Statistical Analysis Plan

Study ID: 218079

Official Title of Study: 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)

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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)
Study Number:	218079
Compound Number or Name:	GSK3511294 (Depemokimab)
Abbreviated Title:	Efficacy and safety of subcutaneous depemokimab in patients with chronic rhinosinusitis with nasal polyps
Acronym:	ANCHOR-2

Sponsor Name: GlaxoSmithKline Research & Development Limited

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	04 Mar 2022	Amendment 1 Approval Date: 09-FEB-2022	Not Applicable	Original version
SAP Amendment 01	15 Jul 2024	Amendment 5 Approval Date: 26-JUN-2024	1. Sections 1.1, 4.3, 4.4: Removed text related to asthma endpoints 2. Section 1.1: SNOT-22 responder definition updated to ">=8.9" instead of ">8.9" 3. Section 1.1: Estimand strategy updated to handle ICE of initiation of medications that may modulate disease course of CRSwNP under composite strategy Previously defined primary estimand becomes a supplementary estimand 4. Section 2.1: Updated text in multiplicity adjustment strategy.	1. To align with change in endpoint hierarchy moving asthma related endpoints to pooled (217095 and 218079) analysis. 2. Section 1.1: SNOT-22 responder definition updated to ">=8.9" instead of ">8.9" 3. To align with FDA guidelines on developing drugs for treatment of CRSwNP 4. To reflect change in endpoint hierarchy

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			5. Section 3: Changed name of modified Intent-To-Treat (mITT) analysis set to Full Analysis Set (FAS), and definition changed to remove site 255403 and 255387. Updated text related to PK analysis set. Updated text related to safety population and added FAS-China, FAS-Japan, Safety-China, Safety-Japan, Screened-China, FAS-Modified, and Safety-Modified analysis sets. Section 4.1.1: added text related to China and Japan FAS and Safety analysis sets. 6. Section 4.1.3: Updated list of countries. 7. Sections 4.2.1, 6.2.4.2: Updated text related to VRS missing data.	related to nasal surgery endpoint based on regulatory feedback. 5. Name of mITT analysis set changed to FAS to align across the depemokimab program. Site removed in FAS definition due to potential GCP breach. Safety analysis set definition clarified so that analysis by actual treatment received does not apply to completers only. China and Japan are added to this reporting plan. 6. To match with

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			8. Section 4.4.2: Removed 28-point SNOT-22 responder endpoint from list of endpoints applying to model 9. Section 5: Text related to sample size determination updated	countries from which participants have been recruited. 7. Updated to match requirements. 8. Only a summary will be provided for this endpoint 9. To incorporate information regarding change to surgery endpoint for pooled (217095 and 218079) analysis.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the clinical study report (CSR) for Study 218079 (ANCHOR-2). Details of the planned final analyses are provided.

The pre-specified pooled analysis across studies 218079 (this study: ANCHOR-2) and 217095 (replicate study: ANCHOR-1) will be described in a separate analysis plan.

1.1. Objectives, Estimands and Endpoints

1.1.1. 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:** 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

Objectives	Endpoints
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 (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	• Achieving an 8.9 point or greater decrease from baseline in SNOT-22 total score at

Objectives	Endpoints
compared to placebo + SoC on health-related quality of life	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 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	• Depemokimab plasma concentration at measured timepoints during the 52-week period

Objectives	Endpoints
participants with a diagnosis of CRSwNP	• Ratio to baseline in absolute blood eosinophil count at measured timepoints during the 52-week period.

1.1.2. 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

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 corticosteroid (CS) for CRSwNP 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 a 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.

1.1.3. Secondary Estimands

The secondary estimands are defined as follows:

Treatment Comparison: As for primary estimand

Population: As for primary estimand

Variables/endpoints:

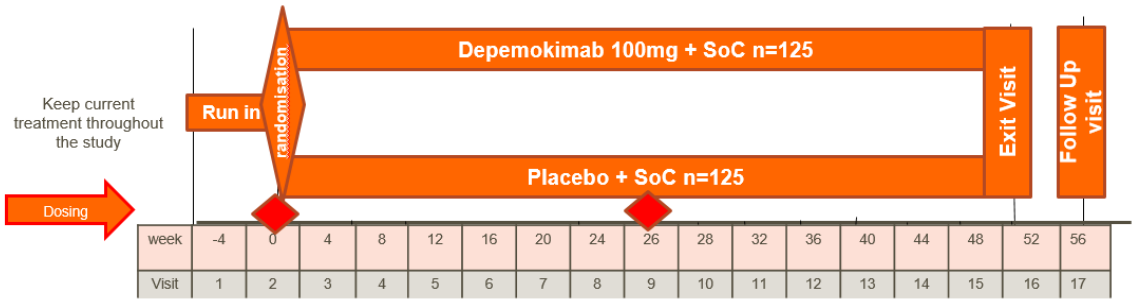
- Change from baseline in mean symptom score for rhinorrhoea (runny nose) (VRS) from Week 49 through to Week 52
- Change from baseline in mean symptom score for loss of smell (VRS) from Week 49 through to Week 52
- Change from baseline in Lund Mackay CT score at Week 52
- Change from baseline in SNOT-22 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

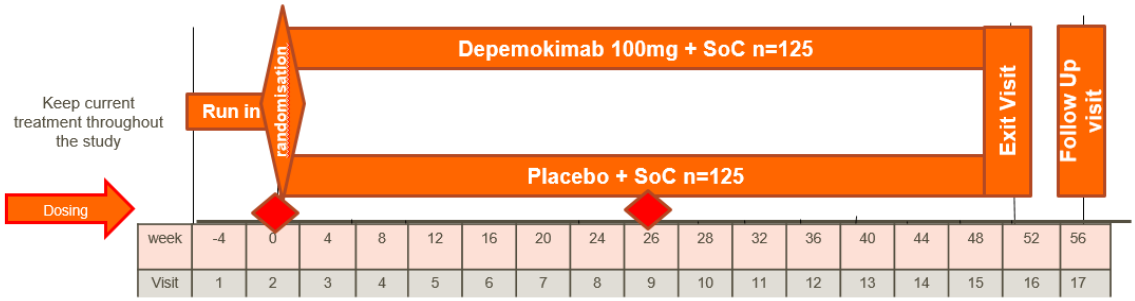
Main Intercurrent events (ICE) anticipated: As for primary estimand

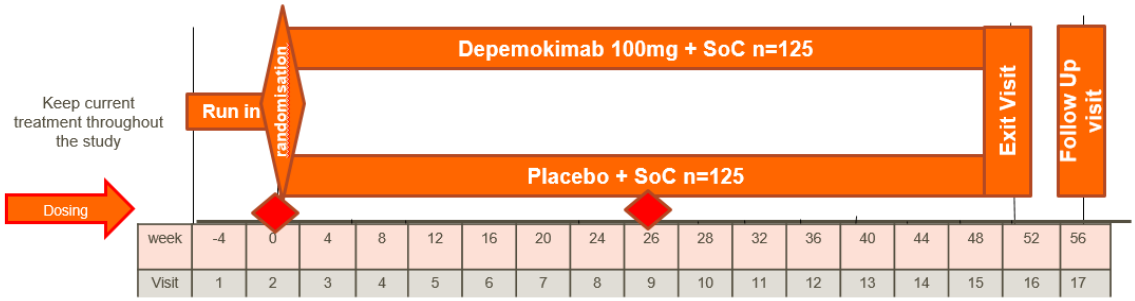
1.2. Study Design

Overview of Study Design and Key Features



Design Features	• Phase 3 • Randomized

Overview of Study Design and Key Features	
	
	• Double-blind • Placebo-controlled • Parallel group • Multi-centre • 4-week run-in period followed by a 52-week treatment period • Adult participants (≥ 18 years of age) with CRSwNP.

Overview of Study Design and Key Features	
	
Study Intervention	• All participants will be on SoC for CRSwNP throughout the study. • At visit 2, participants will be randomized in a 1:1 ratio to one of: o Depemokimab 100 mg SC o Placebo • Two doses of study intervention will be administered in the clinic by SC injection. The first at randomization (Visit 2) and the second at 26 weeks (Visit 9). • The randomization will be stratified based on occurrence of previous surgery for nasal polyps and country. • Approximately 250 participants will be randomized (125 per arm)
Interim Analysis	• No interim analyses of efficacy data are planned. • IDMC review of safety data is planned.

2. 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.

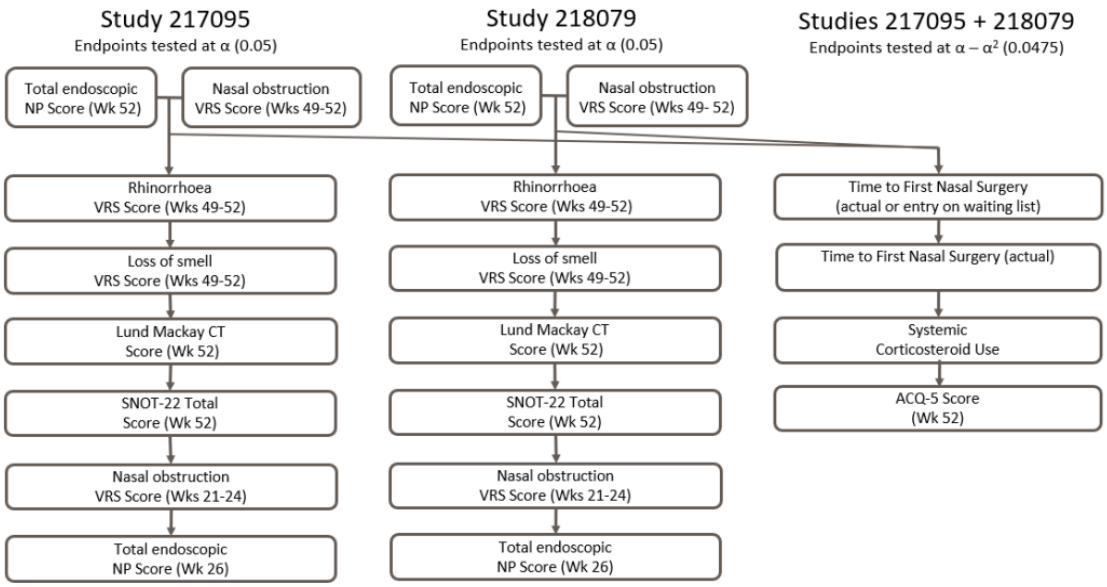
2.1. Multiplicity Adjustment

The hypotheses to be tested are structured as shown in Figure 1. The co-primary endpoints will be tested first and if these comparisons are both significant at the 2-sided 5% level, testing will continue for the secondary endpoints within the study according to the testing procedure detailed in Figure 1. Testing of secondary endpoints will be carried out in a hierarchical manner, dependent on statistical significance having been achieved for the previous endpoint in the hierarchy. Other pairwise comparisons will be performed

but are not 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. The analyses for these other efficacy endpoints and some of the earlier time points for some of the co-primary and secondary endpoints are not adjusted for multiplicity and so nominal significance will be evaluated in a descriptive manner with these analyses using a 5% reference level.

A pre-specified pooled analysis of data from the ANCHOR-1 and ANCHOR-2 studies 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 change from baseline in ACQ-5 score in participants with an ACQ score of >0.75 at baseline. This pooled analysis will be carried out after statistical significance is achieved for both co-primary endpoints within both studies. The closed-testing manner for the pre-specified pooled hierarchy is described further in the pooled SAP.

Figure 1 Conceptualization of Statistical Testing Strategy Across Studies ANCHOR-1 and ANCHOR-2



Note: Endpoint names in Figure 1 are abbreviated. Refer to Section 1.1 for full nomenclature of endpoints.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants screened and for whom a record exists on the study database	• Study population
Screened-China	All participants screened and for whom a record exists on the study database from China	• Study population
Screened-Japan	All participants screened and for whom a record exists on the study database from Japan	• Study population
Enrolled	Nly	• Study population
Randomized	All randomized participants	• Study population
Full Analysis Set (FAS)	All randomized participants who take at least 1 dose of study treatment excluding participants from sites 255403 and 255387. Participants will be analyzed according to the treatment they are allocated at randomization.	• Study population • Efficacy
FAS-China	All participants in the FAS population who are enrolled from China	• Study population • Efficacy
FAS-Japan	All participants in the FAS population who are enrolled from Japan and are of Japanese heritage only	• Study population • Efficacy
FAS-Modified	All participants in the FAS population plus randomised participants from sites 255403 and 255387 who receive at least one dose of study treatment.	• Study population • Efficacy
Safety	All randomized participants who take at least 1 dose of study treatment excluding participants from sites 255403 and 255387. Participants will be analyzed according to the treatment they are allocated at randomization, 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 analyzed according to the actual treatment they received.	• Safety
Safety-China	All participants in the Safety population who are enrolled from China	• Safety
Safety-Japan	All participants in the Safety population who are enrolled from Japan and are of Japanese heritage only	• Safety
Safety-Modified	All randomized participants who take at least 1 dose of study treatment excluding participants from sites 255403 and 255387. Participants will be analyzed according to the treatment they are allocated at randomization, 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	• Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
	will be analyzed according to the actual treatment they received.	
PK	All participants in the FAS population for whom at least one pharmacokinetic sample was obtained, analyzed and was measurable, including imputed values that were below the limit of quantification. Participants will be analyzed according to the treatment they received.	• PK
PK-China	All participants in the PK population who are enrolled from China	• PK

Note: 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 255387 in ANCHOR-2.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Unless otherwise stated, the Safety Analysis Set be used for safety displays and the Full Analysis Set (FAS) will be used for all other displays. FAS-Modified and Safety-Modified analysis sets will be used for a selected number of displays as sensitivity analyses. FAS-China, FAS-Japan, Safety-China and Safety-Japan will be used for China and Japan specific outputs respectively. The Programming Specification document will provide more details.

Unless otherwise stated, all intercurrent events for primary, secondary, or other endpoints will be handled under the primary estimand strategy.

This SAP specifies the analytical approaches for the global submission requirements, unless otherwise specified. Further analytical considerations may be made for the regional displays (i.e. model convergence considerations) where appropriate.

The randomization is stratified based on occurrence of previous surgery for nasal polyps and unless otherwise stated, this variable will be included as a covariate in the statistical models. In the case of an incorrect stratification at the time of randomization, the actual stratum will be used rather than the randomized stratum.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

For all visit-based endpoints, including the co-primary endpoint of endoscopic NP score, baseline will be defined as the latest non-missing measurement collected prior to the first dose of study treatment. This will generally be from the Day 1 (Visit 2) assessment but may be from an unscheduled or screening assessment. In the case a visit-based assessment was collected after the first dose of study treatment, but still on the day of the randomization visit on Day 1 (Visit 2), then that assessment may be used.

For daily efficacy endpoints collected in the eDiary, baseline will be the average score from the 28 calendar days up to and including the date of randomization. This means the average will be based on the non-missing data from Day -27 to Day 1 inclusive. There must be a minimum of 4 non-missing values from Day -6 to Day 1 inclusive in order to derive the baseline, otherwise it will be set to missing.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.1.3. Multicenter Studies

For the purposes of covariate adjustment in the statistical analysis, countries will be grouped into the following 3 regions: Europe (EU); United States (US); Rest of World (RoW). The countries that form these regions will include:

- Europe (EU): Poland; Romania; Spain; Sweden; Italy
- United States (US): United States
- Rest of World (RoW): China; Japan; Turkey

If there are insufficient subjects in each region for the statistical procedures to converge satisfactorily, the combining of regions will be considered.

4.2. Primary Endpoints Analyses

4.2.1. Definition of endpoints

The co-primary endpoints are:

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

The total endoscopic NP score is assessed in the clinic at visits 2, 5, 7, 9, 11, 13, 15 and 16, or early withdrawal visit (weeks 0, 12, 20, 26, 32, 40, 48 and 52). The score is then graded by independent reviewers at a central lab who are blinded to treatment. The total score is reported as the sum of the right and left nostril scores and ranges from 0 to 8, with higher scores indicating greater disease severity. Non-missing scores must be available for both sides for the combined score to be calculated; otherwise the score will be set to a value of 9 to indicate a missing or unreadable value.

The nasal obstruction VRS score will be collected daily in the morning via the eDiary. Each day the participant will indicate the severity of their symptoms giving a score ranging from 0 to 3, with the 4 options indicating no symptoms, mild symptoms, moderate symptoms, and severe symptoms. The daily data will be collapsed into thirteen 4-week time periods, with the value for each time period based on the average of the non-missing days covered by that time period as described in Section 6.3.4.2. For each 4-week time period the average will only be derived if there are non-missing values for at least 4 days out of 7 in at least 3 out of 4 weeks, with at least 15 minimum values, otherwise it will be set to missing.

As described in Section 1.1.2, under the primary estimand, the intercurrent events of (i) surgery and (ii) initiation of a disease-modulating medication for CRSwNP, will be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who experience the intercurrent event will be assigned the worst possible value of the relevant score for all assessments following the intercurrent event (i.e. the worst value that it is possible to select on the given scale). This means that a participant who experiences the intercurrent event will be assigned a total endoscopic NP score of 8 for every scheduled clinic visit after the date of the first intercurrent intercurrent event (regardless of whether the visit occurred) and a nasal obstruction VRS score of 3 for every day after the date of the first intercurrent event. All other intercurrent events described under the primary estimand strategy in Section 1.1.2 will be handled using a treatment policy strategy.

The study is designed to continue collecting data for participants who have prematurely discontinued from randomized treatment and off-treatment data collected for these participants will be included in the analysis. Missing data will be assumed to be missing at random (MAR). Summary statistics will be produced for each visit/4-week time-period by treatment group for the co-primary endpoints.

4.2.2. Main analytical approach

Model Specification
Statistical analyses will be performed using a Mixed Models Repeated Measures (MMRM) model with covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline score and visit by treatment group.
Model Checking & Diagnostics
• The Kenward-Roger (KR) method [Kenward, 1997] for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used in the analyses. This will be achieved by specifying the DDFM=KR option in the MODEL statement within PROC MIXED. • For mixed model repeated measures (MMRM) models, an unstructured covariance structure for the R matrix will be used by specifying 'TYPE=UN' in the REPEATED statement.   ○ In the event that the model fails to converge, model simplification methods will be considered (e.g., adjusting covariate structure, streamlining timepoints)

• Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. These will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values (checking the normality assumption and constant variance assumption of the model, respectively).
Model Results Presentation
• For each visit / time-period, the adjusted mean change from baseline with corresponding standard error for each treatment group will be presented. The estimated treatment difference will be presented together with 95% confidence interval (CI) for the difference and p-value for the inequality comparison. • The adjusted mean change from baseline for each treatment, with corresponding 95% CIs will also be presented graphically across the visits / time-periods. • A cumulative distribution function (CDF) plot will also be provided for the change from baseline by treatment group
Additional Analysis
• The same primary endpoint analysis will be performed using FAS-Modified analysis set • The same analyses will be performed with the intercurrent event strategy described under the supplementary estimand.

4.2.3. Sensitivity analyses

A missing data sensitivity analyses using multiple imputation (MI) methods will be conducted for each of the co-primary endpoints to investigate the impact of missing data and to examine the robustness of the analyses of the primary endpoints to departures from the assumption that missing data are MAR. These analyses will use the same estimand strategy as outlined for the co-primary endpoints in Section 1.1.2. The MI methods are based on pattern-mixture models described by Carpenter [Carpenter, 2013]. The pattern-mixture model approach to sensitivity analysis models the distribution of a response as the mixture of a distribution of the observed responses and a distribution of the missing responses.

Sensitivity Analysis 1

For the first sensitivity analysis, participants with missing data at Week 52 who had taken their Week 26 dose of interventional product (and are 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 are therefore considered off-treatment at Week 52) will have their monotone missing data (i.e. after their final non-missing time point) 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).

Multivariate normal models will be fitted using a Markov Chain Monte Carlo (MCMC) approach. The covariates will be the same as for the primary analysis. The independent samples drawn from the posterior distributions for the mean and variance-covariance matrix provide input into the imputation model. For each participant with missing data, these sampled values of the parameters for mean vectors and the variance-covariance

matrices specify a joint distribution for their observed and unobserved outcome data. Under the J2R approach, the mean estimate is constructed using the estimated beta associated with the reference treatment, as well as the participant's other covariates.

For each participant with missing data, this joint pattern-specific distribution can be used to construct the conditional distribution of their missing data given their observed data. The missing data is sampled once from this distribution to create a single dataset for each imputation. Together these form a series of complete imputed datasets for each of the primary endpoints (with imputed data under either MAR or J2R).

Each imputation dataset will be analyzed using the same methodology as for the primary analysis and the results from each analysis of each sample will then be combined using Rubin's method [Rubin, 1987] as implemented in PROC MIANALYZE in SAS.

Results presentation will be the same for the co-primary analyses described in Section 4.2.2 for the EOS visit / time period. Additionally, for each of the co-primary endpoints, for the EOS visit / time-period only, a forest plot will be produced to present the estimated treatment differences and 95% CIs for the primary estimand using FAS, the supplementary estimand using FAS, the primary estimand using FAS-Modified, and the J2R approach.

Sensitivity Analysis 2

An additional tipping point sensitivity analysis will explore the impact of missing data by using differing assumptions regarding the endoscopic NP score at Week 52 and the nasal obstruction VRS at Weeks 49-52 in subjects who withdraw from the study. Subjects who withdrew from study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit / Week 49 – 52 time period based on a range of values for the mean NP score / mean nasal obstruction VRS following study withdrawal. Assumptions about missing values on the treatment arm and placebo arm will vary independently, and will include scenarios where participants with missing data in the active 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.

As a first step, participants with missing data will have missing data imputed under the assumption of MAR. For each treatment group, the imputed values will vary separately by a value of delta, where delta represents a change in endoscopic NP score / mean nasal obstruction VRS over a 4-week interval. The deltas investigated will cover a range that is plausible for the respective endpoint under the MAR assumption. For NP score, the deltas evaluated will range from -8 to 8 by 0.5 increments. For nasal obstruction VRS, the deltas evaluated will range from -1.5 to 1.5 in 0.25 increments. The final range and increment of deltas will be investigated on final data and may be adjusted to ensure it supports a meaningful tipping point range.

The tipping point multiple imputation method will be based on pattern mixture models [Keene, 2014]. Each imputation dataset will be analyzed using the same methodology as for the primary analysis and the results from each analysis of each sample will then be combined using Rubin's method [Rubin, 1987] as implemented in PROC MIANALYZE in SAS.

A table of p-values for each treatment comparison made across the range of imputed values (deltas) for each respective endpoint will be presented. Graphics depicting treatment difference and non-significant vs. significant surfaces will be produced for the range of imputed values (deltas) for each respective endpoint.

The seeds for all planned MI sensitivity analyses will be '218079'.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoints

The secondary endpoints are:

- 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
- Change from baseline in Lund Mackay (LMK) 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

The VRS endpoints collected daily in the morning via the eDiary will be handled in the same way as the co-primary VRS endpoint, with daily data being collapsed into 4-week time periods as described in Section 6.3.4.2. A CDF plot will also be provided for the change from baseline by treatment group for the endpoints: (1) Change from baseline in mean symptom score for rhinorrhoea (runny nose) (VRS) from Week 49 through to Week 52 and (2) Change from baseline in mean symptom score for loss of smell (VRS) from Week 49 through to Week 52.

A computed tomography (CT) scan is performed at Visit 16 (Week 52) and all image recordings of CT scans will be sent to an independent reviewer for centralized blinded data assessment. The central reading for LMK scoring will be used for analysis. The 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. The combined score will range from 0-24 with higher scores indicating greater disease severity. Non-missing scores must be available for all portions on both sides for the combined score to be calculated; otherwise the score will be set to a value of 9 to indicate a missing or unreadable value.

SNOT-22 is a 22-item questionnaire that will be completed at each of the scheduled clinic visits using the eDiary. 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. All questions must be answered to generate an overall score; if any individual questions are missing then the overall score will be missing.

4.3.2. Main analytical approach

Change from baseline in LMK CT score at Week 52 will be analyzed as described below. All other secondary endpoints will be analyzed in the same way as the co-primary endpoints. Summary statistics will be produced for each visit/4-week time-period by treatment group for each secondary endpoint. The same secondary endpoints analyses will be performed using the FAS-Modified analysis set as an additional analysis.

Model Specification
• Statistical analyses for the change from baseline in Lund Mackay CT score at Week 52 will be performed using an analysis of covariance (ANCOVA) model with covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region and previous surgery for nasal polyps.
Model Checking & Diagnostics
• The Kenward-Roger (KR) method (Kenward, 1997) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used in the analyses. This will be achieved by specifying the DDFM=KR option in the MODEL statement within PROC MIXED. • Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. These will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values (checking the normality assumption and constant variance assumption of the model, respectively).
Model Results Presentation
• The adjusted mean change from baseline with corresponding standard error for each treatment group will be presented. The estimated treatment difference will be presented together with 95% confidence interval (CI) for the difference and p-value for the inequality comparison.

For the co-primary endpoints and the secondary endpoints for the EOS visit/time-period only, a forest plot will be produced to present the estimated treatment differences and 95% CIs.

4.4. Other Endpoints Analyses

4.4.1. Definition of endpoints

The other endpoints are:

- 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
- 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.
- Further details on meaningful decrease for each individual symptom VRS and composite VRS are described in Section 4.4.2
- 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

The overall visual analogue scale (VAS) symptoms score will be collected daily in the morning via the eDiary. Participants will be asked to rate their overall symptoms at their worst over the previous 24 hours. A scale from 0 (None) to 100 (As bad as you can imagine) will be used. 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. This endpoint will be handled in the same way as the co-primary VRS endpoint, with daily data being collapsed into 4-week time periods as described in Section 6.3.4.2.

A nasal obstruction VAS score will also be collected daily in the morning via the eDiary at key time-periods during the study. The data from this endpoint will be collapsed into the expected time periods as described in Section 6.3.4.2.

The VRS composite scores will be derived for each day by taking the mean of the individual VRS scores for that day. All of the individual VRS scores contributing to a composite score must be non-missing in order to derive the mean.

All VRS endpoints will be handled in the same way as the co-primary VRS endpoint, with daily data being collapsed into 4-week time periods as described in Section 6.3.4.2.

The short-form-36 (SF-36) questionnaire consists of 36 self-administered questions that cover 8 health domains: physical functioning (PF), role physical (RP), bodily pain (BP), and general health (GH), vitality (VT), role emotional (RE), social functioning (SF), and mental health (MH) with a recall of 4 weeks. Certified scoring of the SF-36 survey will be performed using OPTUM ™ software. The 8 domain scores are provided by the software. Scale scores range from 0 to 100 where higher scores indicate better quality of life.

The work productivity and activity impairment (WPAI) questionnaire is an instrument to measure impairment in paid and unpaid work and daily activities. Six questions will be collected at each visit including employment status, hours missed from work due to health problems and due to other reasons, hours actually worked, and how much health problems affected productivity and activity.

The following measures will be derived from the 6 WPAI-GH questions ranging from 0 (no impairment) to 100 (full impairment):

Derived Outcomes Derivation	Derived Outcomes Derivation
Work time missed due to health (%)	100 * Q2 / (Q2+Q4)
Impairment while working due to health (%)	10 * Q5
Overall work impairment due to health (%)	100* Q2 / (Q2 + Q4) + [(1 - (Q2 / (Q2+Q4))) x (Q5 / 10)]
Activity impairment due to health (%)	10 * Q6

Note (each question with a recall of 7 days):
Q1 = Currently Employed
Q2 = Time (hours) missed from work due to health problems during the past seven days
Q3 = Time (hours) missed from work due to other reasons during the past seven days
Q4 = Time (hours) actually worked during the past seven days
Q5 = Productivity affected by health problems while working during the past seven days
Q6 = Ability to do regular daily activities affected by health problems during the past seven days
Participants not currently employed will only answer Q6. Participants who answer 0 to Q4 will not answer Q5.
If any of the responses used to derive a score are missing or if a participant is not currently employed then the relevant score (work time missed, impairment while working, overall work impairment) will be set to missing.
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.

For SF-36 and WPAI-GH, the intercurrent event of surgery and disease-modulating medication for CRSwNP will be handled under the composite strategy by assigning participants their worst observed score prior to the event. All other intercurrent events described under the primary estimand strategy in Section 1.1.2 will be handled using a treatment policy strategy.

For all responder endpoints, participants who undergo nasal surgery or initiate a disease-modulating medication for CRSwNP will be included in the analysis as non-responders for all time points following the event, whichever occurred first. For participants with missing baseline data, a responder status will not be derived. Participants with missing data at a particular post-baseline visit / timepoint will be treated as non-responders for that visit/ timepoint. All other intercurrent events described under the primary estimand strategy in Section 1.1.2 will be handled using a treatment policy strategy.

4.4.2. Main analytical approach

Summary statistics by visit will be provided for the SF-36 and WPAI-GH endpoints.

Summary of responder status by visit will be provided for the 28-point SNOT-22 responder endpoint.

Summary statistics for change from baseline at the key time-periods when it was collected will be provided for overall VAS score.

The change from baseline endpoints related to VAS and VRS scores will be analysed in the same way as the co-primary endpoints.

For the endpoint, 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, the clinically meaningful VRS cut-points for mean individual symptoms VRS and composite VRS are as follows:

- Achieving a 1-point or greater decrease from baseline in nasal obstruction VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP
- Achieving a 1-point or greater decrease from baseline in rhinorrhoea VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP
- Achieving a 0.9-point or greater decrease from baseline in loss of smell VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP
- Achieving a 0.8-point or greater decrease from baseline in facial pain VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP
- Achieving a 1-point or greater decrease from baseline in mucous in throat VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP
- Achieving a 0.8-point or greater decrease from baseline in composite nasal polyps symptoms VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP

- Achieving a 0.8-point or greater decrease from baseline in composite CRS symptoms and facial pain VRS total score at Week 52 without first having nasal surgery (actual) or disease-modulating medication for CRSwNP

The remaining other endpoints will be analysed as described below:

Endpoints
• 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. • 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. • 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.
Model Specification
• The conditional treatment effect for the responder analysis endpoints will be estimated using a generalized linear mixed model with a logit link function and covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline score and visit by treatment.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Model Results Presentation
• For each scheduled visit / time-period the following will be presented: • The number and percentage of responders and non-responders for each treatment, together with the odds ratio, 95% CI and p-value will be presented for the NP responder endpoint, and nasal obstruction, loss of smell, and rhinorrhoea VRS responder endpoints only   • Other individual symptom VRS and composite VRS responder endpoints (facial pain, mucous in throat, composite nasal polyps symptoms, composite CRS symptoms and facial pain) will be summarized only

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

Two doses of study treatment will be administered during study treatment period: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Each dose is viewed as providing therapeutic coverage for 26 weeks (182 days). The number of treatments administered, and the number of days exposure will be summarised descriptively and listed. Total subject-year exposure will also be presented.

Number of days of exposure to study treatment will be calculated as follow:

> Duration of Exposure in Days = (Date of Final Dose) – (Date of First Dose) + 182 days (regardless of study withdrawal or death)

Subject years exposure is calculated as follow:

> Subject Years Exposure = ((Date of Final Dose) – (Date of First Dose) + 182)/365.25

4.5.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards. Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary). The details of the planned displays are provided in the Programming Specifications document.

For the standard AE tables, the number and percentage of participants with AEs will be summarized for each treatment group by system organ class (SOC) and preferred term (PT). The ordering of the SOCs and the PTs within the SOCs will both be in descending order of total incidence. A SOC will not be presented when the overall incidence for any AE within the particular system is zero. If the total incidence for any two or more AEs is equal, the events will be presented in alphabetical order.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced.

A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing.

A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing.

4.5.2.1. 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].

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation: AESI of QTc prolongation will be summarized as detailed in Section 4.5.3.3.

A summary table showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created. An additional table will also display the relative risk and risk difference and their 95% CIs between and depemokimab and placebo.

For each type of AESI (excluding QTc prolongation) a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver function test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data. Change from baseline values for clinical chemistry and haematology will be summarised in separate tables using descriptive statistics.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

4.5.3.2. Vital Signs

Systolic blood pressure, diastolic blood pressure, heart rate and body temperature including change from baseline will be summarised at all visits and listed.

4.5.3.3. ECG

Change from baseline (for post-baseline timepoints) values for all ECG measurements and intervals will be summarized by visit. ECG results will also be listed.

Individual maximum QTc(F) values will also be summarized to show the number of subjects with maximum values (msec) that increased to the following categories: ≤450, 450 < to ≤480, 480< to ≤500, 500< to ≤530 and >530. QT uncorrected values will be summarized to show the number of subjects with maximum values in the following categories: <600 and ≥600.

Additionally, individual maximum changes from baseline in QTc(F) values will be summarized to show the number of subjects with maximum changes (msec) in the categories: ≤ 30, > 30 to ≤ 60 and > 60.

All ECG values for participants with protocol defined QT stopping criteria will be listed.

Additional analyses related to ECG will be presented in a separate analysis plan as part of the Integrated Summary of Safety.

4.5.3.4. Immunogenicity Analysis

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding antibody assay and a neutralizing antibody assay (NAb).

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti- depemokimab antibodies.

All participants' baseline immunogenicity samples will be analyzed. Post-baseline immunogenicity samples will only be analyzed for participants receiving depemokimab 100 mg SC.

The following descriptive summaries will be presented for depemokimab 100 mg SC group by visit using the Safety Analysis Set:

- Summary of binding antibody assay results: it will summarize the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarize the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of binding antibody results for participants without positive result prior to dosing: it will summarize the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarize the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of neutralizing antibody assay results: it will summarize the neutralizing antibody assay results for participants with a positive binding antibody confirmatory assay results. Neutralizing antibody assay results will be categorized as positive or negative. It will also summarize the highest post baseline neutralizing antibody assay result obtained.
- Summary of AE by highest post-baseline binding antibody confirmatory assay result

The following descriptive summaries will be presented for the placebo group using FAS:

- Summary of binding antibody assay results for all baseline visit results. Summary will include categories for negative and positive results, and available titre value (min, median and max).

- Summary of neutralizing antibody assay results for all baseline visit results. Summary will include categories for negative and positive results.

Note: Visits will include pre-dose baseline visit and all post-baseline visits where immunogenicity assessments were performed. The binding antibody confirmatory assay results are categorized as negative or positive. The positive results will have two sub categories: transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). For the summary of highest post baseline binding antibody confirmatory assay result and neutralizing antibody assay result, subjects with both positive and negative results will be identified in the positive category. If a subject had titer results that fall into multiple titer result categories, they will be included in the highest category.

4.6. Clinical Pharmacology Data Analyses

4.6.1. Pharmacokinetic Analyses

Depemokimab plasma concentration samples are collected at discrete timepoints during the 52-week treatment period. Depemokimab plasma concentration will be summarised by visit (Depemokimab + SoC arm only) using the PK Analysis Set.

For the PK summaries, any premature discontinuation of study treatment will be handled using while on-treatment strategy where data will be included in the summary while a participant was on-treatment. Other intercurrent events such as surgery, all changes in background medication or start of a prohibited medication, COVID-19 related events and courses of systemic CS to be handled under the treatment policy strategy.

The PK data from this study will be included in a meta-analysis of the PK and PKPD data across all depemokimab studies available at the time of the analysis. Details of meta-analysis will be in a separate CPMS analysis plan.

4.6.2. Pharmacodynamic Analyses (PD) - Blood Eosinophils

Blood eosinophil counts will be loge-transformed. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be imputed with a value of 0.005GI/L prior to log transformation. PD analyses will be analyzed using FAS.

Ratio to baseline during W52 will be analyzed using a MMRM analysis. Model specification, model checking, and diagnostics are the same as described for co-primary endpoints statistical analyses, see Section 4.2.2. Analysis will include data from all visits that blood eosinophils data is collected. The LS Geometric Mean (SE Logs) blood

eosinophil, the LS Geometric Mean ratio to baseline (SE Logs) blood eosinophil in each treatment group and the treatment ratio of LS Geometric Mean ratio to baseline (95% CI) for depemokimab versus placebo will be presented in a table. The LS Geometric Mean and 95% CI of ratio to baseline blood eosinophil will also be presented graphically.

Absolute and ratio to baseline blood eosinophil counts will be summarized by treatment group and visit. Only results from the central laboratory will be included in the summary, however all data will be listed.

For the PD endpoint, the intercurrent event of initiation of a disease-modulating medication for CRSwNP will be handled under the hypothetical strategy, where PD data will be set to missing after the intercurrent event happened. Any premature discontinuation of study treatment will be handled using while on-treatment strategy where data will be included in the summary while a participant was on-treatment. Other intercurrent events such as NP surgery, all other changes in background medication or start of a prohibited medication (other than disease-modulating medications for CRSwNP), COVID-19 related events and courses of systemic CS to be handled under the treatment policy strategy.

The PK and eosinophils data from this study will be included in a meta-analysis of the PKPD data across all depemokimab studies available at the time of the analysis. Details of meta-analysis will be in a separate CPMS analysis plan.

4.7. IL-5 Analyses

The IL-5 data from this study will be analyzed in the future and is not planned for reporting of the CSR.

4.8. Analyses to Support Regional Submission

Since the study will be used to support China and Japan regulatory submissions, a subset of study population, safety and efficacy analyses will be repeated using Safety-China and Safety-Japan analysis sets for safety analyses and FAS-China and FAS-Japan for study population and efficacy analyses. The Programming Specifications document will provide further details.

The China and Japan subpopulation analyses will employ the same model as the overall population analyses. For MMRM analyses, if the model cannot converge from what was originally defined (including repeated visits and covariates in the model), those will be adjusted to ensure model convergence and obtain stable estimations. Alternatively, no analyses will be performed, and only descriptive summaries will be produced.

4.9. Risk Benefit Analysis

A forest plot will be produced to display efficacy and safety data from analyses in adjacent panels using FAS and Safety Analysis Set respectively. The efficacy results will include co-primary endpoints. The efficacy results will be obtained from analyses described in Section 4.2. The AE results will be obtained from the analyses as described in Section 4.5.2.1 for the following categories of AEs:

- On treatment SAE
- Systemic reactions
  - Allergic (Type 1 hypersensitivity reactions)
    - Anaphylaxis
  - Other systemic reactions
- Type III hypersensitivity/vasculitis
- Local injection site reactions

4.10. Other Analyses

4.10.1. Subgroup analyses

This section details the subgroups of interest within this study.

Table 1 Subgroups of Interest

Subgroup	Category
Age 1	12-17, 18-64, ≥65
Age 2	12-17, 18-64, 65-74, ≥75
Age 3	18-39, 40-64, ≥65
Sex	Male, Female
Race 1	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White
Region 1	Europe (Poland; Romania; Spain; Sweden; Italy), United States (US), Rest of the World (RoW) (China; Japan; Turkey)
Region 2	Asia, Non-Asia
Region 3	East Europe (Poland; Romania), Other Europe (Sweden; Italy; Spain), US, Rest of the World (China; Japan; Turkey)
Number of Previous NP Surgeries	0, 1, 2, >2
Baseline Eosinophil Category	<0.30 GI/L, >=0.30 GI/L
Participant with Asthma	Yes, No

Subgroup analyses should be interpreted with caution, especially when low numbers are observed in subgroups. If any subgroup category contains <20 participants, then the subgroup categories may be refined, if appropriate. Alternatively, no analyses will be performed, and only descriptive summaries will be produced for the subgroup.

4.10.1.1. Co-Primary and Pharmacodynamic Endpoint Subgroup Analyses

Subgroup analyses will be performed for the co-primary endpoints and the pharmacodynamic endpoint:

- 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

- Ratio to baseline in absolute blood eosinophil count at measured timepoints during the 52-week period.

The subgroup analyses for all three endpoints will be conducted by the following subgroups: Age 3, Sex, Region 1, Number of Previous NP Surgeries, Baseline Eosinophil Category, and Participant with Asthma. The co-primary endpoints will also include an additional subgroup analysis for Region 3.

The subgroup analyses will be analyzed in the same way as the co-primary endpoint analyses described in Section 4.2.2; however, it will be adjusted for additional covariates. The additional covariate terms include: subgroup, subgroup by treatment, and subgroup by visit by treatment. The subgroup by treatment interaction term will be tested at the 10% significance level. When a subgroup assesses the same or a similar parameter as one of the covariates already in the model (e.g. region subgroup similar to baseline region covariate), the covariate will be removed from the model.

In the event the subgroup analysis model fails to converge, model simplification methods may be addressed (i.e. adjusting covariate structure, streamlining time points, combining subgroups, running model separately for each subgroup level).

The following will be presented for each endpoint:

- For each visit / time-period, the adjusted mean change from baseline (or ratio to baseline where applicable) with corresponding standard error for each treatment group will be presented. The estimated treatment difference will be presented together with 95% CI for the difference.
- For the end-of-study (EOS) visit / time-period only, a forest plot will be produced to present estimated treatment differences and 95% CIs including all subgroups. The subgroup by treatment interaction p-value will also be presented.

4.10.1.2. Safety Subgroups

The summary of exposure to study medication will be summarized by the following subgroups: Age 1 and Sex, Race 1, and Region 2.

The summary of overview of all on-treatment AEs will be summarized by the Region 2 subgroup.

The summary table of on-treatment AEs by SOC and PT will be summarized by the following subgroups: Age 1, Age 2, Sex, Race 1, Region 1, and Region 2.

For the subgroups related to age, if there are no subjects within a particular age category (i.e. 12-17), then that age category will not be displayed.

4.11. Interim Analyses

No interim analyses of efficacy data are planned.

An independent data monitoring committee (IDMC) will periodically review unblinded safety data from this study and study ANCHOR-1.

4.12. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol.

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 first nasal surgery (actual or entry on waiting list).

Approximately 250 participants will be randomised in this study in a ratio of 1:1 giving 125 randomised participants per arm. This sample size allows for up to 5% of randomised 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 (ANCHOR-2) and ANCHOR-1 is planned for the endpoint of time to first nasal 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 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 requiring first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP using data from this study (ANCHOR-2) and ANCHOR-1 is >90%.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the FAS, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and study treatment compliance will be based on GSK Core Data Standards.

6.1.1. Participant Disposition

Summary tables showing the reasons for screen failure and run-in failure will be provided using the Screened Analysis set.

A summary of participant status and reason for study withdrawal will be provided. This display will show the number and percentage of participants who completed the study and who withdrew from the study, including the primary reason for study withdrawal. A participant is considered to have completed the study if they complete the Week 52 visit.

A summary of study treatment status will be provided. This display will show the number and percentage of participants who have completed the scheduled study treatment or have discontinued study treatment prematurely and a summary of the primary reason for discontinuation of study treatment.

A summary of the number of participants in each of the analysis sets describe in Section 3, along with the number of participants randomized will be provided using the Screened Analysis Set.

The number of participants randomized to each strata and number of participants with each actual strata (in cases of incorrect strata allocation) will also be summarized.

The number of participants enrolled by region, country and center will be summarized.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., sex, age, ethnicity, race, region, height, weight and derived BMI) will be summarized by descriptive statistics. An additional summary of age ranges using the EMA clinical trial results disclosure requirement categories will be produced and is based on the Enrolled Analysis Set. If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version should be produced.

Summaries of disease history and characteristics will be provided. Tables will include duration of chronic rhinosinusitis, duration of nasal polyps, history of nasal polyps surgery prior to screening, history of systemic corticosteroid use for nasal polyps, baseline blood eosinophils count, total Immunoglobulin E (IgE), intranasal corticosteroid (INCS) use at baseline, and aspirin-exacerbated respiratory disease (AERD) at baseline.

Summary statistics for the baseline values of efficacy and safety endpoints will be included in the efficacy and safety summary tables for those endpoints respectively. Additionally, a summary table for the baseline efficacy for the co-primary and secondary endpoints within the hierarchy will be summarized by treatment group and overall.

Additionally, asthma status, asthma exacerbation history in the 12 months prior to screening, ACQ-5 score at baseline, and tobacco history will also be summarized.

Medical conditions collected at screening will be summarized for current and past conditions separately.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications (CM) will be coded using the WHO Drug dictionaries. Summaries of the number and percentage of participants taking concomitant medications will be displayed by ingredient only (not by ATC classification). These summaries will include single-ingredient medications and will present multi-ingredient medications according to the combination of the component ingredients. Separate summaries will be produced for those medications taken pre-, during, and post-treatment.

Pre-Treatment: CM Start Date < Study Treatment Start Date

On-Treatment (During): If CM Start Date < Study Treatment Start Date and CM Stop Date >= Study Treatment Start Date

Or

If Study Treatment Start Date < CM Start Date < Last Dose of Study Treatment Date + 182 days

Post-Treatment: If CM Start Date < Last Dose of Study Treatment Date + 182 days

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

The compliance of eCOA data (e.g., assessments collected via electronic patient diary cards) will be derived at the study-level (overall) and at the endpoint-level across all participants and by treatment group.

An eCOA will be considered complete if there is no missing data within the assessment.

6.2.1. Study-Level (Overall) Compliance

The study-level (overall) compliance for all eCOA assessments collected in the study will be assessed for all participants at all time-points between baseline through to the date of the participant's study completion or withdrawal. If an eCOA is only assessed for a certain sub-population, the compliance for only that sub-population will be included in the compliance calculation (i.e. ACQ-5 only administered in participants with asthma). The list of eCOA assessments that comprise the study-level (overall) compliance include all eCOA assessments collected within the study: VRS, VAS, Nasal Obstruction VAS, SNOT-22, PGIS, PGIC, ACQ-5, SF-36, and WPAI-GH.

The analyses related to the ACQ-5 endpoint are described in the pooled SAP, but are included in the compliance metrics for completeness.

The target overall compliance for the study is 70%.

Overall eCOA compliance (across all eCOAs and all participants) for the study is calculated as:

$$\frac{Total\ number\ of\ complete\ eCOAs\ across\ all\ participants}{Total\ expected\ number\ of\ complete\ eCOAs\ across\ all\ participants} \times 100$$

$$Expected\ number\ of\ complete\ eCOAs = \sum_{i=1}^{n}\sum_{j=1}^{c} data\ points\ expected\ for\ eCOA_j(participant\ i)$$

where c represents the total number of eCOAs collected and n represents the total number of participants.

For daily diary data this means every day is a data point in the denominator. For visit-based endpoints, each visit is a data point in the denominator. The study-level (overall) compliance metric will be summarized by treatment group and total across treatment groups.

A supplemental overall compliance metric will also be calculated for the study. The supplemental calculation will be based on an interval-based definition for daily diary data that is defined within Section 6.3.4.2 for a four-week interval result to be non-missing in the analysis. The number of data points in the denominator for the interval-based definition becomes the number of four-week time periods that are assessed, including the baseline assessment. Participants are considered compliant for the daily diary endpoints if

the appropriate number of non-missing values for each interval per the criteria described in Section 6.3.4.2. The denominator for the visit-based endpoints will remain the same. For visit-based endpoints, participants are considered compliant if they complete the assessment at that visit. This calculation will only include the eCOA endpoints in the multiplicity hierarchy: VRS, SNOT-22, and ACQ-5.

Both the study-level compliance and the supplemental overall compliance will be summarized at the participant level by pre-defined ranges for compliance (<40%, 40-<60%, 60-<80% >=80%). These will be summarized by treatment group and total across treatment groups.

6.2.2. Endpoint-Level Compliance

The daily eCOA assessments will be assigned a single four-weekly analysis time point as detailed within Section 6.3.4.2. Participants are considered compliant if the appropriate number of non-missing values for each interval per the criteria described in Section 6.3.4.2.

All visit-based eCOA assessments will be assigned analysis time points as detailed within Section 6.3.4.1. Participants are considered compliant if they complete the assessment at that visit.

The compliance for all eCOA endpoints in the multiplicity hierarchy (VRS, SNOT-22, ACQ-5) will be reported for each analysis time point by treatment group and total across treatment groups.

6.3. Appendix 3 Data Derivations Rule

6.3.1. Criteria for Potential Clinical Importance

6.3.1.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1	12+ years	0.201	0.599
Haemoglobin	G/L	12+ years	71	199
Platelet Count	$x10^9$/L	1+ years	31	1499
While Blood Cell Count (WBC)	$x10^9$/L	12+ years	1.1	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L	3+ years	1.50	3.24
Creatinine	IU/L	12+ years		>5 x ULN
Glucose	mmol/L	1+ years	2.2	27.8
Potassium	mEq/L	3+ years	2.8	6.5
Magnesium	mmol/L	6+years	0.3	2.5
Phosphorus	mmol/L	3+years	0.32	
Sodium	mEq/L	0+ years	120	160
ALT	U/L	12+ years		>239
Creatine Phosphokinase	IU/L	12+years		>5xULN

Liver Function			
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**
			High Flag (>x)
ALT/SGPT	U/L	High	3 x ULN
AST/SGOT	U/L	High	3 x ULN
AlkPhos	U/L	High	3 x ULN
T Bilirubin	µmol/L	High	1.5 x ULN

6.3.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-treatment is defined as time prior to the first dose of study intervention.

Assessment/Event Date ≤ Study Treatment Start Date

On-treatment is defined as time from first dose to last date plus 182 days.

Study Treatment Start Date < Assessment/Event Date ≤ Date of Last Dose of Study Treatment + 182 days

Post-treatment is defined as any time post on-intervention window, i.e. > last dose date plus 182 days.

Assessment/Event Date > Date of Last Dose of Study Treatment + 182 days

Assessments collected on the date of randomization, for which there is no time of assessment will be considered pre-intervention.

Assessments will be considered on-treatment if the assessment start date is missing.

6.3.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The efficacy reference date is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.3.4. Assessment Window

6.3.4.1. Visit Based Assessments

No assessment windows are defined for visit based assessments. Nominal visits will be used for all reporting and analysis. Further details on the mapping of unscheduled visits are provided in the Programming Specifications document.

6.3.4.2. Daily Diary

Participants are to complete a daily diary assessment each morning. Table 2 below displays which daily diary records are included for each analysis time period. Any daily diary data collected post the 52-week time period will not be included in the Weeks 49-52 analysis of diary data.

Table 2 Daily Diary Assessment Windows

Analysis for AM Measures		Analysis Time Period
Beginning Timepoint (Day)	Ending Timepoint (Day)	
-27	1	Baseline
2	29	Weeks 1 – 4
30	57	Weeks 5 – 8
58	85	Weeks 9 – 12
86	113	Week 13 – 16
114	141	Weeks 17 – 20
142	169	Weeks 21 – 24
170	197	Weeks 25 – 28
198	225	Weeks 29 – 32
226	253	Weeks 33 – 36
254	281	Weeks 37 – 40
282	309	Weeks 41 – 44
310	337	Weeks 45 – 48
338	365	Weeks 49 – 52

Note: There is no Day 0 in CDISC reporting. Days -27 to -1 are immediately pre-randomization and Day 1 is the day of randomization (Visit 2). For the baseline time period, all values from Day -27 to Day 1 will be included in the baseline average; however, there must be a minimum of 4 non-missing values from Day -6 to Day 1 inclusive in order to derive the baseline, otherwise it will be set to missing.

Note: For each 4-week post-baseline time period the average will only be derived if there are non-missing values for at least 4 days out of 7 in at least 3 out of 4 weeks, with at least 15 minimum values, otherwise it will be set to missing.

6.3.5. Multiple measurements at One Analysis Time Point

Unless otherwise specified, if there are multiple measurements reported under the same nominal visit and planned time, the value of the first assessment will be used in any derivation of summary statistics, all individual measurements will be presented in any data listings.

Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

6.3.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If month and year of start date = month and year of study intervention start date, then
  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
  • Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		• *If year of start date = year of study intervention start date, then* • *If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.* • *Else set start date = study intervention start date.* *Else set start date = January 1.*
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	**If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.** **Else if study intervention start date is not missing:** **If month and year of start date = month and year of study intervention start date, then** **If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.** **Else set start date = study intervention start date.** **Else set start date = 1st of month.**

Element	Reporting Detail	
	Missing start day and month	*If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.* *Else if study intervention start date is not missing:* *If year of start date = year of study intervention start date, then* *If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.* *Else set start date = study. intervention start date.* *Else set start date = January 1.*
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

6.3.7. Early PK Access Key Activities

Designated representative(s) may be unblinded for performing population PK, PKPD dataset preparation and draft PK, PKPD model development using scrambled (random reassignment of subject identification numbers) PK, PKPD unblinded datasets.

The PK and PKPD datasets will include information on PK concentration, actual dosing information, demographics (including race and ethnicity), vital signs, concomitant medications, antidrug antibodies, biomarkers (e.g. eosinophils and IL5 concentration) and laboratory information. No information on adverse event and efficacy will be included.

6.3.8. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

7. REFERENCES

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