4) Serum samples collected at baseline will be frozen and stored for later analyses, if necessary: anti-MPO antibody, anti-PR3 antibody, ANA including anti-dsDNA antibody			

Abbreviations: ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; MPO, myeloperoxidase; PR3, proteinase 3; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; UACR, urinary albumin-creatinine ratio; WBC, white blood cell; WOCBP, women of childbearing potential; WONCBP, women of non-childbearing potential; GGT, Gamma-glutamyl transferase.

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 chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio(INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK as an SAE.
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for all visits (except Screening Visit and Exit Visit) unless serum testing is required by local regulation or IRB/IEC.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (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. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments 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). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: – Possible Hy's Law case: ALT≥3x ULN AND total bilirubin ≥2x ULN (>35% direct bilirubin) 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 Cardiovascular Events

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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Follow-up of AE and SAE

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

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will

be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned Competent Authority (CA) via the national spontaneous reporting system. These will be classified as spontaneous Individual Case Safety Reports (ICSR).
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence

of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

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

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

Woman of Non-childbearing Potential (WONCBP)
Women in the following categories are considered WONCBP:

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

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

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

2. Postmenopausal female A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high 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 enrolment.

10.4.2. Contraception Guidance:

Female participants

Use of effective contraceptive methods will be required from at least 14 days prior to first dose and until 30 weeks after the last administered dose:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
a. Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
b. Intrauterine device (IUD)
c. Intrauterine hormone-releasing system (IUS)[c]
d. Bilateral tubal occlusion
e. 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. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
f. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
g. Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable

h.	Sexual abstinence – *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
i.	Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
j.	Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
k.	Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)

Male participants

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

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease 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.
- DNA samples will be used for research related to depemokimab or CRSwNP. 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.
- DNA samples will be analysed. Additional analyses 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. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on depemokimab (or study interventions of this class) or CRSwNP continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

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

10.6.1. Liver Chemistry Stopping Criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria- Liver Stopping Event	
ALT Absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 5xULN but <8xULN **and** cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks
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 Assessments	
Actions	**Follow Up Assessments**
• **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 assessments as described in the Follow up Assessment column • Monitor the participant until liver	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, within a week of meeting increased liver monitoring criteria[5] • Obtain a Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum

Liver Chemistry Stopping Criteria- Liver Stopping Event	
chemistries resolve, stabilize, or return to within baseline (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 assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** **Do not restart/rechallenge** participant with study intervention since **not allowed per protocol;** continue participant in the study for any protocol specified follow up assessments.	albumin • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia. This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's treatment assignment is required. Also note that the mechanism of action of depemokimab leads to lowering of eosinophils • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease: complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form.

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

10.6.2. Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥ 5xULN and <8xULN and total bilirubin <2xULN or INR≤1.5 without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks. OR ALT ≥ 3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical Monitor **within 24 hours**of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabiliseor return to within baseline. • If at any time participant meets the liver chemistrystopping criteria, proceed as described above. • If ALT decreases from ALT ≥ 5xULN and <8xULNto ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN andtotal bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

References

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

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

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and 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 medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved 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 adverse event **that:**	
a.	Led to death
b.	Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

A Medical Device SAE is any serious adverse event **that:**
– A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. – 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 ADEs 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 ADEs that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

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

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

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency

information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- 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.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Other measures to evaluate AEs and SAEs may be used (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

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

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 eCRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Monitor by telephone. • 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. • Contacts for SAE reporting can be found in the SRM.
SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the GSK Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK
• NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must 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 GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Refer to the paper medical device deficiency report form for details on transmission of this information to the Sponsor.

10.7.7. Reporting of Medical Device Deficiencies for Associated Person

Reporting to GSK

- If an Associated Person (i.e., 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 non-serious 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, to **both** uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax +44(0)20 8754 7822) **and** gsk-rd.complaints@gsk.com. The associated SAE form should also be reported to uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax +44(0)20 8754 7822).
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.8. Appendix 8: Anaphylaxis Criteria

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

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

10.9. Appendix 9: Lund-Mackay CT score

Change in the Lund-Mackay CT score percentage of maxillary sinus volume occupied by disease will be assessed in all participants.

The Lund-Mackay CT score evaluates the patency of each sinus using a 0 to 2 scale (0 = normal; 2 = total opacification) and has a total score range from 0 to 24 (higher scores indicate more opacification) [Lund, 1993; Bhattacharyya, 1999].

Sinus	Right sinus	Left sinus
Frontal	0-2	0-2
Anterior ethmoids	0-2	0-2
Posterior ethmoids	0-2	0-2
Maxillary	0-2	0-2
Sphenoid	0-2	0-2
Ostiomeatal complex	0 or 2	0 or 2
Total	0-12	0-12

For the sinuses: 0 = no opacification; 1 = partial opacification; 2 = total opacification.

For the ostiomeatal complex: 0 = not occluded; 2 = occluded.

Maximum total score: 24

10.10. Appendix 10: Country-specific requirements

Country-specific local requirements will be added, as and when applicable.

Japan-specific requirements

Additional Japan-specific requirements will be captured within a separate addendum. The content of the Japan addendum is considered administrative.

China-specific requirements

Urinalysis: Urine dipstick will not be performed in China, all urine sample will instead be sent for central laboratory urinalysis. Investigators should be aware of the time needed for central laboratories to return results, and should perform appropriate local investigations if any urgent result is required.

Exploratory biomarkers: Exploratory biomarkers samples will not be collected from participants in China.

Genetics: Genetic Informed Consent will not be collected from participants in China.

10.11. Appendix 11: Recommended Measures Related to COVID-19 Pandemic

10.11.1. Overall Rationale for this Appendix:

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

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

10.11.2. Study Procedures During COVID-19 Pandemic

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

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

- Clinical investigators should document in site files and in participant notes/Electronic Health Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.11.3. Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the investigator). It is the responsibility of the investigator to inform GSK when this occurs and to document in source notes.
- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the investigator deems that a sitevisit is necessary.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating proceduresand applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then the medical evaluation of the participant's CRSwNP may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.

- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.
- The participant should be informed of the plan and any potential risks associatedwith the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.
- The revised schedule of study activities is provided in the SoA in Section 1.3.

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

10.11.4. Study Intervention:

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

10.11.5. Data Management/Monitoring:

- If the eDiary was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 17 Exit Visit).
- If on site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

- eCRF/CRF Final or Interim Sign off Process: The PI is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistentwith source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this mustbe documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub- investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.11.6. Assessments that can be Conducted Outside Clinical Study Site:

Activities/assessments that may be conducted outside of a clinical study site are indicated in Table 1.

10.12. Appendix 12: Protocol Amendment History

Amendment 4 (12 March 2024)

Overall rationale for the current Amendment: The protocol has been amended primarily to change the pooled analysis endpoint of time to first nasal surgery (actual) from 'Other' to 'Secondary' to address feedback from the FDA. Additional participant analysis sets have been added and updates to existing analysis sets have been made to exclude data from sites managed by Medipharma, a Japanese Site Management Organisation, in response to the Japan Ministry of Health, Labour and Welfare (MHLW) confirming GCP violations in several studies involving Medipharma. Other changes to the protocol reflect updates to the GSK protocol template.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Abbreviations	Addition of abbreviations	Added abbreviations introduced in this protocol amendment.
Terms	Addition of terms	For clarification of terms used in the protocol.
Section 1.1 Synopsis, Section 3.2 Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)	Changed the pooled analysis endpoint of 'time to first nasal surgery (actual)' from 'Other' to 'Secondary'.	Based on regulatory authority feedback.
Section 1.1 Synopsis, Section 3.2 Objectives and Endpoints for Pre-specified	Added 'for CRSwNP' for the endpoint related to systemic corticosteroids.	For clarification of endpoint assessment.

Section # and title	Description of change	Brief rationale
Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)		
Section 1.1 Synopsis, Section 3.2 Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study)	Added 'up to Week 52' for the endpoint related to need for surgery.	For clarification of endpoint assessment.
Section 1.3 Schedule of Activities (SoA)	Deleted the additional description about the nasal obstruction score assessment being performed in the morning.	For correction.
Section 2.2.1.1 Depemokimab (GSK3511294) Long-Acting IL-5 and Section 2.3 Benefit/Risk Assessment	Reference to the Investigator's Brochure has been updated to the latest effective version of the IB.	To update to the current effective IB version 5.0.
Section 3.5 Secondary Estimands for Pre-specified Pooled Analysis Across Studies 217095 (This study) and 218079	Addition of estimand definition for the pooled secondary endpoint of 'Time to first nasal surgery (actual)'.	To provide the estimand definition for this endpoint, which is now a pooled analysis secondary endpoint.
Section 6.1 Study Intervention(s) Administered Table 3	Updated to indicate 'Depemokimab' as IMP instead of 'Experimental' and that Non-IMP and authorized AxMP/unauthorized AxMP are Not Applicable.	Updated for clarity and to reflect changes made to the GSK protocol template.
Section 6.8.2 Prohibited Medications Table 4	Corrected the washout period prior to Screening visit for non-biologic and biologic investigational products; corrected the dupilumab trade name.	Editorial correction.
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Updated terminology: replaced 'study discontinuation' with 'study withdrawal'.	To provide clarity and consistency in terminology between "discontinuing treatment" and "withdrawal from study" and to reflect changes made to the GSK protocol template.
Section 7.3 Lost to Follow Up	Updated to clarify that other contact methods can be used along with telephone calls for follow up.	For clarification and to reflect changes made to the GSK protocol template.
Section 8.4.9 Medical Device Deficiencies	Updated to clarify that if the sites use non-sponsor medical devices, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly.	For clarification and to reflect changes made to the GSK protocol template.

Section # and title	Description of change	Brief rationale
Section 9.1.1 Multiplicity Adjustment and Figure 4	This section and the figure were updated to reflect the addition of time to first nasal surgery (actual) as a secondary endpoint for the pooled analysis. Updates to indicate that the time to first nasal surgery (actual) will only be tested if statistical significance is achieved for time to first nasal surgery (actual or entry on waiting list). Updated the number of secondary endpoints to 4.	To align with changes to the statistical hierarchy.
Section 9.2 Analysis Sets	Update to the Full Analysis Set (FAS) to exclude participants from sites managed by Medipharma, and addition of modified analysis sets including these participants. Added additional participant analysis sets for PK and specific analysis sets for China and Japan.	Updated to align with the Statistical analysis plan in response to the Japan Ministry of Health, Labour and Welfare (MHLW) confirming GCP violations in several studies involving Medipharma and to describe analysis sets required for PK analyses and submissions in China and Japan.
Section 9.3.1 Co-primary and Key Secondary Endpoint(s) Analyses	Added the time to first nasal surgery (actual) endpoint under secondary pooled analyses and detailed the pooled analysis description.	Updated to align with updates in other sections of the protocol and Statistical analysis plan.
Section 10.1.5 Data Protection	Added a statement related to GSK internal policy for reporting data incidents or breaches.	To comply with requirements to protect personal data and to reflect changes made to the GSK protocol template.
Section 10.1.7 Dissemination of Clinical Study Data	• Updated plain language terminology to layperson summary of results. • Added a statement that where required by regulation, the names of the sponsor signatory and investigator signatory will be made public. • Deleted the wording related to SHARE initiative. • Added a statement related to data sharing and protecting PI.	Updated to align with GSK's disclosure requirement and regulatory disclosure requirement and to reflect changes made to the GSK protocol template.
Section 10.1.11 Publication Policy	Updated wording around GSK seeking to publish medically or scientifically significant results in peer-reviewed scientific literature.	Updated to align with the new policy on Ethical Scientific Research and to reflect changes made to the GSK protocol template.

Section # and title	Description of change	Brief rationale
Section 10.3.5 Reporting of SAE to GSK; Section 10.7.4 Recording and Follow-Up of AE and/or SAE and Device Deficiencies; Section 10.7.5 Reporting of SAEs	Additional instruction to the site to report to the concerned Competent Authority via the national spontaneous reporting system if they become aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product/device that is not part of the study design.	Updated for clarification and to reflect changes made to the GSK protocol template.
Section 11 References	Deleted references (Bretz 2009, Wang 2003) which were not cited in the protocol	Correction as these references were not cited.
All sections	Other minor editorial changes to improve readability.	

Amendment 3 17 October 2023

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

Overall Rationale for the Amendment:

- To reduce the number of participants required to provide PK samples at Week 52 (Visit 16/EW Visit) to approximately 200.
- To add an optional nasal biopsy sample collection at Week 52 (Visit 16).
- To update the statistical testing hierarchy.
- To move the asthma-related endpoints to the pooled analyses.
- To amend the definition of the nasal surgery endpoint included in the pooled analysis statistical hierarchy from ‘actual’ to ‘required’.
- Other changes include clarification on NP Scoring guidance and updates to language related to regulatory, ethical, and study oversight considerations.

List of Main Changes in the Protocol and Their Rationale:

Section # and title	Description of Change	Brief Rationale
Terms	Addition of terms and definitions.	For clarification of terms used in the protocol.
Section 1.1. Synopsis, **Section 3.1. Objectives and Endpoints,** **Section 3.2. Objectives and Endpoints for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095 (Replicate Study),** **Section 3.4. Secondary Estimands,** **Section 3.5. Secondary Estimands for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095**	To move the asthma-related endpoints (ACQ-5 Score and exacerbations) to the pooled analyses. To amend the definition of the nasal surgery objective and endpoint included in the pooled analysis statistical hierarchy from 'actual' to 'required'. To update the definition of the 'Other' objective and endpoint for nasal surgery to count actual surgery only.	To ensure sufficient power for the asthma-related endpoint analyses. To account for (1) the fact that there may be some delay between the requirement for surgery and actually having a surgery, during which time participants will be on a waiting list and (2) country-level variations in medical practices including potential for extended waiting list durations.
Section 1.3. Schedule of Activities (SoA)	PK samples at Week 52 (Visit 16/EW Visit) will be collected for approximately 200 participants rather than all participants. Optional nasal biopsy sample collection added at Week 52.	Samples from approximately 200 participants at Visit 16 are sufficient for PK analysis. To better understand the biological responses to depemokimab within the tissue and the relationship to clinical responses.
Section 2.3.1. Risk Assessment, **Section 10.3.5. Reporting of SAE to GSK,** **Section 10.7.5. Reporting of SAEs**	Deleted reference to the SAE Coordinator.	The SAE Coordinator role no longer exists.
Section 3.5. Secondary Estimands for Pre-specified Pooled Analysis Across Studies 218079 (This Study) and 217095	Addition of secondary estimand information for the ACQ-5 Score endpoint.	To align with changes to the statistical hierarchy.
Section 4.4. End of Study Definition	Updates to the definition of study completion.	For clarification and alignment across the clinical development program.
Section 5.1. Inclusion Criteria	Replaced reference to "Appendix 10" with "Clario Video Guideline".	To clarify the endoscopic NP scoring guidance used by sites and central reader.
Section 5.3. Randomization Criteria	Updated Randomization Criteria 9 on maintenance therapy to prohibit new use of systemic corticosteroids during the run-in period.	To clarify what medications are permitted during the run-in period.
Section 6.8.1. Permitted CRSwNP and Asthma Medications	Added clarifications on the use of short courses of systemic corticosteroids, antibiotics, and saline nasal douches during the study.	To clarify what medications are permitted during the study.

Section # and title	Description of Change	Brief Rationale
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Participants who are prematurely withdrawn from study should be encouraged to complete their eDiary up until their EW Visit.	To clarify eDiary requirements for participants who are withdrawn from study.
Section 8. Study Assessments and Procedures	Removed requirement for NP scores to be blinded to study and site staff.	NP scores do not pose a risk of unblinding the participant's intervention assignment.
Section 8.2.1. Endoscopic NP Score	Replaced reference to "Vendor manual" with "Clario Video Guideline".	To clarify the endoscopic NP scoring guidance used by sites and central reader.
Section 8.5. Pharmacokinetics	PK samples at Week 52 (Visit 16/EW Visit) will be collected for approximately 200 participants rather than all participants.	Samples from approximately 200 participants at Visit 16 are sufficient for PK analysis.
Section 8.6.4.3.2. Nasal Biopsy	Optional nasal biopsy sample collection added at Week 52.	To better understand the biological responses to depemokimab within the tissue and the relationship to clinical responses.
Section 9.1.1. Multiplicity Adjustment	Text and Figure 4 updated: ACQ-5 Score endpoint moved to the pooled analysis statistical hierarchy and definition of the nasal surgery secondary endpoint in the pooled analysis hierarchy updated to include entry on waiting list.	To align with changes to the statistical hierarchy.
Section 9.2. Analysis Sets	The "modified Intent-to-treat" population has been renamed as the "Full Analysis Set".	To align on analysis set naming across the clinical development program.
Section 9.5. Sample Size Determination	Updates to assumptions and power to reflect inclusion of entry on waiting list as an event for the nasal surgery secondary endpoint.	To align with the updated definition of the nasal surgery secondary endpoint included in the statistical hierarchy.
Section 10.1.5. Data Protection	Added a statement related to protection of the personal data of the investigator and site staff.	To comply with requirements to protect personal data.
Section 10.1.7. Dissemination of Clinical Study Data	Added timing for disclosure of clinical study data.	To align with sponsor policies on the dissemination of clinical study data.
Section 10.1.8. Data Quality Assurance	Added a statement related to external sharing of source documents for review and storage.	To state how long documents will be stored by the external body.
Previous Section 10.10 Appendix 10: Endoscopic NP Score	Deleted Appendix 10 (nasal polyps scoring).	Now referencing 'Clario Video Guideline' to clarify the endoscopic NP scoring guidance used by sites and central reader.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

Amendment 2 26 October 2022

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

Overall Rationale for the Amendment:

This protocol was modified following release of a protocol clarification letter in April 2022. All details included in the protocol clarification letter are now incorporated into the study protocol. . Protocol changes are described in the table below.

Section	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Updated notes for • Medical history; Past and current medical conditions' • Physical exam • 12-lead ECG • Assessment of endoscopic NP score • CT Scan • eDiary Compliance Check • Parasitic Screening • Urinalysis • Pregnancy test (WOCBP only) • Footnote Deleted row on Optional Nasal filter samples for biomarkers	Modified to align with the corresponding amendments made in rest of the protocol.
Section 1.3 Schedule of Activities	Physical examination to be performed prior to dosing at Visit 9 as well	Correction/Clarification
Section 1.3 Schedule of Activities	Updated footnote to provide information on urinalysis in China	To comply with local policy
Section 5.1 Inclusion Criteria	Updated definition of severe NP symptoms	Clarification
Section 5.2. Exclusion Criteria	Exclusion criteria 24 on prior/concurrent clinical study experience updated to include washout period for non-biologics besides biologics, by adding a reference to Section 6.8.2	Clarification
Section 6.8 Concomitant Therapy	Modified heading to "Prior and Concomitant therapy"	Correction
Section 6.8.2 Table 4	Table 4 Prohibited medicated updated to include more clarity on 'time period prior to screening visit'	Correction/ Clarification

Section	Description of Change	Brief Rationale
	for non-biologic and biologic products	
Section 6.8.3. COVID-19 Vaccines and treatments	Updated information on the permitted COVID-19 treatment	Clarification
Section 7.1.3.QTc Stopping Criteria	Added the definition for baseline QTcF value and the procedure to assess QTc stopping criteria after randomization and at Visit 9 (Week 26)	Clarification
Section 8.2.1. Endoscopic NP Score	Updated window period for nasal endoscopic assessment	Correction
Section 8.2.2.2. Overall Visual Analogue Scale (VAS) Symptoms Score	Update regarding final VAS scores assessment/interpretation	Correction/ Clarification
Section 8.2.3. Computed Tomography (CT) Scan	Text modified to clarify that CT scan must be performed prior to randomization and should be the last assessment performed, where possible. Protocol updated to outline minimum criteria that need to be verified prior to the first CT scan, if it cannot be performed as the last assessment before randomization, in line with a protocol clarification letter released in April 2022.	Correction/ Clarification
Section 8.6.4.3. Surgical Samples	Section on Nasal Filter Samples removed	Correction
Section 9.1. Statistical Hypotheses	Replaced the statistical term superiority with inequality	Clarification
Section 10.1.4. Recruitment Strategy	New section added on recruitment strategy employed for the study	To comply with EU CTR
Section 10.1.5. Data Protection	More information added on data protection as per the new protocol template	To comply with EU CTR
Section 10.1.10. Study and site start and closure	Added a new appendix Section 10.1.10 on Study and Site start and closure as per new protocol template (effective 29 June 2022)	To comply with EU CTR
Section 10.2. **Appendix 2: Clinical Laboratory Tests**	Appendix Table 1 updated with the visit days for pregnancy testing, and the parasitic screening tests (stool microscopy for ova and parasites) for central laboratory testing.	Clarification
Section 10.11. Appendix 11: Country-specific requirements	Updated that urine samples from China will be sent for central laboratory urinalysis	Clarification
All sections	Other minor, grammatical, or typographical corrections made to improve readability.	

Amendment 1 09 February 2022

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

Overall Rationale for the Amendment:

This protocol was modified in response to a regulatory agency request and alignment with the new draft FDA guidelines on clinical development in CRSwNP. The main changes are (1) addition of an inclusion criterion: participants (except for those in Japan) are required to be on daily INCS for at least 8 weeks before screening as this reflects the global SoC (except in Japan); (2) removal of text (in Section 4.1 for participants in Japan) stating "if a participant is not on INCS or LTRA prior to screening, the participant is prohibited to start any INCS or LTRA during the study"; (3) clarification that participants in Japan are permitted to start INCS during the study if required for symptom management and that those participants who start INCS should remain on INCS for the duration of the study; (4) addition of 2 exclusion criteria: participants with a concurrent condition or medical history of (a) nasal cavity tumor and (b) fungal rhinosinusitis; (5) addition of subgroup analyses (age, gender, race, region, and baseline blood eosinophil category) for the co-primary endpoints. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Added text to clarify that participants (except those in Japan) should take INCS throughout the study per SoC.	Clarification and alignment with added inclusion criterion 4.
Section 1.2 Schema	Revised footnote to clarify that participants (except those in Japan) should take INCS throughout the study per SoC.	Clarification and alignment with added inclusion criterion 4.
Section 1.3 Schedule of Activities	Added note for exploratory blood biomarker samples to clarify that a serum sample will be collected at the indicated visits, while a whole blood sample is collected at Visits 2 and 16 only.	Clarification.
Section 3 Objectives, Endpoints and Estimands	Corrected text to reflect that start of INCS therapy is not prohibited in Japan.	Correction.
Section 4.1 Study Design	Added text to clarify that participants (except those in Japan) should take INCS throughout the study per SoC. Revised text to clarify that participants in Japan are permitted to start INCS (and should remain on INCS if started) during the study.	Alignment with added inclusion criterion 4 and regulatory request.
Section 5.1	Added inclusion criterion 4: participants (except those in Japan) must be on treatment with daily INCS for at	Reflects the use of INCS as SoC

Section # and Name	Description of Change	Brief Rationale
Inclusion Criteria	least 8 weeks prior to screening.	globally (except Japan).
Section 5.2 Exclusion Criteria	Added exclusion criterion 4: Concurrent condition or medical history of nasal cavity tumor (malignant or benign).	Regulatory request.
Section 5.2 Exclusion Criteria	Added exclusion criterion 5: Concurrent condition or medical history of fungal rhinosinusitis.	Regulatory request.
Section 5.2 Exclusion Criteria	In "nasal biopsy prior to Visit 0 for diagnostic purposes only is excepted": corrected Visit 0 to Visit 1.	Correction.
Section 5.3 Randomisation Criteria	Revised randomisation criterion 9: Removed the list of CRSwNP maintenance therapies and removed the requirement for dose and regimen to remain unchanged during the run-in period.	Clarification.
Section 6.8 Concomitant Therapy; Section 6.8.1 Permitted Medications; Section 6.8.2 Prohibited Medications	Added text to align with inclusion criterion 4. Revised text to clarify that participants in Japan are permitted to start INCS (and should remain on INCS if started) during the study. Added statement that initiation or changes in dosing regimen of leukotriene receptor antagonist are permitted. Removed row in prohibited medication table specifying changes in INCS treatment.	Alignment with added inclusion criterion 4 and regulatory request.
Section 8.5.1. Blood Eosinophil Counts	Modified text to clarify that absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study.	Clarification.
Section 9.2 Analysis Sets	Removed "enrolled" analysis set and added "screened" and "randomised" analysis sets.	Consistency with terminology in other protocols.
Section 9.3.1 Co-Primary and Key Secondary Endpoint(s) Analyses	Added statement that subgroup analyses (age, gender, race, region, and baseline blood eosinophil category) will be conducted for the co-primary endpoints.	Regulatory request.
All sections	Other minor, grammatical, or typographical corrections to improve readability.	

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