Statistical Analysis Plan Amendment 3

Study ID: 206785

Official Title of Study: A 52-week, randomised, double-blind, double-dummy, parallel group,multi-centre, non-inferiority study assessing exacerbation rate, additional measures of asthma control and safety in adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with GSK3511294 compared with mepolizumab or benralizumab

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Division	:	Worldwide Development
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TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, double-dummy, parallel group, multi-centre, non-inferiority study assessing exacerbation rate, additional measures of asthma control and safety in adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with GSK3511294 compared with mepolizumab or benralizumab

Protocol Number: 206785

Compound Number: GSK3511294 (depemokimab)

Short Title: Non-inferiority study of GSK3511294 compared with mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype

Acronym: NIMBLE

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s).

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	03-Mar-2021	Amendment 1 01-Dec-2020	Not Applicable	Original version
2	26-Aug-2022	Amendment 1 01-Dec-2020	Section 1.1.2 Estimand: updated intercurrent event definition for change in maintenance therapy and use of prohibited medication to require classification of important protocol deviation.	Clarification. These will be defined as intercurrent events if classified as important protocol deviations.
			Section 3 Analysis Sets: Updated text related to enrolled, randomised, full analysis set, and safety population	Section 3 Analysis Sets: Updated text related to enrolled, randomised, full analysis set, and safety population
			Minor changes to outputs and terminology in	Clarifications

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			primary analysis Section 4.2. (i) p-value not reported for non-inferiority study, (ii) "tipping point" is "tipping point-style" for this study.	
			Clarification of intercurrents events handled with hypothetical strategy in Section 4.2.4 (supplementary analyses). These must be classified as important protocol deviations.	Clarifications
			Section 4.5.2: updated imputation method for non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification.	Correction of transformation.

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.4.8: added a summary of systemic corticosteroids use associated with clinically significant exacerbations	Update in order to include all type of corticosteroids use.
3	22 Feb 2024	Amendment 3 07-Dec-2023	Change strategy for handling important prohibited medications in primary estimand to treatment policy.	CCI [redacted] CCI and part of protocol amendment 2 update.
			Include reference to interim analysis for safety that will support submission.	Addition to protocol amendment 2
			Update to analysis set wording in Section 3.	Updated to match latest template and to account for site with GCP non-compliance.

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Inclusion of additional analyses on the FAS-modified analysis set	Inclusion of additional supplementary analyses.
			Remove the covariate of baseline maintenance OCS therapy throughout Section 4.	Covariate removed as not enough of the participants recruited were on maintenance OCS therapy at baseline. Also, part of protocol amendment 2 update.
			Minor corrections to description of tipping point methodology in Section 4.2.3	Correction of typos.
			Minor correction to baseline definition of daily endpoints in Table 3 and addition of a footnote.	Correction of error.

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Removal of references to a tipping point sensitivity analysis for the secondary endpoints.	Tipping point analysis not relevant to secondary endpoints as there is no hypothesis test. Also, part of protocol amendment 2 update.
			Additional subgroup analyses subsection added to Section 4.3.1.2	Include analyses of secondary endpoints by pre-study biologic treatment for asthma.
			Additional sentence added at end of 4.5.2.1	Reference to additional AE display for broad SMQ 'Torsade de pointes/QT Prolongation'
4	23 Jul 2024	Amendment 3 07-Dec-2023	Addition of Appendix 2	Provide information on Electronic Clinical Outcome Assessment (eCOA) compliance calculations.

1. INTRODUCTION

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on health-related quality of life (HRQoL) and additional efficacy assessments	• Weighted mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks • Weighted mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks • Weighted mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) calculated over 52 weeks
Other	
• To investigate depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on incidence of hospitalisation and/or Emergency Department (ED) visit and measures of asthma control, night sleep and lung function	• Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks • Time to first clinically significant exacerbationa • Change from baseline in the percentage of nights free from awakenings due to asthma symptoms requiring rescue medication use over 2-week periods • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in percentage of rescue medication-free 24-hour periods over 2-week periods • Mean number of days with OCS usage over 52 weeks • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • Change from baseline in pre-bronchodilator FEV1 at discrete timepoints during the 52-week period
CCI [redacted]	

Objectives	Endpoints
	• CCI [redacted] CCI [redacted] CCI [redacted]
• To investigate the PD effects of depemokimab	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to depemokimab

a. Clinically significant exacerbations will be defined as worsening of asthma requiring systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 4.2.1). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

1.1.2. Estimands

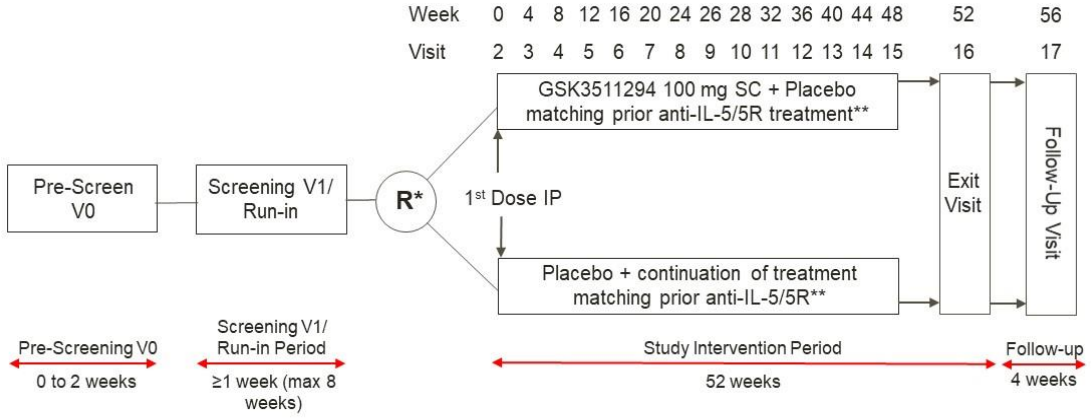
Primary and secondary objectives with associated estimand strategies are presented in Table 2. Estimands relating to other study objectives, where applicable, are described within each endpoint analysis in Section 4.

Table 2 Estimands for primary and secondary objectives

Objective	Estimand Category	Estimand			
		Endpoint	Population	Main Intercurrent Events Anticipated and Corresponding Strategies	Summary Measure
Primary Objective: To demonstrate non-inferiority of depemokimab +SoC compared to active comparator (mepolizumab or benralizumab) + SoC in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy.	Primary	Annualised rate of clinically significant exacerbations over 52 weeks	Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy.	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical • Change in maintenance therapy (excluding prohibited medication use listed in PDMP): treatment policy • Use of prohibited medication (listed in PDMP) which is classified as an important deviation: treatment policy	Exacerbation rate ratio for depemokimab +SoC compared to active comparator (mepolizumab or benralizumab) + SoC
	Supplementary 1 (Per-Protocol Style)		Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy in the population of participants who fulfill the main inclusion criteria of the study.	• Study intervention discontinuation (for any reason): hypothetical • Change in maintenance therapy (excluding prohibited medication use listed in PDMP): treatment policy • Use of prohibited medication (listed in PDMP) which is classified as an important deviation: hypothetical	

Objective	Estimand Category	Estimand			
		Endpoint	**Population**	**Main Intercurrent Events Anticipated and Corresponding Strategies**	**Summary Measure**
Secondary Objective: To evaluate depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on health-related quality of life (HRQoL) and additional efficacy assessments.	Primary	• Weighted mean (WM) change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks • Weighted mean (WM) change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks • Weighted mean (WM) change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) calculated over 52 weeks	Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy.	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical • Change in maintenance therapy (excluding prohibited medication use listed in PDMP): treatment policy • Use of prohibited medication (listed in PDMP) which is classified as an important deviation: treatment policy	Difference in mean WM change from baseline for depemokimab +SoC compared to active comparator (mepolizumab or benralizumab) + SoC
	Supplementary 1 (Per-Protocol Style)		Adult and adolescent participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy in the population of participants who fulfill the main inclusion criteria of the study.	• Study intervention discontinuation (for any reason): hypothetical • Change in maintenance therapy (excluding prohibited medication use listed in PDMP): treatment policy • Use of prohibited medication (listed in PDMP) which is classified as an important deviation: hypothetical	

1.2. Study Design

Overview of Study Design and Key Features
 ** R = Randomisation* *** Participants randomised to GSK3511294 will receive placebo treatment matching their prior anti-IL-5/5R medication while subjects randomised to receive placebo matching GSK3511294 will receive active treatment matching their prior anti-IL-5/5R (either mepolizumab 100 mg every 4 weeks or benralizumab 30 mg every 8 weeks). All injections will be administered by a prefilled safety syringe (PFS)*

Design Features	• Phase 3a • Non-inferiority study • 52-week intervention period • Adult and adolescent participants with an eosinophilic phenotype currently receiving either mepolizumab 100 mg SC or benralizumab 30 mg SC for at least 12 months prior to screening. Participants must have a documented benefit to their anti-IL-5/5R therapy on a SoC regimen of medium to high dose ICS and at least one other controller medication. • Active comparator controlled • Randomised • Double-blind • Double-dummy • Parallel group • Multi-centre • Pre-screening period: 0-2 weeks; screening/run-in period: 1-8 weeks; follow-up period: 4 weeks
Study intervention	• Participants will be randomized to: o **Depemokimab** 100mg SC administered every 26 weeks (total of 2 doses: week 0 and week 26) alongside placebo SC intervention matching the active comparator (participant's anti-IL-5/5R treatment prior to randomisation: either placebo matching mepolizumab every 4 weeks or placebo matching benralizumab every 8 weeks). Injections related to depemokimab/placebo at randomisation and Week 26 will be administered in the clinic via a PFS. o **Active comparator** according to the participant's treatment prior to randomisation (either mepolizumab every 4 weeks or benralizumab every 8 weeks) and placebo SC matching depemokimab administered every 26 weeks. All injections will be administered via a PFS. • 52-week intervention period • Participants will continue their baseline SoC asthma therapy throughout the study
Study intervention Assignment	• 1:1 randomisation ratio • Stratification factor: pre-study asthma biologic (mepolizumab or benralizumab)

Overview of Study Design and Key Features	
Interim Analysis	An independent data monitoring committee (IDMC) will periodically review unblinded safety data from the three Phase III studies in the program: 206713, 213744 and 206785, in accordance with the IDMC Charter. The IDMC will review all safety data, including AEs and serious adverse events (SAEs) and adverse events of special interest (AESI), laboratory parameters, including haematological and clinical chemistry parameters and ECG assessments from the three studies for identification of any potential safety signals. To provide benefit-risk context, the IDMC will also review limited efficacy data for the primary endpoint. The data analyses for the IDMC reviews will be performed by an independent statistician. As the study will be ongoing at the time of regulatory submission, an interim analysis will be performed in order to provide unblinded safety data in an interim Clinical Study Report (CSR) to inform on the risk-benefit assessment of depemokimab in asthma. The OPS (Output & Programming Specification) will detail the specific subset of outputs that will be included in the interim analysis and a separate document (Blinding Plan for NIMBLE Interim Analysis) will provide details on how the study integrity will be maintained.

2. STATISTICAL HYPOTHESES

The treatment comparison of depemokimab + SoC with active comparator (mepolizumab or benralizumab) + SoC on the primary endpoint of annualised rate of clinically significant exacerbations will be made in order to assess the primary objective of non-inferiority. The null hypothesis that the exacerbation rate ratio for depemokimab + SoC compared with active comparator (mepolizumab or benralizumab) + SoC is at least 1.28 will be tested at the one-sided 2.5% significance level i.e. non-inferiority will be met if the upper bound for the 95% confidence interval (CI) is less than 1.28. Should non-inferiority be met, the primary endpoint will then be tested for superiority at the 5% two-sided significance level.

2.1. Multiplicity Adjustment

A statistical hypothesis is provided only for the primary endpoint.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	• Study Population
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure). Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Randomised	All participants who were randomly assigned to study intervention in the study.	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention excluding participants from sites with GCP non-compliance/significant data integrity concerns. Data will be analysed according to randomised study intervention.	• Study Population • Efficacy • Safety • Pharmacodynamic
FAS-Modified	All randomised participants who receive at least one dose of study intervention. Data will be analysed according to randomised study intervention.	• Efficacy
FAS-Japan	All participants in the FAS who are enrolled from Japan and with Japanese heritage only	• Study Population • Efficacy • Safety • Pharmacodynamic
FAS-Non-Japan	All participants in the FAS who are not in FAS-Japan analysis set	• Pharmacodynamic
Important Entry Criteria (IEC)	Participants in FAS who met all key inclusion/exclusion/randomisation criteria as described in Section 2.3.1 of the OPS (Output & Programming Specification)	• Efficacy
IEC-Modified	Participants in FAS-modified who met all key inclusion/exclusion/randomisation criteria as described in Section 2.3.1 of the OPS (Output & Programming Specification)	• Efficacy
Safety	All randomised participants who receive at least one dose of study intervention excluding participants from sites with GCP non-compliance/significant data integrity concerns. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received. (Further details are given in Section 3.5.1 of the OPS). This population will serve as the primary population for analyses of safety endpoints.	• Safety
Safety-Modified	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received. (Further details are given in Section 3.5.1 of the OPS).	• Safety
Safety-Japan	All participants in the Safety analysis set who are enrolled from Japan and with Japanese heritage only	• Safety
Safety-Non-Japan	All participants in the Safety analysis set who	• Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
	are not in FAS-Japan analysis set	

Note: At the time of SAP approval, GCP non-compliance/significant data integrity concerns had been identified at Site 250366 and Site 250886. Any additional sites that are subsequently identified as having concerns significant enough to warrant exclusion from analysis sets will be documented prior to unblinding.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Full Analysis Set (FAS) and FAS-Japan will be used for study population, efficacy and pharmacodynamic analyses unless otherwise stated. The Safety and Safety-Japan analysis sets will be used for safety analyses.

Continuous data that is normally distributed will be summarised using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Continuous data that is non-normally distributed will be summarised with geometric mean, SD of logs, median, minimum and maximum. Categorical data will be summarised as the number and percentage of participants in each category. Confidence intervals will use 95% confidence intervals unless otherwise specified.

Randomisation is stratified by pre-study biologic treatment for asthma (mepolizumab or benralizumab). All statistical models will include a categorical covariate for pre-study biologic treatment for asthma.

Where statistical models are used, if there are important departures from the distributional assumptions, transformations of covariates or alternative models may be explored as supporting analyses.

4.1.2. Baseline Definition

Baseline values for visit based assessments and eDiary assessments are defined in Table 3.

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

Table 3 Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy, Health Outcomes and Other			
SGRQ total score		X	Day 1 pre-dose (visit 2)
ACQ-5 score	(X)[a]	X	Day 1 pre-dose (visit 2)
Pre-bronchodilator FEV1		X	Day 1 pre-dose (visit 2)
Percentage of nights free from awakenings		X (daily)	Average of measurements from Day -6 to Day 1 inclusive (at least 4 days must be

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
due to asthma symptoms requiring rescue medication use			non-missing)
Morning PEF		X (daily)	Average of measurements from Day -6 to Day 1 inclusive (at least 4 days must be non-missing)
Daily asthma symptom score		X (daily)	Average of measurements from Day -6 to Day 1 inclusive (at least 4 days must be non-missing)
Percentage of rescue medication-free 24-hour periods		X (daily)	Average of measurements from Day -6 to Day 1 inclusive (at least 4 days must be non-missing)
Mean number of occasions of rescue medication use/day		X (daily)	Average of measurements from Day -6 to Day 1 inclusive (at least 4 days must be non-missing)
CCI [redacted]			
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
Clinical Chemistry	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
Hematology with differential (including eosinophil count)	X	X	Most recent individual value prior to first dose of study treatment
Complement C3 and C4		X	Day 1 pre-dose (visit 2)
Immunogenicity		X	Day 1 pre-dose (visit 2)

NOTES:

- There is no Day 0 in CDISC reporting. Day -1 is the day immediately before the date of randomization and Day 1 is the day of randomization.
- [a] ACQ-5 may be conducting at Screening if need to meet inclusion criteria 3 (documented benefit of ant-IL-5/5R therapy)
- Only records that have been assigned a treatment phase of 'pre-treatment' will be considered as baseline assessments.
- Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

4.1.3. Multicentre Studies

This is a global, multicentre study. Enrolment will be presented by site and country. Endpoints that are statistically modelled will include a covariate of region (Europe, US, Rest of the World).

Region	Countries
Europe	UK, Germany, France, Italy, Spain, Poland, Austria, Finland, Slovenia, Norway, Switzerland, Sweden, Netherlands, Ireland, Portugal.
US	US
Rest of the World	Japan, Canada, Australia, Taiwan, Israel, Puerto Rico.

4.2. Primary Endpoint/Estimand Analysis

4.2.1. Definition of endpoint

The primary endpoint is the annualised rate of clinically significant exacerbations over 52 weeks

Clinically significant exacerbations of asthma are defined by:

Worsening of asthma which requires use of systemic CSs1 and/or hospitalisation and/or

Emergency Department (ED) visit.

1For 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 recorded in the eCRF are considered as verified clinically significant exacerbations and will be included in the primary analysis.

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

exacerbation.

4.2.2. Main analytical approach

Endpoint

- Annualised rate of clinically significant exacerbations over 52 weeks

Model Specification

- A negative binomial model will be used. The number of events will be modelled with the log link function and an offset used for logarithmic length of time in the study in years.
- The covariates to be included in the model

Type	Variable
Continuous	• Baseline pre-bronchodilator % predicted FEV1
Categorical	• Treatment group (depemokimab, active comparator) • Pre-study biologic therapy for asthma (mepolizumab, benralizumab) • Region (Europe, US, Rest of the World) • Number of exacerbations in the year prior to the study (0, 1, 2+)
Offset	• Log_e(Length of time in the study in years)

Model Checking & Diagnostics

- The fit of the negative binomial generalised linear model will be investigated by calculating standardised deviance residuals and plotting these on a "Q-Q" plot with simulation-generated tolerance boundaries

Endpoint

Anticipated key intercurrent events

ICE	Strategy
Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic	Treatment policy
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	Hypothetical
Change in maintenance therapy (excluding prohibited medication use listed in PDMP)	Treatment policy
Use of prohibited medication (listed in PDMP) which is classified as an important deviation	Treatment policy

Handling of missing data and data excluded due to intercurrent events

Reason for missing/excluded data	Assumption	Details
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	Negative binomial model assumes data is MAR directly through the likelihood. Data up until study withdrawal and/or study intervention discontinuation due to reasons related to the COVID-19 pandemic will be included in the analysis.
Study withdrawal		

Results Presentation

- The number of exacerbations that each participant experienced will be summarised along with the proportion of participants in each category.
- The percentage of participants experiencing at least one exacerbation will be summarised by treatment group
- Model-adjusted exacerbation rate ratio and 95% confidence interval for depemokimab compared to active comparator (mepolizumab or benralizumab)
- Annualised exacerbation rates and 95% confidence intervals for each treatment group will be estimated using the observed margins in the analysis dataset.

Subgroup Analyses

- Separate models will be fitted to each subgroup of pre-study biologic treatment for asthma (mepolizumab, benralizumab)
  - For each subgroup, the model-adjusted exacerbation rate ratio and 95% confidence interval for depemokimab compared to active comparator will be presented
  - For each subgroup, model-adjusted annualised exacerbation rates and 95% confidence intervals for each treatment group will be estimated using the observed margins in the analysis dataset will be presented.

Additional Analysis

- The primary analysis will be repeated for the FAS-modified analysis set (including participants from sites with GCP non-compliance/significant data integrity concerns)

4.2.3. Sensitivity analyses

For the main analytical approach, data that is missing due to study withdrawal is assumed to be missing at random. The aim of sensitivity analyses is to assess the robustness in the treatment effect and conclusion in the main analytical approach when departing from the missing at random assumption. Two methods will be used to investigate this:

Sensitivity analysis 1 (MNAR based on off-treatment data only): basing the unobserved/excluded period of data on off-treatment data (data collected from participants who have discontinued intervention). This analysis may not be conducted if it is deemed there is not enough off-treatment data collected to provide effective imputation. If the total unobserved/excluded time in the study is <3% of the total study

duration time, or if <50% of the total off-treatment period is observed, then the analysis may not be conducted.

Sensitivity analysis 2 (delta method/tipping point-style): assumes participants in the period following withdrawal from the study have, on average, a higher or lower exacerbation rate than during the period of time within the study. A value of delta is added to the exacerbation rate in the period in which data is included in the analysis to demonstrate this change in efficacy.

The assumption for data following study intervention discontinuation due to reasons related to the COVID-19 pandemic will remain MAR.

Endpoint			
• Same as main analytical approach (see Section 4.2.2)			
Model Specification			
• Same as main analytical approach (see Section 4.2.2)			
Handling of missing data and excluded data due to intercurrent events			
Sensitivity Analysis #	**Reason for missing/excluded data**	**Assumption**	**Details**
#1 Off-treatment data	Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	Each participant's time in the study (52 weeks) is divided into 3 periods: on-treatment when data is collected (period 1), off-treatment when data is collected (period 2) and missing (due to study withdrawal) (period 3). Note: data excluded due to study intervention discontinuation due to reasons related to the COVID-19 pandemic will fall into period 3 but will be handled separately. The steps are described after the off-treatment imputation method. The number of exacerbations occurring in period 3, for which data is either not observed or excluded (based on the estimand strategy), is based on the rate in period 2 (off-treatment data). To implement the imputation step, a Poisson-gamma model can be fitted to the count data in a Bayesian framework with non-informative priors on all parameters where the number of exacerbations (y_{ij}) follows a Poisson distribution with a rate that is specific to each participant (*i*) and period (*j*) (λ_{ij}). Covariates in the model will be those included in the main analytical approach plus an interaction term between treatment group and period, where period is equal to 1 for the on-treatment period and 2 for both the off-treatment and missing/excluded periods plus a participant-specific random effect with a gamma distribution (s_i). There interaction term means that off-treatment rates are estimated for treatment arms separately. If there is limited off-treatment data to provide effective imputation then the model may be fitted without the interaction term (treatment group and period are just main effects) to pool the off-treatment
	Study withdrawal	MNAR (off-treatment data) [Keene, 2014; Roger, 2018]	

Endpoint			
			rate across treatment arms. $y_{ij} = Poisson(\lambda_{ij} t_{ij})$ $\log(\lambda_{ij}) = X_{ij}\beta + s_i$ where t_{ij} is the length of time for participant *i* in period *j*. A series of independent samples from the model parameters (β) posteriors will be drawn, one for each imputed dataset (minimum 1000). The annualised rate for each participant in the missing/excluded period is then predicted. This rate is then multiplied by the length of time for this period and the number of exacerbations is sampled from the Poisson distribution. As an alternative to the Poisson-gamma model, a negative multinomial model can be fitted [Roger, 2008]. **Note**: if data is excluded due to study intervention discontinuation due to reasons related to the COVID-19 pandemic period then the assumption for this period will remain MAR (on and off-treatment data). The imputation steps will be the same as described above except the model will assume that both on- and off-treatment periods have the same rate (there will be no period term in the model). Thus, the same rate as assumed throughout the duration of the study. The imputations are combined with the observed data to form complete datasets. A participant's total number of exacerbations during the study will be summed: $y_{i1} + y_{i2} + y_{i3} = Y_i$. The primary analysis model (described in 4.2.2) will be fitted to each of these completed datasets to give an estimate and standard error. The results will then be combined using Rubin's rules to give a final estimate and 95% confidence interval.
#2 Delta method / tipping point-style	Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	This sensitivity analysis assumes that participants in the period following withdrawal from the study have, on average, higher or lower exacerbation rates than otherwise. The exacerbation rate for this missing/excluded data will be increased or reduced by a value of delta beyond that in the main analytical approach MAR assumption. A Poisson-gamma model (described in the MNAR off-treatment analysis) can be fitted without the interaction term between treatment group and period (since on and off-treatment periods are treated in the same way no term for period will be in the model). The imputations for the missing/excluded period then follow as described above from the Poisson distribution. Following imputation, a value of delta will be added/subtracted. No delta will be added to data imputed following the
	Study withdrawal	Delta method/Tipping point-style [Roger, Akacha, 2014; Keene, 2014]	

Endpoint			
			ICE of study intervention discontinuation due to reasons related to the COVID-19 pandemic. The assumption for this data remains MAR. The primary analysis model (described in 4.2.2) will be fitted to each of these completed datasets to give an estimate and standard error. The results will then be combined using Rubin's rules to give a final estimate and 95% confidence interval. The modelling, imputation and analysis methods described above will be repeated for a range of delta values applied to treatment arms independently (i.e. δ_1 to the active comparator arm and δ_2 to depemokimab). This will result in an estimate and standard error for each combination of δ_1 and δ_2. The results will be presented. Specifically, a heat map plot with the range of deltas added/subtracted to each treatment arm on the x and y-axes will be presented. For each delta combination the upper bound of the 95% CI will be given on the respective coordinate, along with a colour gradient representing the magnitude of the upper bound. A tipping point is the delta (δ_1 and δ_2) combination that result in non-inferiority being declared to not. **Alternative model based on negative trinomial [Keene, 2014]**: Conditional on a participant's withdrawal time, the number of exacerbations before and after withdrawal/ICE can be modelled under a MAR assumption as having a joint negative trinomial distribution. [Keene et al, 2014]. The missing/excluded data can be imputed using this model. In the delta method, a fixed delta value is added to the annualised rate prior to the sampling of imputed values in the unobserved/excluded period. To implement this, the model in the main analytical approach will be fitted in a Bayesian framework with non-informative priors on all parameters. A series of independent samples from the model parameters (β) posteriors will be drawn, one for each imputed dataset (minimum 1000). Using the posterior samples, the expected annualised exacerbation rate before and after withdrawal/ICE is estimated for each participant. These estimates, along with the length of time following withdrawal/exclusion until the end of the study, the observed response prior to withdrawal/ICE and the dispersion parameter are used to update the negative binomial parameters for the unobserved/excluded period (from which the participant's number of exacerbations is sampled from):

Endpoint			
			$k^* = k + y_1$ k *is inverse of dispersion* y_1 *is the observed count* $p^* = \frac{k + \hat{y}_1}{k^* + \hat{y}_1 + \hat{y}_2}$ $\hat{y}_1 =$ *pred rate during the obs period* $\hat{y}_2 =$ *pred rate during the unobs period* To apply the delta method, a pre-specified delta value will be added to the predicted annualised rate for the unobserved/excluded period ($\hat{y}_2$) **before** sampling the imputed values.
Results Presentation			
• Exacerbation rate ratio and 95% confidence interval for depemokimab compared to active comparator (following back-transformation on to the original scale) • Annualised exacerbation rates and 95% confidence intervals for each treatment group will be estimated using the observed margins from the analysis dataset.			

4.2.4. Supplementary analyses

A supplementary estimand will be conducted by **handling both the intercurrent event of study intervention discontinuation (for any reason) and the intercurrent event of prohibited medication use with a hypothetical strategy**. The strategy for dealing with the intercurrent event of change in maintenance therapy will remain the same as described for the main estimand. In the spirit of a per protocol analysis, this estimand targets the treatment effect in the absence of study intervention discontinuation and use of prohibited medication in the population of participants who fulfil the main inclusion criteria of the study. **Intercurrent events (classified as important protocol deviations that would affect the primary endpoint) that emerge during the study will also be dealt with using a hypothetical strategy. Important protocol deviations handled using a hypothetical strategy are listed in Section 2.3.1 of the Output and Programming Specification (OPS)**. Data for the period following the intercurrent event will be excluded and assumed MAR (using on and off-treatment data). Sensitivity analyses (MNAR off-treatment data and delta method/tipping point-style) will be conducted as described in the main estimand. Protocol deviations will be captured throughout the study (as described in the protocol deviation management plan (PDMP)). Decisions to exclude data due to a protocol deviation will be made by the study team and documented prior to freezing the database.

4.3. Secondary Endpoints/Estimands Analyses

4.3.1. Weighted mean (WM) change from baseline in SGRQ total score / ACQ-5 score / pre-bronchodilator FEV1 over 52 weeks

4.3.1.1. Definition of endpoints

- Weighted mean (WM) change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks **(calculated over weeks 4, 12, 26, 52)**
- Weighted mean (WM) change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks **(calculated over weeks 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48, 52)**
- Weighted mean (WM) change from baseline in pre-bronchodilator forced expiratory volume **(calculated over weeks 12, 26, 40, 52)**

Derivation of weighted mean (WM)

- WM will be calculated using the linear trapezoidal rule (see formula below).
- The WM will be calculated as the $AUC_{(tf-tl)}$ divided by the t_f- t_l weeks time interval for each participant (t_f = time of first observation, t_l = time for last observation).

$$\text{WM}\ (f-l) = \frac{1}{2}\sum_{f-l}\frac{(C_{i+1}+C_i)(t_{i+1}-t_i)}{t_f - t_l}$$

where,

C_i = Change from baseline value at timepoint I
t_i = Time in weeks for planned relative time point i
i = planned relative time
f = first I
l = last I

If an observation is missing between two non-missing observations (non-monotone missingness), the AUC will be linearly interpolated between the two non-missing values i.e., the participant's profile will be assumed to be linear between the two available values.

4.3.1.2. Main analytical approach

Endpoint	
• WM change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks **(calculated over weeks 4, 12, 26, 52)** • WM change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks **(calculated over weeks 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48, 52)** • WM change from baseline in pre-bronchodilator forced expiratory volume 1 (FEV1) **(calculated over weeks 12, 26, 40, 52)**	
Model Specification	
• An analysis of covariance (ANCOVA) model will be used. • The covariates to be included in the model:	
Type	**Variable**

Endpoint

Continuous	• Baseline (as described in Section 4.1.2 for each endpoint) • Baseline pre-bronchodilator % predicted FEV1 *(for ACQ-5 and SGRQ endpoints only)*
Categorical	• Number of exacerbations in the year prior to the study (0, 1, 2+) • Treatment group (depemokimab, active comparator) • Pre-study biologic therapy for asthma (mepolizumab, benralizumab) • Region (Europe, US, Rest of the World)

- Two models will be fitted to each endpoint: one with a response variable of change from baseline and one with the response variable as the absolute value

Model Checking & Diagnostics

- Residuals should be normally distributed (assessed with a histogram or normal probability plot). Residuals and fitted values should be uncorrelated (assessed by plotting against each other and should appear random with no structure). The same plot can be used to examine if there is constant variance.

Anticipated key intercurrent events

ICE	Strategy
Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic	Treatment policy
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	Hypothetical
Change in maintenance therapy (excluding prohibited medication use listed in PDMP)	Treatment policy
Use of prohibited medication (listed in PDMP) which is classified as an important deviation	Treatment policy

Handling of missing data and excluded data due to intercurrent events

Reason for missing/excluded data	Assumption	Details
Study intervention discontinuation due to reasons related to the COVID-19 pandemic Study withdrawal	MAR (on- and off-treatment data)	Multiple imputation will be implemented via a series of linear regression models (the imputation model differs from the analysis model described in above) where the dependent variable is the value for a specific timepoint and the independent variables are the covariates specified in the analysis model (ANCOVA) along with any earlier timepoints i.e. the values at previous timepoints are used to predict the value at the timepoint, along with any baseline covariates. Models will be fit separately for treatment arms with the linear predictor: $\mu_{i,j} = \alpha_{j,0} + \sum_{k=0}^{k=j-1} \beta_{j,k} y_{i,k} + \sum_{l=1}^{p} \alpha_{j,l} X_{i,l}$ where $y_{i,j} \sim N(\mu_{i,j}, \sigma_j)$ where i specifies the participant, j specifies the timepoint, p is the number of baseline covariates and $X_{i,l}$ is the value of covariate l for participant i in the primary analysis model. This model will be fitted in a Bayesian framework (assuming non-informative priors for the regression coefficients and the residual variance σ_j) and a posterior sample of at least $M = 1000$ iterations of the model parameters α_j's, β_j's and σ_j will be extracted (to correspond to the number of times M multiple imputation will occur). For each participant with missing/excluded values, the calculation of

Endpoint		
		the posterior predicted mean of the missing data given the observed data and covariates will occur chronologically i.e. the earliest missing/excluded predicted mean will be calculated first. Then the missing value for that visit will then be imputed by randomly drawing from a normal distribution (see below). The next earliest posterior predicted mean for the missing/excluded value will be calculated based on the extracted model parameters and observed (+ imputed) data. For example, consider a participant that has monotone missing data from Week 13 onwards (Week 13 being the earliest non-baseline assessment). At imputation $m = 1, \dots, M$, the posterior predictive mean for their Week 13 value, given covariates and baseline value, is: $\mu_{i,1}^{(m)} = \alpha_{1,0}^{(m)} + \beta_{1,0}^{(m)} y_{i,0} + \sum_{l=1}^{p} \alpha_{1,l}^{(m)} X_{i,l}$ The m^{th} imputed value will be a random draw $y_{i,1}^{(m)} \sim N\left(\mu_{i,1}^{(m)}, \sigma_1^{(m)}\right)$. The predicted mean for their Week 26 (the next earliest timepoint) value is: $\mu_{i,2}^{(m)} = \alpha_{2,0}^{(m)} + \beta_{2,0}^{(m)} y_{i,0} + \beta_{2,1}^{(m)} y_{i,1}^{(m)} + \sum_{l=1}^{p} \alpha_l X_{i,l}$ The imputed value would be sampled from the normal distribution $y_{(i,2)}^{(m)} \sim N\left(\mu_{i,2}^{(m)}, \sigma_2^{(m)}\right)$. This process would continue chronologically for monotone missingness. This will result in M complete datasets made up of data included under the estimand strategy and data imputed. The summary measure of WM will then be derived using the calculation described in Section 4.3.1.1 to each participant in each imputed dataset. The analysis model will be applied to each of these imputed datasets to obtain estimates of the parameter of interest and associated standard error. These will be combined using Rubin's rules to give final estimates.
Results Presentation		
• Summary statistics for change from baseline and absolute response will be presented by timepoint and treatment group including mean, SD and 95% CI • Summary statistics will be presented for WM change from baseline and WM absolute response by treatment group • Model-adjusted estimate for the difference in mean WM change from baseline for depemokimab compared to active comparator will be provided alongside 95% confidence interval • Model-adjusted estimates for the mean and 95% confidence interval (for both WM change from baseline and WM absolute response) for each treatment group will be estimated using the observed margins from the analysis dataset.		
Subgroup Analyses		
• Separate models will be fitted to each subgroup of pre-study biologic treatment for asthma (mepolizumab, benralizumab) ○ For each subgroup, model-adjusted estimate for the difference in mean WM change from baseline for depemokimab compared to active comparator will be provided alongside 95% confidence interval. ○ For each subgroup, model-adjusted estimates for the mean and 95% confidence interval (for both WM change from baseline and WM absolute response) for each		

Endpoint
treatment group will be estimated using the observed margins from the analysis dataset.
Additional Analyses
• The main analysis for each secondary endpoint will be repeated for the FAS-modified analysis set (including participants from sites with GCP non-compliance/significant data integrity concerns)

4.3.1.3. Sensitivity analyses

Endpoint

- Same as main analytical approach (see Section 4.3.1.2)

Model Specification

- Same as main analytical approach (see Section 4.3.1.2)

Handling of missing data and excluded data due to intercurrent events

Sensitivity Analysis #	Reason for missing/excluded data	Assumption	Details
#1 Off-treatment data	Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	The imputation process will be as described in main analytical approach (Section 4.3.1.2).
	Study withdrawal	MNAR (off-treatment data)	This analysis may not be conducted if it is deemed there is not enough off-treatment data collected to provide effective imputation. If the proportion of off-treatment and unobserved/excluded data in the study is <3% of the total or if <50% of the total off-treatment data is observed then the analysis may not be conducted. The approach will be similar to that described in the main analytical approach with some key modifications. Data will fall into three categories: collected on-treatment, collected off-treatment and missing/excluded. Off-treatment data will be used as a basis for data that is missing/excluded. To impute missing/excluded data based on off-treatment data, the imputation should occur chronologically i.e. starting with imputing the first timepoint j with missing/excluded data. The imputation model will be similar to the one described above, but it will include an additional term $\gamma_j z_{i,j}$, where $z_{i,j} = 0$ if visit j of subject i occurred on-treatment and $z_{i,j} = 1$ if it occurred off-treatment. To calculate the posterior predictive mean $\mu_{i,j}$ for subjects with missing $y_{i,j}$, the value of $z_{i,j}$ will be set to 1 to implement the assumption that the missing value is similar to other data collected off-treatment. Note: if there is limited off-treatment data to provide effective imputation then the model may be fitted without the interaction term (treatment group and period are just main effects) to pool the off-treatment estimate across treatment arms.

			Following the imputation steps, all data (including under the estimand strategy and imputed) will be combined to make 1000s of complete datasets. Data will be imputed as MAR (on and off-treatment) for the ICE of study intervention discontinuation due to reasons related to the COVID-19 pandemic and will follow the same process described in the main analytical approach (Section 4.3.1.2). Data imputed here under the MAR assumption will replace the data for the same participants described in the MNAR imputation above. As a result, the final completed datasets will be made up of data imputed as MNAR (off-treatment data) for missing data due to study withdrawal and data imputed as MAR (on and off-treatment data) for data excluded due to study intervention discontinuation due to reasons related to the COVID-19 pandemic. The summary measure of WM will then be derived using the calculation described in Section 4.3.1.1 to each participant in each dataset. The analysis model described in the main analytical approach will be applied to each of these datasets to obtain multiple estimates of the mean and standard error. These will be combined using Rubin's rules to give final estimates.

Results Presentation

- Model-adjusted estimate for the difference in mean WM change from baseline for depemokimab compared to active comparator will be provided alongside 95% confidence interval
- Model-adjusted estimates for the mean and 95% confidence interval (for both WM change from baseline and WM absolute response) for each treatment group will be estimated using the observed margins from the analysis dataset

4.3.1.4. Supplementary analyses

A supplementary estimand will be conducted by **handling both the intercurrent event of study intervention discontinuation (for any reason)** and the intercurrent event of prohibited medication use **with a hypothetical strategy**. The strategy for dealing with the intercurrent event of change in maintenance therapy will remain the same as described for the main estimand. In the spirit of a per protocol analysis, this estimand targets the treatment effect in the absence of study intervention discontinuation and use of prohibited medication in the population of participants who fulfil the main inclusion criteria of the study. **Intercurrent events (classified as important protocol deviations that would affect the primary endpoint) that emerge during the study will also be dealt with using a hypothetical strategy. Important protocol deviations handled using a hypothetical strategy are listed in Section 2.3.1 of the Output and Programming Specification (OPS)**. Data for the period following the intercurrent event will be excluded and assumed MAR (using on and off-treatment data). Sensitivity

analyses (MNAR off-treatment data) will be conducted as described in the main estimand. Protocol deviations will be captured throughout the study (as described in the protocol deviation management plan (PDMP)). Decisions to exclude data due to a protocol deviation will be made by the study team and documented prior to freezing the database.

4.4. Other Endpoints Analyses

4.4.1. Annualised rate of exacerbations requiring hospitalisation and/or ED visit

Endpoint

- Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

Model Specification

- See main analytical approach for primary endpoint (see Section 4.2.2)

Model Checking & Diagnostics

- See main analytical approach for primary endpoint (see Section 4.2.2)

Anticipated key intercurrent events

ICE	Strategy
Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic	Treatment policy
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	Hypothetical
Change in maintenance therapy (excluding prohibited medication use listed in PDMP)	Treatment policy
Use of prohibited medication (listed in PDMP) which is classified as an important deviation	Treatment policy

Handling of missing data and data excluded due to intercurrent events

Reason for missing/excluded data	Assumption	Details
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	Negative binomial model assumes data is MAR directly through likelihood. Data up until study withdrawal and/or study intervention discontinuation due to reasons related to the COVID-19 pandemic will be included in the analysis.
Study withdrawal		

Results Presentation

- The number of exacerbations requiring hospitalisation and/or ED visit that each participant experienced will be summarised along with the proportion of participants in each category.
- The percentage of participants experiencing at least one exacerbation requiring hospitalisation and/or ED visit will be summarised by treatment group
- Model-adjusted rate ratio and 95% confidence interval for depemokimab compared to active comparator (mepolizumab or benralizumab)
- Annualised rates and 95% confidence intervals for each treatment group will be estimated using the observed margins in the analysis dataset.

4.4.2. Time to first clinically significant exacerbation

Endpoint

- Time to first clinically significant exacerbation (defined in 4.2.1)

Model Specification

- A Cox proportional hazards model will be used.
- The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used.

Covariates to be included in the model:

Type	Variable
Continuous	• Baseline pre-bronchodilator % predicted FEV1
Categorical	• Number of exacerbations in the year prior to the study (0, 1, 2+) • Treatment group (depemokimab, active comparator) • Pre-study biologic therapy for asthma (mepolizumab, benralizumab) • Region (Europe, US, Rest of the World)

Model Checking & Diagnostics

- To assess the proportional hazards assumption, plot the log-cumulative hazard log(-log(S(t))) against time to observe if the two lines are broadly parallel.
- A plot of Schoenfield residuals vs. time (or log(time)) can be examined graphically for departures from the proportional hazards assumption. A large residual indicates that the event that occurred is unlikely under the model.
- Deviance residuals or Martingale residuals can be used to assess model fit.

Anticipated key intercurrent events

ICE	Strategy
Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic	Treatment policy
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	Hypothetical
Change in maintenance therapy (excluding prohibited medication use listed in PDMP)	Treatment policy
Use of prohibited medication (listed in PDMP) which is classified as an important deviation	Treatment policy

Handling of missing data and data excluded due to intercurrent events

Reason for missing/excluded data	Assumption	Details
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	Participants who withdraw from the study or discontinue study treatment due to reasons related to the COVID-19 pandemic will be censored. A censoring at random (CAR) assumption will be made. Analysis model is Cox regression, compatible with CAR, therefore no imputation is needed.
Study withdrawal		

Results Presentation

- Kaplan Meier estimates and 95% CI over time by treatment group will be presented.
- Hazard rate ratio and 95% confidence interval for depemokimab compared to active comparator

4.4.3. Change from baseline in SGRQ total score / ACQ-5 score / pre-bronchodilator FEV1 at discrete timepoints during the 52-week period

Endpoint

- Change from baseline in SGRQ total score at discrete timepoints during the 52-week period **(weeks 4, 12, 26, 52)**
- Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period **(weeks 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48, 52)**
- Change from baseline in pre-bronchodilator FEV1 at discrete timepoints during the 52-week period **(weeks 12, 26, 40, 52)**

Model Specification

- A repeated measures mixed model (MMRM) will be used.
- The response variable will be values at the discrete timepoints.
- An unstructured variance-covariance matrix will be used by first intent. In the event that the model fails to converge alternative correlations may be considered. If alternative structures are considered, the model with the smallest Akaike's Information Criterion (AICC) may be used.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used
- Covariates to be included in the model:

Type	Variable
Continuous	• Baseline (as described in Section 4.1.2 for each endpoint) • Baseline % predicted FEV1 *(for ACQ-5 and SGRQ endpoints only)* • Baseline by visit interaction
Categorical	• Number of exacerbations in the year prior to the study (0, 1, 2+) • Treatment group (depemokimab, active comparator) • Pre-study biologic therapy for asthma (mepolizumab, benralizumab) • Region (Europe, US, Rest of the World) • Visit • Visit by treatment group interaction

- Two models will be fitted to each endpoint: one with a response variable of change from baseline and one with the response variable as the absolute value

Model Checking & Diagnostics

- Residuals should be normally distributed (assessed with a histogram or normal probability plot). Residuals and fitted values should be uncorrelated (assessed by plotting against each other and should appear random with no structure). The same plot can be used to examine if there is constant variance.

Anticipated key intercurrent events

ICE	Strategy
Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic	Treatment policy
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	Hypothetical
Change in maintenance therapy (excluding prohibited medication use listed in PDMP)	Treatment policy
Use of prohibited medication (listed in PDMP) which is classified as an important deviation	Treatment policy

Endpoint		
Handling of missing data and data excluded due to intercurrent events		
Reason for missing/excluded data	**Assumption**	**Details**
Study intervention discontinuation due to reasons related to the COVID-19 pandemic	MAR (on- and off-treatment data)	MMRM applies MAR directly through the likelihood
Study withdrawal		
Results Presentation		
• Model-adjusted estimate for difference in mean change from baseline and 95% confidence interval for depemokimab compared to active comparator at each discrete timepoint will be presented. • Model-adjusted estimates for the mean and 95% confidence interval (for both change from baseline and absolute response) for each treatment group at each timepoint will be estimated using the observed margins from the analysis dataset and will be presented.		

4.4.4. Change from baseline in the percentage of nights free from awakenings due to asthma symptoms requiring rescue medication over 2-week periods

Participant level data will be aggregated over 2-week intervals. A 2-week interval will be evaluable if, for that interval, 8 out of 14 days is non-missing.

Summary statistics will be presented by treatment group and time interval.

4.4.5. Change from baseline in morning peak expiratory flow (PEF) 2-week mean

See Section 4.4.4. Separate outputs will be produced for:

- all data included in the Full Analysis Set
- excluding data where asthma medication was taken up to 6 hours prior to spirometry assessment

4.4.6. Change from baseline in daily asthma symptom score 2-week mean

See Section 4.4.4.

4.4.7. Change from baseline in percentage of rescue medication-free 24-hour periods over 2-week periods

See Section 4.4.4.

4.4.8. Mean number of days with OCS usage over 52 weeks

The following will be summarised by treatment group:

- The number of days with OCS usage associated with an exacerbation **per exacerbation**
- The number of days with OCS usage associated with an exacerbation **per participant**
- The number of participants experiencing a clinically significant exacerbation
- The number of participants experiencing a clinically significant exacerbation treated with OCS
- The total number of days with use of OCS associated with clinically significant exacerbations.

In addition, mean number of days with systemic corticosteroids will be summarised in the same way.

CCI

CCI

4.4.12. Ratio to baseline in absolute blood eosinophil count

- Separate summaries will be provided by pre-study biologic for asthma (mepolizumab or benralizumab) because the different mechanisms of actions are known to result in different pharmacological effects between mepolizumab and benralizumab.
- Absolute and ratio to baseline will be summarised by each timepoint (**weeks 4, 8, 12, 20, 26, 28, 40, 48, 52**) and treatment group
- Summary statistics will be presented (geometric mean, 95% CI, SD of logs, median, min, max).
- Any zero values will be imputed with a small constant (value of 0.005) prior to log transformation.

4.5. Safety Analyses

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

All safety analyses will be produced displaying 4 columns (depemokimab, active comparator, mepolizumab, benralizumab).

4.5.1. Extent of Exposure

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 follows:

Study intervention	Duration of exposure (days)
Mepolizumab	Day of last dose – Day of first dose + 28 days
Benralizumab	Day of last dose – Day of first dose + 56 days
Depemokimab	Day of last dose – Day of first dose + 182 days

Subject years of exposure will be calculated as duration of exposure (days) divided by 365.25.

Extent of exposure will only be calculated should the participant receive at least one active (depemokimab, benralizumab, mepolizumab) administration. Participants that have only received placebo-matching administrations will not have exposure calculated.

The exposure summary will also be presented by age subgroup (12-17, 18-64, ≥65).

4.5.2. Adverse Events

Adverse events including the analysis of adverse events (AEs), serious AEs (SAEs), and other significant AEs will be based on GSK Core Data Standards.

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, study intervention related AEs leading to 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. These summaries will also be produced by age subgroup (12-17, 18-64, ≥65). Common (>=3%) AEs will be summarised by overall frequency and summarised by time to onset.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

The frequency and percentage of AEs will be summarised in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT), where exposure-adjusted incidence rate will also be summarised. 2) in descending order by PT only.

A summary will be provided for study intervention-related AEs. 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. The summary table will be displayed by SOC and PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary tables will be displayed by SOC and PT.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing. The summary table will be displayed in descending order by SOC and PT.

4.5.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for the depemokimab program include:

- Allergic reactions including anaphylaxis

Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (See Protocol Appendix 8).

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

AESI reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Vasculitis events and local injection site reactions are also collected via targeted eCRF within the study.

Separate summary tables showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created.

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.

The relative risk of each AESI (excluding QTc prolongation) between depemokimab and each active comparator (mepolizumab, benralizumab) with 95% confidence intervals will also be presented.

AESI of QTc prolongation will be summarised as detailed in 4.5.3.3.

Two additional outputs will be produced that separate events by active and placebo-matching injections. For injection site reactions, each treatment group will be separated by active and placebo-matching injections. In addition, for systemic reactions reported on the day of dosing, each treatment group will be separated by active and placebo-matching injections at all visits with study drug administration with the exception of Week 0 (visit 2) where systemic reactions will be listed for both injections.

An additional output will be produced to summarize AEs within the broad SMQ 'Torsade de pointes/QT Prolongation'. The display will include both an "Any Event" row and the individual PTs.

4.5.2.2. Additional Adverse Event Outputs on Safety-Modified Analysis Set

The following additional safety analysis will be provided on Safety-Modified analysis set:

- Overview of all adverse events (including sites with GCP non-compliance/significant data integrity concerns)
- Summary of on-treatment serious adverse events and adverse events of special interest: incidence, relative risk and risk difference (including sites with GCP non-compliance/significant data integrity concerns)
- Listing of all adverse events from sites with GCP non-compliance/significant data integrity concerns

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data. Blood eosinophils are a pharmacodynamic assessment with the analysis outlined in 4.4.12.

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.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA and antidsDNA antibody are collected at baseline visit and if clinically indicated post baseline, analysed on as needed basis and will be summarised only for participants with data available.

Urinalysis results (screening and week 52) will be summarised.

4.5.3.2. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure pulse rate and body temperature including change from baseline at all visits will be summarised and listed.

4.5.3.3. ECG

Actual and change from baseline (for post-baseline timepoints) values for QTc(F) and heart rate will be summarised by treatment for Baseline, Week 26, Week 52. ECG findings will be summarised by visit.

Individual maximum QTc(F) values will also be summarised to show the number of subjects with maximum values (msec) in the following categories: <= 450, 450 < to <= 480, 480 < to <= 500, 500 < to <= 530 and > 530. QT uncorrected values will be summarised to show the number of subjects with maximum values (msec) post-baseline relative to baseline in the following categories: Decrease, no change or increase to <600 and increase to >=600.

Additionally, individual maximum changes from baseline in QTc(F) values will be summarised to show the number of subjects with maximum changes (msec) in the categories: increase of <= 30, increase of ≥31 to 60 and increase of >60.

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

4.5.3.4. Immunogenicity

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. A sample that is positive in the confirmation assay is considered positive for anti-depemokimab antibodies. 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.

All participants' baseline immunogenicity samples will be analysed. Post-baseline immunogenicity samples will only be analysed for participants receiving depemokimab.

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

- Summary of binding antibody assay results: it will summarise 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 summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of binding antibody assay results for participants without positive result prior to dosing: it will summarise 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). The highest post-baseline binding antibody confirmatory assay result obtained will also be summarised.
- Summary of neutralizing antibody assay results: results summarised for participants with a positive binding antibody confirmatory assay result. Neutralising antibody

assay results will be categorised as positive or negative. The highest post-baseline neutralizing antibody assay result obtained will also be summarised.

- Summary table of baseline ADA assay positive participants in the depemokimab treatment group. The output will first categorise these ADA assay positive participants at baseline for the NAb assay (positive and negative categories). The output will then categorise week 52 (or last visit) into two categories of titer fold-change from baseline (low: 0-3, and high: >3) separated by ADA assay and NAb assay result at baseline (positive and negative).
- Summary of AE by highest post-baseline binding antibody confirmatory assay result

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 categorised 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 titre results that fall into multiple titre result categories, they will be included in the highest category.

4.5.3.5. Complement

Complement (C3 and C4) will be summarised by parameter and visit and presented as a table and as a figure. The summary table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, SD of logs, median, minimum and maximum.

4.5.4. Subgroup analyses

Subgroup analyses of the primary and secondary endpoints will be made to assess consistency of the study intervention effect across the following groups:

- Pre-study biologic therapy for asthma: mepolizumab vs. benralizumab

4.6. Interim Analyses

An independent data monitoring committee (IDMC) will periodically review unblinded safety data from the three Phase III studies in the program: 206713, 213744 and 206785, in accordance with the IDMC Charter.

The IDMC will review all safety data, including AEs and serious adverse events (SAEs) and adverse events of special interest (AESI), laboratory parameters, including haematological and clinical chemistry parameters and ECG assessments from the three studies for identification of any potential safety signals. To provide benefit-risk context, the IDMC will also review limited efficacy data for the primary endpoint The data analyses for the IDMC reviews will be performed by an independent statistician.

As the study will be ongoing at the time of regulatory submission, an interim analysis will be performed in order to provide unblinded safety data in an interim Clinical Study Report (CSR) to inform on the risk-benefit assessment of GSK3511294 in asthma. The OPS (Output & Programming Specification) will detail the specific subset of outputs that will be included in the interim analysis and a separate document (Blinding Plan for NIMBLE Interim Analysis) will provide details on how the study integrity will be maintained.

4.7. Changes to Protocol Defined Analyses

The definition of the Screened Analysis Set has been updated to: "All participants who were screened for eligibility".

The definition of the Full Analysis Set (FAS) has been updated to exclude participants from sites with GCP non-compliance/significant data integrity concerns.

5. SAMPLE SIZE DETERMINATION

5.1. Sample Size Assumptions

The sample size of 850 participants per arm (equal allocation) is based on sufficient power to conclude non-inferiority with a margin of 1.28 using a one-sided 2.5% significance level.

The assumption of 0.8 for the dispersion parameter was observed in two mepolizumab phase 3 studies [Pavord, 2012; Ortega, 2014]. The assumption of 0.7 for the annual exacerbation rate for depemokimab and the active comparator arm was estimated from two mepolizumab open-label extension (OLE) studies [Khatri, 2019; Lugogo, 2016] when taking into account the inclusion criteria for this study. Missing/excluded data (based on the estimand strategy described in Section 1.1.2) is assumed at 10% of participant-years data (proportion of missing data observed in the first year of a mepolizumab OLE study [Lugogo, 2016]). An exacerbation rate ratio of 1 is assumed (depemokimab and comparator therapies are equally efficacious). Based on these assumptions, the power of the study is 91% [PASS, 2020].

Based on the assumptions above, the maximum treatment effect (i.e. observed rate ratio of depemokimab + SoC compared to active comparator (mepolizumab or benralizumab) + SoC estimated to result in a conclusion of non-inferiority is 1.11.

5.2. Sample Size Sensitivity

The power calculation is based on assumptions. Table 4 illustrates how changes in assumptions for two parameters (annualised exacerbation rate of the active comparator [mepolizumab or benralizumab] + SoC and exacerbation rate ratio for depemokimab + SoC compared with active comparator + SoC) affect the power.

Table 4 Estimates of Power for Assumed Active Comparator + SoC Exacerbation Rate and True Exacerbation Rate Ratio (depemokimab + SoC Compared with Active Comparator + SoC)

Annualised exacerbation rate of active comparator + SoC	Exacerbation rate ratio for depemokimab + SoC compared with active comparator (mepolizumab or benralizumab) + SoC				
	0.9	0.95	**1**	1.05	1.1
0.6	99	96	88	72	50
0.7	>99	98	**91**	76	54
0.8	>99	98	93	79	57
0.9	>99	99	95	82	60
1	>99	99	96	84	63

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ANCOVA	Analysis of Covariance
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment

Abbreviation	Description
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
MAR	Missing at Random
MNAR	Missing Not at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities
Min	Minimum
Mg	Milligram
MMRM	Mixed Models Repeated Measures
NAb	Neutralising antibody
OCS	Oral corticosteroids
OPS	Output and Programming Specification

Abbreviation	Description
PD	Pharmacodynamics
PDMP	Protocol Deviation Management Plan
PEF	Peak expiratory flow
PT	Preferred Term
CCI	[redacted]
PRO	Patient-reported outcomes
QTcF	QTc corrected by Fridericia's formula
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SoC	Standard of care
SOC	System Organ Class
WM	Weighted Mean

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

The compliance of eCOA data 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. The study-level (overall) compliance will be derived using all eCOA assessments in the study (i.e. both secondary and other endpoints).

The target overall compliance for the study is 80%.

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 3.5.3 of the OPS. The number of data points in the denominator for the interval-based definition becomes the number of two-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 the OPS are present. 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.

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

For endpoint-level compliance summaries of daily diary data, the calculation will be based on the interval-based definition that is defined within Section 3.5.3 of the OPS. The compliance will be summarized for each two-week interval.

The compliance calculation for visit-based assessments will be based on whether the participant completed the assessment for that particular visit. The compliance will be summarized for each visit.

6.2.3. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

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