Statistical Analysis Plan Amendment 2

Study ID: 215360

Official Title of Study: A Phase 3, 52 week, open-label, single arm study to investigate the efficacy and safety of mepolizumab SC in participants aged 6 to 17 years with hypereosinophilic syndrome.

NCT number: NCT04965636

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TITLE PAGE

Protocol Title:	A Phase 3, 52 week, open-label, single arm study to investigate the efficacy and safety of mepolizumab SC in participants aged 6 to 17 years with hypereosinophilic syndrome.
Study Number:	215360
Compound Number:	*SB240563*
Abbreviated Title:	Study in Paediatrics with HypEREosinophilic syndrome
Acronym:	SPHERE

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	28 October 2021	Protocol Amendment 1 (02 August 2021)	Not Applicable	Original version
SAP Amendment 1	25 October 2024	Protocol Amendment 3 (21 August 2023)	Section 6.3 – Electronic Clinical Outcome Assessment (eCOA) compliance added into SAP	Reporting on overall eCOA compliance in the study
SAP Amendment 2	12 May 2025	Protocol Amendment 4 (16 December 2024)	Removal of endpoint regarding peripheral blood genomic and transcriptomic analysis In Section 1.1 (Objectives, Endpoints, and Estimands), Additionally updated intercurrent event text within multiple analysis endpoint sections Updates to Section 1.2 (Study Design) and Section 5 (Sample Size Determination), where Sample size reduced from 25 participants to 15 participants Section 3 (Analysis Sets), Section 4.7.2.2 (COVID-19 Assessment and COVID-19 AEs), Section 6.1.3 (Protocol Deviations) and Section 6.1.6 (Additional Analyses Due to the COVID-19 pandemic)	Removed endpoint regarding peripheral blood genomic and transcriptomic analysis as data no longer being collected Clarification on identification of the intercurrent event of changes in background HES therapies to focus on those medications which modulate the disease course of HES Clarification of the change in sample size requirements, with at least 11 participants to be children (aged 6 to 11 years) and at least 4 participants to be adolescents (aged 12 to 17 years for alignment with Protocol Amendment 4. Further clarifications added into Section 1.2 regarding the study dosing regimen of mepolizumab Removed COVID-19 analyses set and updated displays related to the COVID-19 pandemic.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is based	Change	Rationale
			Included text regarding the Minimum Required Listings in Section 4.1.	Clarification inserted
			Added baseline definition for oral corticosteroids, immunosuppressive / cytotoxic medication analyses in Section 4.1.2 (Baseline Definition) and added medication assessment windows in Section 6.2.4.2.	Clarified on the change from baseline analyses in medication endpoints and the handling of medication data within each medication assessment window
			Inserted clarification of handling of BFI item-3 data within Section 4.3.4 and Section 6.2.4.1	Clarified the study days which will be considered at Baseline and Week 52. Removed requirement for a minimum of 4 days over each 7 day window for consistency with the 200622 study of mepolizumab HES in adults.
			Additional summary table required of the reduction in HES flares detailed in Section 4.4.2	Clarified on the additional summary table required of the reduction in HES flares
			Additional details inserted in Section 4.6. (Pharmacokinetic Analyses)	Clarified that Population PK modelling will be generated as part of a separate study report.
			Typographical errors updated across multiple SAP sections	Where requiring clarification text addressed throughout

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 215360. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES.	• Frequency of HES flares over the 52-week study treatment period.
Secondary	
• To assess the effect of mepolizumab SC given every 4 weeks on the change in oral corticosteroid (OCS) dose in participants aged 6 to 17 years with HES that are taking OCS at baseline.	• Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52. • Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52. • Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52.
• To assess the effect of mepolizumab SC given every 4 weeks on the change in oral corticosteroid (OCS) dose in participants aged 6 to 17 years with HES.	• Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52.
• To assess the efficacy of mepolizumab SC given every 4 weeks on fatigue in participants aged 12 to 17 years with HES.	• Change from baseline in fatigue severity based on weekly average score of Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) for Week 52.
• To evaluate the immunogenicity of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES.	• Occurrence of anti-drug antibodies (ADA) and neutralising antibodies (NAb).
• To assess the effect of long-term use of mepolizumab SC on a pharmacodynamics (PD) marker in participants aged 6 to 17 years with HES.	• Ratio to baseline in absolute blood eosinophil count at discrete time points during the 52-week study treatment period.
• To assess the pharmacokinetics (PK) of mepolizumab SC in participants aged 6 to 17 years with HES.	• Mepolizumab plasma concentration at discrete time points during the 52-week study treatment period.

Objectives	Endpoints
Other	
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Objectives	Endpoints
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• To evaluate the safety of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES.	• Occurrence of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs (blood pressure, heart rate and temperature). • Change from baseline in 12-lead electrocardiogram (ECG). • Haematological and clinical laboratory tests.

Primary estimand

The primary clinical question of interest is: What is the rate of HES flares during 52 weeks of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years, regardless of treatment discontinuation for any reason and regardless of changes in background HES therapy?

The estimand is described by the following attributes:

Population: participants with HES aged 6 to 17 years with or without maintenance SoC therapy.

Treatment condition: Mepolizumab given every 4 weeks in addition to SoC.

Variable/endpoint: Frequency of HES flares over 52 weeks.

Summary measure: Annualised rate of HES flares.

Intercurrent events:

- Study treatment discontinuation – treatment policy strategy.
- Change in background HES medication which might modulate the disease course of HES, determined either by published data or by proposed or known mechanism of action (other than changes due to a clinically documented protocol-defined flare) - treatment policy strategy.

Rationale for estimand:

- Interest lies in the rate of flares when medication is taken for the entire study duration. For participants discontinuing study medication or changing background medication which might modulate the disease course of HES, use of a treatment policy strategy recognises that this could be due to an unfavourable cause.

Secondary efficacy estimands

Secondary efficacy estimands address changes in OCS use and effects on fatigue severity.

Estimands for changes in OCS use will use the subpopulation of participants with HES aged 6 to 17 years who are taking OCS at baseline. Treatment condition will be the same as for the primary estimand. The following 3 endpoints and summary measures will be used:

1. Endpoint: Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52; summary measure: mean across participants.
2. Endpoint: Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52; summary measure: proportion of participants with this reduction.
3. Endpoint: Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52; summary measure: proportion of participants with this level of OCS usage.

For the intercurrent event of study treatment discontinuation, a treatment policy strategy will be used. Use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication which might modulate the disease course of HES will use a treatment policy strategy.

An additional estimand for changes in OCS use will use the whole population of participants with HES aged 6 to 17 years. Treatment condition will be the same as for the primary estimand. The following endpoint and summary measure will be used:

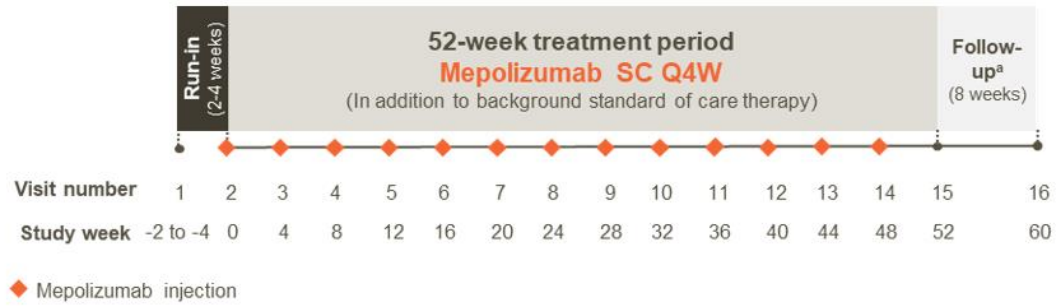
- Endpoint: Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52; summary measure: proportion of participants with this level of OCS usage.

For the intercurrent event of study treatment discontinuation, a treatment policy strategy will be used. Use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication which might modulate the disease course of HES will use a treatment policy strategy.

The secondary estimand for fatigue severity will use the subpopulation of participants with HES aged 12 to 17 years. Treatment condition will be the same as for the primary estimand. A treatment policy strategy will be used for the intercurrent events of study treatment discontinuation and changes to background HES therapy which might modulate the disease course of HES. The endpoint will be the change from baseline in weekly average score of the BFI item 3 (worst level of fatigue during past 24 hours) for Week 52 and the summary measure will be the mean value.

1.2. Study Design

Overview of Study Design and Key Features



[a] Participants who enrol in an expanded access program (EAP) of mepolizumab are not required to have a follow-up visit.

Design Features	• A 52-week, open-label, single arm, multicentre study of SC mepolizumab in children and adolescent participants with HES receiving SoC therapy. • Approximately 15 participants who are on a stable dose of HES therapy for at least 4 weeks prior to Visit 2 will be enrolled. • All participants will need to attend a study-site visit at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 24 (Visit 8), and the Week 52 exit visit (Visit 15). The other visits may be performed remotely where applicable country and local regulations allow. • Investigators may adjust the participants' background HES therapy (SoC) as needed starting at visit 3 (approximately 4 weeks after the first dose of mepolizumab). • Participants who complete assessments at Visit 15 (Week 52) may continue with mepolizumab treatment via expanded access program (EAP), where local regulation permits. Study participants who do not continue with EAP will have an additional follow-up assessment 12 weeks after the last dose of mepolizumab.
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Overview of Study Design and Key Features	
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Interim Analysis	• An external Independent Data Monitoring Committee (IDMC) will review ongoing data from study 215360 to ensure external objective review of safety data at regular intervals throughout the study. The safety data summaries for the IDMC reviews will be described in a separate analysis plan and performed by an independent statistical analysis data centre (SDAC). • An analysis to present cumulative data may be completed if required.

2. STATISTICAL HYPOTHESES

The primary endpoint in this study is the frequency of HES flares over the 52-week study treatment period. No formal statistical hypotheses will be tested.

2.1. Multiplicity Adjustment

No multiplicity adjustment is planned for this study.

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 (post screening) for whom a record exists on the study database.	• Study Population
Full Analysis Set (FAS)	• All participants received at least one dose of study treatment (mepolizumab).	• Efficacy • Safety • Pharmacokinetic • Pharmacodynamics

4. STATISTICAL ANALYSES

4.1. General Considerations

Summaries will be presented by the treatment group (dose or dose combination) the participant received. With the exception of pharmacokinetic and pharmacodynamic data, summaries will also be presented for mepolizumab all doses.

Unless otherwise specified, all analyses will be performed on the full analysis set.

Treatment group descriptors will be assigned as follows:

Treatment Group Descriptions	
Data Displays for Reporting	
Description	Order [1]
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NOTES:
1. Order of treatments presented in Tables, Figures and Listings (TFLs), as appropriate.

If a particular dose combination is not required in the study, this will be omitted from the displays.

The minimum required listings (MRL) will be generated for inclusion in the CSR. All other participant-level data will be available interactively within the GSK internal dynamic RAPIDO Data Viewer tool at Statistical Analysis Complete (SAC).

4.1.1. General Methodology

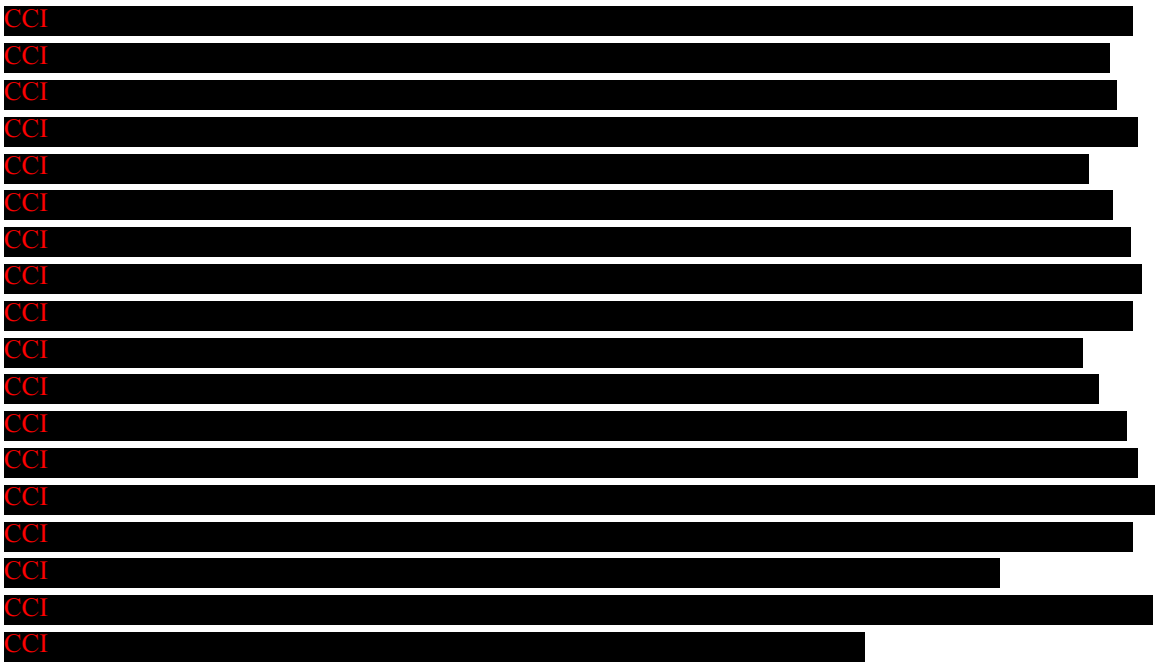
Confidence intervals will use 95% confidence levels unless otherwise specified.

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

It is anticipated that participant accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

For the primary analyses, region will be grouped into Europe (Italy, Netherlands, Spain and United Kingdom), United States and Rest of the World (Argentina, Brazil, Israel, Mexico, Russian Federation and Turkey). If the number of participants is too small for model convergence, then the subgroup categories may be redefined prior to database lock for the study.

4.1.2. Baseline Definition



For all other endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

4.2. Primary Efficacy Endpoint(s) Analyses

The primary endpoint (variable) for this study is the frequency of HES flares during the treatment period.

4.2.1. Definition of endpoint/estimands

Definition of HES flare:

A HES flare is defined as a HES-related clinical manifestation based on a physician documented change in clinical signs or symptoms (worsening symptoms and/or elevated blood eosinophil level) resulting in the need for either of the following:

- An increase from the most recent dose in the maintenance OCS dose (prednisone/prednisolone equivalent) by at least 10 mg/day for 5 days.
- An increase in or addition of any immunosuppressive and/or cytotoxic HES therapy from/to the most recent dose of HES therapy.

To be considered as a HES flare, the most recent dose of HES therapy must not have changed for at least 4 weeks prior to the flare. This ensures that failed reductions in HES therapy are not misclassified as a HES flare.

The start date for a HES flare will be defined as the date of therapy escalation confirmed by the investigator attributable to a HES-related clinical manifestation.

Derivation of Endpoint

HES flares are recorded by the investigators in the HES flares details form. The number of observed HES flares will be calculated for each participant as the number of unique starting dates for HES flares which occur at least 14 days after the date of resolution from any preceding HES flare. Both on- and off-treatment flares will be included within the analysis of the primary endpoint, however any post-treatment flares recorded will not be included (see Section 6.2.2.1).

Primary Estimand

The primary estimand is described in Section 1.1 and summarised below.

Target Participant Population	Participants with HES aged 6 to 17 years with or without maintenance SoC therapy.
Primary Endpoint	Frequency of HES flares over 52 weeks.
Intercurrent events	The anticipated intercurrent events and corresponding strategies are:- • Study treatment discontinuation: treatment policy strategy. • Change to background HES medication which might modulate the disease course of HES, determined either by published data or by proposed or known mechanism of action (other than changes due to a clinically documented flare): treatment policy strategy.
Summary measure	Annualised rate of HES flares.

4.2.2. Main analytical approach

A summary of the number of HES flares reported for each participant will be presented by treatment group. A plot of the cumulative number of HES flares over time will also be produced.

The annualised rate of HES flares will be estimated using a negative binomial generalised linear model with a log-link function, including terms for baseline OCS dose (continuous scale), region, age (6 to 11 years or 12 to 17 years), and $\log_e$ observed time (as an offset variable). The model estimated mean flare rate per year will be weighted according to the observed proportion of the categorical covariates in the study data by inclusion of the OM (obsmargins) option in the LSMEANS statement of the SAS PROC GENMOD procedure. Adaptions to the statistical model may be made in the case of any convergence issues, including but not limited to, reducing covariates within the model in order to ensure convergence and obtain stable estimates.

For participants withdrawing prematurely from the study during the 52-week treatment period, all data up to the time of study withdrawal will be used to calculate the rate of HES flares.

The fit of the negative binomial generalised linear model will be investigated by calculating and plotting standardised deviance residuals.

The flare rate will be summarised for all participants in the study and separately for participants aged 6 to 11 years and aged 12 to 17 years.

4.2.3. Sensitivity analyses

A sensitivity analysis to assess the impact of missing data will be performed only if there is sufficient off-treatment data (i.e., data collected following treatment discontinuation prior to study withdrawal, Section 6.2.2.1). A multiple imputation approach will be used using this off-treatment data to impute missing data.

4.3. Secondary Efficacy Endpoint Analyses

All secondary endpoints will be summarised descriptively. Each four-week period from Weeks 0-4 through to Weeks 48-52 is shown in Section 6.2.4.2.

4.3.1. Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52

Derivation of Endpoint

For each participant, the OCS dose on each day of the study will be identified from the concomitant medications data (see Section 6.2.1). The mean daily OCS (prednisone or equivalent) dose for each 4-week period (Weeks 0-4 through to Weeks 48-52) for each participant will be calculated as the sum of the daily doses of OCS during each period divided by the total number of days (see Section 6.2.1.1).

Participants withdrawing from the study prematurely will have mean daily OCS (prednisone or equivalent) dose calculated using available data up to study withdrawal date only (divided by the number of days for which there is available data).

The change in the mean daily OCS dose from Week 0 to 4 to Week 48 to 52 will be calculated for each participant as the mean daily OCS dose for Week 48 to 52 minus the mean daily OCS dose for Week 0 to 4. The change in the mean daily OCS dose from Week 0 to 4 to each 4-week period from Weeks 4-8 through to Weeks 48-52 will be calculated using the same formula.

The estimand for this endpoint is described in Section 1.1 and summarised below.

Target Participant Population	Participants with HES aged 6 to 17 years that are taking OCS at baseline, i.e. mean Week 0 to 4 OCS dose >0 mg/day.
Endpoint	Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52.
Intercurrent events	The anticipated intercurrent events and corresponding strategies are:- • Study treatment discontinuation: treatment policy strategy. • Changes to OCS therapy: composite strategy (part of endpoint). • Other changes to background HES medication which might modulate the disease course of HES, determined either by published data or by proposed or known mechanism of action: treatment policy strategy.
Summary measure	Mean change from Weeks 0 to 4 to Weeks 48 to 52 across participants.

Main analytical approach

Summary statistics for mean daily OCS (prednisone or equivalent) dose for each 4-week period from Weeks 0-4 through to Weeks 48-52 will be presented by treatment group, including change in the mean daily OCS dose.

Additional Estimands

An additional estimand for this endpoint will use the whole population of participants with HES aged 6 to 17 years.

4.3.2. Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52

Derivation of Endpoint

Participants who achieve a mean daily OCS dose (prednisone/prednisolone or equivalent) reduction of 50% or more from Week 0-4 to each 4-week period from Weeks 4-8 through to Weeks 48-52 will be determined based on the change in mean OCS dose defined in Section 4.3.1. For each 4-week period a reduction of 50% or more is defined as:

$$\frac{Mean\ OCS\ dose - Mean\ OCS\ dose\ during\ Week\ 0\ to\ 4}{Mean\ OCS\ dose\ during\ Week\ 0\ to\ 4} \times 100 \leq -50$$

The estimand for this endpoint is described in Section 1.1 and summarised below.

Target Participant Population	Participants with HES aged 6 to 17 years that are taking OCS at baseline, i.e. mean Week 0 to 4 OCS dose >0 mg/day.
Endpoint	Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52.
Intercurrent events	The anticipated intercurrent events and corresponding strategies are:- • Study treatment discontinuation: treatment policy strategy. • Changes to OCS therapy: composite strategy (part of endpoint). • Other changes to background HES medication which might modulate the disease course of HES, determined either by published data or by proposed or known mechanism of action: treatment policy strategy.
Summary measure	Proportion of participants with reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52.

Main Analytical Approach

The number and percentage of participants who achieve a reduction in mean daily OCS (prednisone/prednisolone or equivalent) dose of 50% or more during Week 48 to 52 will be presented by treatment group. The number and percentage of participants who achieve a reduction in mean daily OCS dose of 50% or more during each 4-week period from Weeks 0-4 to each 4-week period from weeks 4-8 through to Weeks 48-52 will also be tabulated.

Participants withdrawing prematurely from the study who have no available data during Weeks 48 to 52 will be summarised as not having met the endpoint criteria, i.e., a treatment failure. The same approach will be used for the summary for each of the other 4-week periods.

4.3.3. Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52

Derivation of Endpoint

Participants who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of 7.5mg or less during each four-week period from Weeks 0-4 through to Weeks 48-52 will be determined based on the mean OCS dose in each 4-week period defined in Section 4.3.1.

The estimand for this endpoint is described in Section 1.1 and summarised below.

Target Participant Population	Participants with HES aged 6 to 17 years that are taking OCS at baseline, i.e. mean Week 0 to 4 OCS dose >0 mg/day.
Endpoint	Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52.
Intercurrent events	The anticipated intercurrent events and corresponding strategies are:- • Study treatment discontinuation: treatment policy strategy. • Changes to OCS therapy: composite strategy (part of endpoint). • Other changes to background HES medication which might modulate the disease course of HES, determined either by published data or by proposed or known mechanism of action: treatment policy strategy.
Summary measure	Proportion of participants with mean daily OCS dose (prednisone/prednisolone or equivalent) ≤7.5 mg during Weeks 48 to 52.

Main Analytical Approach

The number and percentage of participants who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of 7.5mg or less during Weeks 48 to 52 will be presented by treatment group. This includes participants with an increase in mean daily OCS dose, as long as the mean OCS dose remains ≤7.5mg. The number and percentage of participants who achieve a mean daily OCS dose of 7.5mg or less during each four-week period from Weeks 0-4 through to Weeks 48-52 will also be tabulated.

Participants withdrawing prematurely from the study who have no available data during Weeks 48 to 52 will be summarised as not having met the endpoint criteria i.e., a treatment failure. The same approach will be used for the summary for each of the other 4-week periods.

Additional Estimands

An additional estimand for this endpoint will use the whole population of participants with HES aged 6 to 17 years using the same derivations as above.

4.3.4. Change from baseline in fatigue severity based on weekly average score of Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) for Week 52

Derivation of Endpoint

The BFI has 9 items. In the first 3 items, the participant rates their fatigue level right now, their usual fatigue level over the last 24 hours and their worst level of fatigue over the last 24 hours using an 11-point rating scale anchored at 0 (no fatigue) and 10 (as bad as you can imagine). The participant also rates how, during the past 24 hours, fatigue has influenced each of the following on an 11-point rating scale anchored at 0 (does not interfere) and 10 (completely interferes) in the remaining 6 items: general activity, mood, walking ability, normal work, relations with other people and enjoyment of life. The

participant completes item 3 (worst level of fatigue during past 24 hours) of the BFI daily at home on the eDiary.

The mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment will be considered within the baseline assessment window and the mean of the 7 daily assessments up to but not including the Week 52 clinic visit date will be considered within the Week 52 assessment window. If any of the 7 daily assessments are missing at baseline or at the Week 52 visit, the mean of the observed daily assessments over the 7-day period will be used. Section 6.2.4.1 shows the assessment windows for calculating the mean BFI-item 3 values during each 7-day period. The change from baseline in fatigue severity (worst level of fatigue during past 24 hours) at Week 52 will be calculated as the Week 52 assessment minus the baseline assessment.

The estimand for this endpoint is described in Section 1.1 and summarised below.

Target Participant Population	Participants with HES aged 12 to 17 years with or without maintenance SoC therapy
Endpoint	Change from baseline BFI item 3 at Week 52
Intercurrent events	The anticipated intercurrent events and corresponding strategies are:- • Study treatment discontinuation: treatment policy strategy • Changes to background HES medication which might modulate the disease course of HES, determined either by published data or by proposed or known mechanism of action: treatment policy strategy
Summary measure	Mean change from baseline to Week 52 across participants

Main analytical approach

Summary statistics for absolute and change from baseline in weekly average score of the BFI item 3 (worst level of fatigue during past 24 hours) will be presented for each visit (weekly timepoint) by treatment group.

For participants withdrawing prematurely from the study, available data up to the time of study withdrawal will be summarised.

4.4. Other Efficacy Endpoint Analyses

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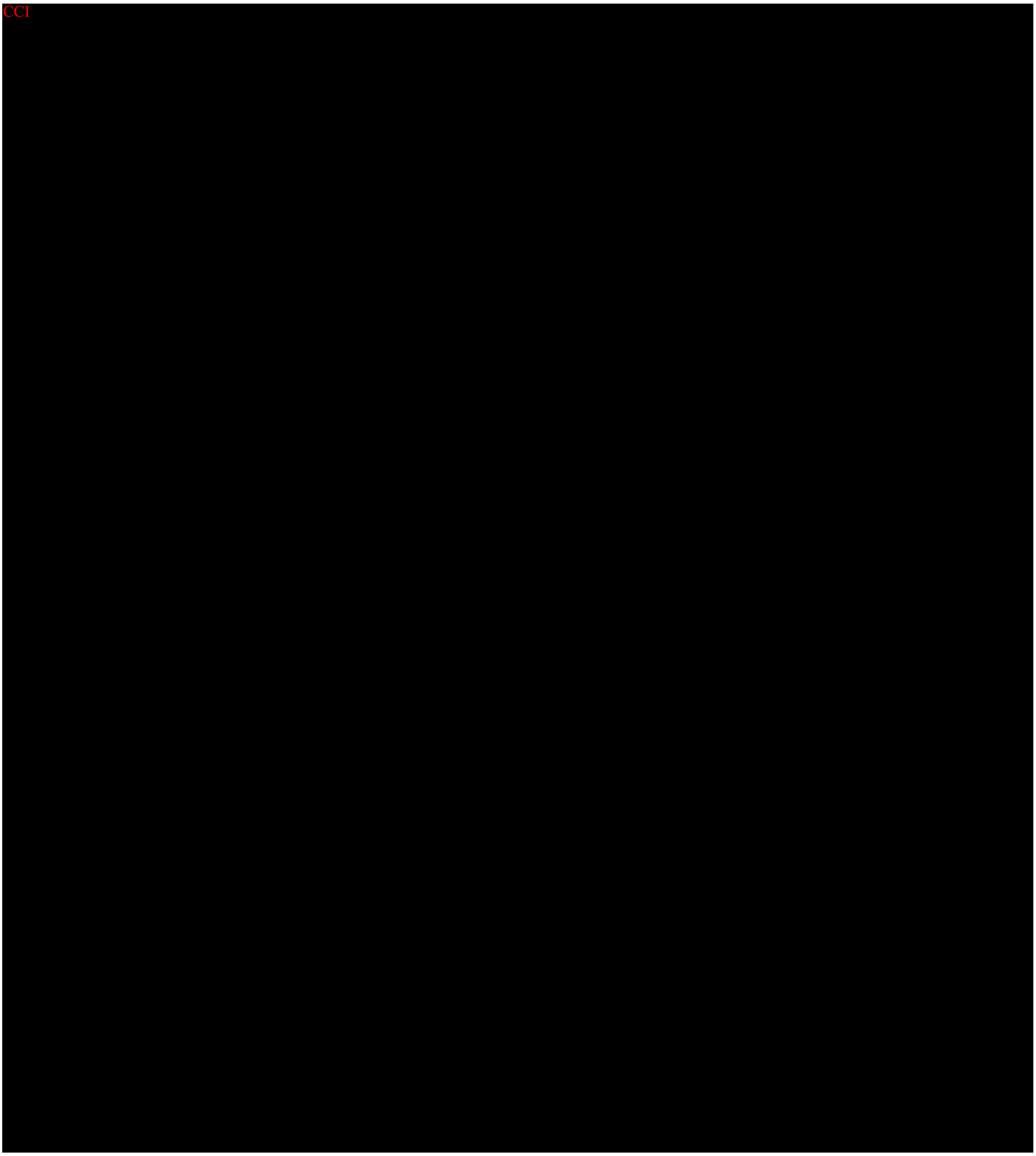

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4.7. Safety Analyses

The safety analyses will be based on the full analysis set, unless otherwise specified.

4.7.1. Extent of Exposure

Summary statistics and a categorical overview will be generated for the number of study interventions administered.

The number of days of exposure (therapeutic coverage) to study drug will be calculated based on the formula:

$$Duration\ of\ exposure\ in\ days = Date\ of\ last\ dose\ of\ study\ treatment - date\ of\ first\ dose\ of\ study\ treatment + 29.$$

Exposure in months will be calculated using the formula:

$$Exposure\ (months) = \left(\frac{Exposure\ in\ days}{365.25}\right) * 12$$

Total participant years exposure will be calculated using the formula:

Total participant-years exposure = (Sum across participants of exposure in days)/365.25

The extent of exposure (in months) to mepolizumab will be summarised by treatment group. The number and percentage of participants exposed for 1 to 3 months, 3 to 6 months, 6 to 9 months and 9 to 12 months will be presented. The total participant-years exposure will also be presented.

4.7.2. Adverse Events

Summary of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. AEs will be summarised for all participants by treatment group and overall.

4.7.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) 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. Local injection site reactions are also collected via targeted eCRF within the study.

AESIs of opportunistic infections, malignancies, serious cardiac, vascular and thromboembolic (CVT) events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset created based on the MedDRA dictionary available at the time of Database Lock for this study. In addition, the information as to whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] will be collected on the AE and SAE eCRF pages. See Appendix 4 (Section 6.4) for further details.

Separate summary tables showing the number and percent of participants with each type of AESI, broken down by preferred term will be created.

For each type of AESI 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.

4.7.2.2. COVID-19 AEs

The COVID-19 will be reported as part of AE/SAE tables, listings and figures.

4.7.3. Additional Safety Assessments

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

4.7.3.1. Laboratory Data

Laboratory evaluations including the analyses of Chemistry laboratory tests, Urinalysis, Haematology laboratory tests and liver function tests will be based on GSK Core Data Standards.

A scatter plot of maximum ALT vs baseline ALT, and maximum ALT vs 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.

4.7.3.2. Height, Weight and Vital signs

A summary of the vital signs data (height, weight, temperature, systolic and diastolic blood pressure, and heart rate) will be produced by test, treatment group and visit. A summary of change from baseline in vital signs will be also produced.

4.7.3.3. ECG

12-lead ECG measures (PR, QRS, QT, and QTc intervals) will be reported based on GSK Core Data Standards. Change from baseline in ECG measures will be summarised by treatment group and visit. Multiple assessments recorded on the same day will be dealt with as per Section 6.2.5

4.8. Immunogenicity Analyses

4.8.1. Occurrence of anti-drug antibodies (ADA) and neutralising antibodies (NAb)

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

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.

The binding ADA results at each visit will be categorised as negative, 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 excluding the baseline visit, or a single result at the final study assessment). In addition, the highest post-baseline binding ADA confirmatory result obtained for a participant will be summarised. Participants with both positive and negative results will be identified in the positive category. Summary statistics for the titre result by visit will also be presented.

Neutralizing antibody assay results will be summarised by visit. In addition, the highest post-baseline neutralising antibody assay result during the treatment period of the study will be summarised, with participants with both positive and negative results identified in the positive category.

Furthermore, a summary of on-treatment adverse events (AEs) by highest post-baseline binding ADA confirmatory assay result [positive / negative] will also be generated.

Immunogenicity data will be listed for participants within the Full Analysis Set.

4.9. Other Analyses

4.9.1. Subgroup analyses

The primary analysis of HES flare rate, key secondary endpoints and safety data will be summarised for all participants in the study and also summarised by age group (6 to 11 years and 12 to 17 years).

4.10. Interim Analyses

An analysis to present cumulative data may be completed if required, e.g. for early regulatory review.

4.11. Changes to Protocol Defined Analyses

Changes or deviations from the statistical analysis specified in the Protocol Amendment 4 (Dated: 16-Dec-2024) [Document Number TMF-20082402] are detailed in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
As listed in the following protocol sections - Section 3 – Objectives and Endpoints - Section 8.1.3 – Reduction in Use of OCS, Immunosuppressive and/or Cytotoxic HES Therapy - Section 9.4.3 – Other Endpoints The protocol endpoint is defined as - Taking immunosuppressive and/or cytotoxic HES therapy at Week 52 in participants that are taking immunosuppressive and/or cytotoxic HES therapy at baseline	As listed in - Section 1.1 – Objectives and Endpoints - Section 4.4.3 - Taking immunosuppressive and/or cytotoxic HES therapy during Weeks 48 to 52 The protocol endpoint is defined as - Taking immunosuppressive and/or cytotoxic HES therapy during Weeks 48 to 52 in participants that are taking immunosuppressive and/or cytotoxic HES therapy at baseline	For consistency in the reporting of other medication data (such as changes in OCS medication) during the final four weeks of the treatment period (Weeks 48 to 52) the changes in this endpoint will be summarized and tabulated during each four-week period from Weeks 0-4 through to Weeks 48-52. The wording of this endpoint has therefore been clarified as 'during Weeks 48 to 52' rather than 'at Week 52' since this is considering all study days between Week 48 and Week 52 (as per Section 6.2.4.2) and this clarification has been added within each impacted sections of this analysis plan.

5. SAMPLE SIZE DETERMINATION

At least 15 participants aged 6 to 17 years will be enrolled. Due to the rare nature of HES in pediatrics, there is minimal data available to predict the age distribution in the study. CCI [redacted]

CCI [redacted]

Sample size was chosen based on the expected precision of the estimate. No sample size reassessment is planned.

Expected Precision of Estimate

The expected variance in annualised flare rate has been estimated based on the data from the completed Study 205203, which used the same definition of HES flare. In that study, flare rate was estimated using the negative binomial model with the standard error (SE) expressed on the log scale, therefore the uncertainty around the expected point estimates of effect is presented in terms of 95% confidence intervals (CIs) rather than by the variance.

CCI [redacted]

CCI [redacted] The observed flare rate in Study 205203 was 0.26/year. If the same rate was observed in this study with 15 participants, the 95% CI would be (0.07, 0.93).

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Full Analysis Set. A summary of the number of participants in each of the participant level analysis sets will be provided.

In this multi-centre global study, enrolment will be presented by region, country and site.

6.1.1. Participant Disposition

A summary of the screening status will be provided. Reasons for screen failure will be summarized. A summary of the number and percentage of participants who enrolled by country, site ID and investigator ID will be provided.

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

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, those who withdrew from treatment but continued follow-up, or have discontinued study treatment prematurely, as well as primary reasons for discontinuation of study treatment. The total number of scheduled treatments, on-treatment, off-treatment and missed treatment will be summarized in terms of subject years.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, height/weight, BMI at screening, race, race detail will be summarized. In addition, the following age categories will be summarized: 6-11 and 12-17 based on the Enrolled Analysis Set. Past medical conditions and current medical conditions as of screening will be summarized respectively.

A summary of baseline HES therapy, duration of HES, number of flares 12 months prior to screening, and baseline OCS doses will be summarized (refer section 6.2.1). The number of L-HES patients based on T-cell profile data and baseline laboratory information (including CD3-CD4+, Interleukin-5, Immunoglobulin E and blood eosinophil count data) will be summarized

If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identification version will be produced.

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 database lock to ensure all important deviations are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for summaries of important protocol deviations.

In addition to the overall summary of important protocol deviations, a separate summary of significant protocol deviations, categorized by those related and unrelated to the COVID-19 pandemic, will also be produced.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be summarized.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only. The summary of concomitant medications will be provided by ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

Concomitant medications include any medication that was taken at some point during the study.

6.2. Appendix 2: Data Derivations Rule

6.2.1. Oral Prednisone/Prednisolone or Equivalent Daily Dose

For each subject, oral prednisone equivalent daily dose (mg) on each day of the study will be identified from the concomitant medications form. Corticosteroids will be identified from the list of coded concomitant medications for the study, by merging with the GSK respiratory medication class (RMC) reference data set by component code. This reference data is created by dictionary specialists who identify a list of component terms for corticosteroids, which then undergo clinical review to ensure the correct classification is assigned.

Only corticosteroids recorded with route = "Oral" will be considered as oral corticosteroids. Subjects not receiving OCS therapy on any day of the study will be assigned a prednisone equivalent daily dose of 0 mg for that day. The corticosteroid conversion factors in the table below will be used to scale each corticosteroid dose to a prednisone equivalent dose.

Medication Name	Scaling Factor
Betamethasone	8.33
Budesonide[1]	0
Cortisone	0.2
Dexamethasone	6.67
Deflazacort	0.83
Hydrocortisone	0.25
Methylprednisone	1.25
Meprednisone	1.25
Prednisone	1
Prednisolone	1
Prednisone acetate	1
Triamcinolone	1.25

[1]Budesonide has negligible systemic exposure and will be classed as "Other HES therapy" rather than oral corticosteroid therapy.

Where the frequency of the recorded corticosteroid dose is not once daily, the following calculations will be used to determine the daily dose.

Medication Frequency	Daily Dose Equivalent
BID	2 x dose
TID	3 x dose
QID	4 x dose
QOD	dose / 2
2XWK	(2 x dose) / 7
3XWK	(3 x dose) / 7
4XWK	(4 x dose) / 7
5XWK	(5 x dose) / 7

6.2.1.1. Mean Daily OCS Dose

The change in the mean daily OCS dose from Weeks 0-4 to Weeks 48-52 will be calculated as follows:

The mean daily OCS dose for weeks 0-4 will be calculated as:

$$\frac{Sum\ of\ daily\ OCS\ dose\ for\ weeks\ 0-4}{28}$$

The mean daily OCS dose for weeks 48-52 will be calculated as:

$$\frac{Sum\ of\ daily\ OCS\ dose\ for\ weeks\ 48-52}{28}$$

The change in the mean daily OCS dose from Weeks 0-4 to Weeks 48-52 will be the difference of mean daily OCS dose for weeks 48-52 minus mean daily OCS dose for Weeks 0-4.

6.2.2. Study Period

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

6.2.2.1. Treatment Phases for HES Flare

Study Phase	Definition
Pre-Treatment	Flare onset date < Date of first dose of study treatment
On-Treatment	Date of first dose of study treatment ≤ Flare onset date ≤ Date of last dose of study treatment + 28 days
Off-Treatment	Date of last dose of study treatment + 28 days < Flare onset date ≤ Date of Week 52 visit /Study withdrawal date
Post-Treatment	Flare onset date > Date of Week 52 visit

6.2.2.2. Treatment Phases for other Efficacy Assessments

Study Phase	Definition
Pre-Treatment	Assessment date ≤ Date of first dose of study treatment
On-Treatment	Date of first dose of study treatment < Assessment date ≤ Date of last dose of study treatment + 28 days
Off-Treatment	Date of last dose of study treatment + 28 days < Assessment date ≤ Date of Week 52 visit /Study withdrawal date
Post-Treatment	Assessment date > Date of Week 52 visit

6.2.2.3. Treatment Phases for Adverse Events

Study Phase	Definition
Pre-Treatment	AE onset date/time < Date/time of first dose of study treatment
On-Treatment	Date/time of first dose of study treatment ≤ AE onset date/time ≤ Date of last dose of study treatment + 28 days
Post-Treatment	AE onset date > Date of last dose of study treatment + 28 days

6.2.2.4. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before the date of first dose of study treatment
Concomitant	Any medication that is not a prior medication

6.2.3. Study Day and Reference Dates

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

The efficacy reference date is the study treatment start date 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 Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

For summaries by visit, data recorded at an unscheduled visit will be re-assigned in the ADaM data sets to the closest nominal visit at which collection of data was scheduled, unless information already exists at that visit. Unscheduled data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Unscheduled data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. Unscheduled data that is not re-assigned to a scheduled visit will be considered in the derivation of baseline and highest/worst case post baseline result for relevant summary tables.

Data recorded at the early withdrawal visit will be re-assigned in the ADaM data sets to the next scheduled visit, unless information already exists at that visit. Early withdrawal data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Early withdrawal visit data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit, but will be considered in the derivation of highest/worst case post baseline result for relevant summary tables.

6.2.4.1. BFI Item 3 and PROMIS Weekly Assessment Windows

Daily assessments of BFI item 3 and assessment of PROMIS will be assigned to a single weekly analysis time point according to the table below.

Table 3 BFI Item 3 and PROMIS Weekly Assessment Windows

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
Week 52	Week 52 (Visit 15) visit date – 7 days	Week 52 (Visit 15) visit date – 1 day	
Week 51	Week 52 (Visit 15) visit date – 14 days	Week 52 (Visit 15) visit date – 8 days	If assessment falls into Week 51/Week 50/Week 49 and Week 48, assign assessment as Week 48. If assessment date is less than Week 48 (Visit 14) visit date, assign a relevant timepoint less than Week 48.
Week 50	Week 52 (Visit 15) visit date – 21 days	Week 52 (Visit 15) visit date – 15 days	
Week 49	Week 52 (Visit 15) visit date – 28 days	Week 52 (Visit 15) visit date – 22 days	
Week 48	Week 48 (Visit 14) visit date – 7 days	Week 48 (Visit 14) visit date – 1 day	
Week 47	Week 48 (Visit 14) visit date – 14 days	Week 48 (Visit 14) visit date – 8 days	If assessment falls into Week 47/Week 46/Week 45 and Week 44, assign assessment as Week 44. If assessment date is less than Week 44 (Visit 13) visit date, assign a relevant timepoint less than Week 44.
Week 46	Week 48 (Visit 14) visit date – 21 days	Week 48 (Visit 14) visit date – 15 days	
Week 45	Week 48 (Visit 14) visit date – 28 days	Week 48 (Visit 14) visit date – 22 days	
Week 44	Week 44 (Visit 13) visit date – 7 days	Week 44 (Visit 13) visit date – 1 day	
Week 43	Week 44 (Visit 13) visit date – 14 days	Week 44 (Visit 13) visit date – 8 days	If assessment falls into Week 43/Week 42/Week 41 and Week 40, assign assessment as Week 40. If assessment date is less than Week 40 (Visit 12) visit date, assign a relevant timepoint less than Week 40.
Week 42	Week 44 (Visit 13) visit date – 21 days	Week 44 (Visit 13) visit date – 15 days	
Week 41	Week 44 (Visit 13) visit date – 28 days	Week 44 (Visit 13) visit date – 22 days	
Week 40	Week 40 (Visit 12) visit date – 7 days	Week 40 (Visit 12) visit date – 1 day	
Week 39	Week 40 (Visit 12) visit date – 14 days	Week 40 (Visit 12) visit date – 8 days	If assessment falls into Week 39/Week 38/Week 37 and Week 36, assign assessment as Week 36.
Week 38	Week 40 (Visit 12) visit date – 21 days	Week 40 (Visit 12) visit date – 15 days	

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
Week 37	Week 40 (Visit 12) visit date – 28 days	Week 40 (Visit 12) visit date – 22 days	If assessment date is less than Week 36 (Visit 11) visit date, assign a relevant timepoint less than Week 36.
Week 36	Week 36 (Visit 11) visit date – 7 days	Week 36 (Visit 11) visit date – 1 day	
Week 35	Week 36 (Visit 11) visit date – 14 days	Week 36 (Visit 11) visit date – 8 days	If assessment falls into Week 35/Week 34/Week 33 and Week 32, assign assessment as Week 32. If assessment date is less than Week 32 (Visit 10) visit date, assign a relevant timepoint less than Week 32.
Week 34	Week 36 (Visit 11) visit date – 21 days	Week 36 (Visit 11) visit date – 15 days	
Week 33	Week 36 (Visit 11) visit date – 28 days	Week 36 (Visit 11) visit date – 22 days	
Week 32	Week 32 (Visit 10) visit date – 7 days	Week 32 (Visit 10) visit date -1 day	
Week 31	Week 32 (Visit 10) visit date – 14 days	Week 32 (Visit 10) visit date – 8 days	If assessment falls into Week 31/Week 30/Week 29 and Week 28, assign assessment as Week 28. If assessment date is less than Week 28 (Visit 9) visit date, assign a relevant timepoint less than Week 28.
Week 30	Week 32 (Visit 10) visit date – 21 days	Week 32 (Visit 10) visit date – 15 days	
Week 29	Week 32 (Visit 10) visit date – 28 days	Week 32 (Visit 10) visit date – 22 days	
Week 28	Week 28 (Visit 9) visit date – 7 days	Week 28 (Visit 9) visit date – 1 day	
Week 27	Week 28 (Visit 9) visit date – 14 days	Week 28 (Visit 9) visit date – 8 days	If assessment falls into Week 27/Week 26/Week 25 and Week 24, assign assessment as Week 24. If assessment date is less than Week 24 (Visit 8) visit date, assign a relevant timepoint less than Week 24.
Week 26	Week 28 (Visit 9) visit date – 21 days	Week 28 (Visit 9) visit date – 15 days	
Week 25	Week 28 (Visit 9) visit date – 28 days	Week 28 (Visit 9) visit date – 22 days	
Week 24	Week 24 (Visit 8) visit date – 7 days	Week 24 (Visit 8) visit date – 1 day	
Week 23	Week 24 (Visit 8) visit date – 14 days	Week 24 (Visit 8) visit date – 8 days	If assessment falls into Week 23/Week 22/Week 21 and Week 20, assign assessment as Week 20. If assessment date is less than Week 20 (Visit 7) visit date,
Week 22	Week 24 (Visit 8) visit date – 21 days	Week 24 (Visit 8) visit date – 15 days	
Week 21	Week 24 (Visit 8) visit date – 28 days	Week 24 (Visit 8) visit date – 22 days	

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
			assign a relevant timepoint less than Week 20.
Week 20	Week 20 (Visit 7) visit date – 7 days	Week 20 (Visit 7) visit date -1 day	
Week 19	Week 20 (Visit 7) visit date – 14 days	Week 20 (Visit 7) visit date – 8 days	If assessment falls into Week 19/Week 18/Week 17 and Week 16, assign assessment as Week 16. If assessment date is less than Week 16 (Visit 6) visit date, assign a relevant timepoint less than Week 16.
Week 18	Week 20 (Visit 7) visit date – 21 days	Week 20 (Visit 7) visit date – 15 days	
Week 17	Week 20 (Visit 7) visit date – 28 days	Week 20 (Visit 7) visit date – 22 days	
Week 16	Week 16 (Visit 6) visit date – 7 days	Week 16 (Visit 6) visit date – 1 day	
Week 15	Week 16 (Visit 6) visit date – 14 days	Week 16 (Visit 6) visit date – 8 days	If assessment falls into Week 15/Week 14/Week 13 and Week 12, assign assessment as Week 12. If assessment date is less than Week 12 (Visit 5) visit date, assign a relevant timepoint less than Week 12.
Week 14	Week 16 (Visit 6) visit date – 21 days	Week 16 (Visit 6) visit date – 15 days	
Week 13	Week 16 (Visit 6) visit date – 28 days	Week 16 (Visit 6) visit date – 22 days	
Week 12	Week 12 (Visit 5) visit date – 7 days	Week 12 (Visit 5) visit date – 1 day	
Week 11	Week 12 (Visit 5) visit date – 14 days	Week 12 (Visit 5) visit date – 8 days	If assessment falls into Week 11/Week 10/Week 9 and Week 8, assign assessment as Week 8. If assessment date is less than Week 8 (Visit 4) visit date, assign a relevant timepoint less than Week 8.
Week 10	Week 12 (Visit 5) visit date – 21 days	Week 12 (Visit 5) visit date – 15 days	
Week 9	Week 12 (Visit 5) visit date – 28 days	Week 12 (Visit 5) visit date – 22 days	
Week 8	Week 8 (Visit 4) visit date – 7 days	Week 8 (Visit 4) visit date – 1 day	
Week 7	Week 8 (Visit 4) visit date – 14 days	Week 8 (Visit 4) visit date – 8 days	If assessment falls into Week 7/Week 6/Week 5 and Week 4, assign assessment as Week 4. If assessment date is less than Week 4 (Visit 3) visit date, assign a relevant timepoint less than Week 4.
Week 6	Week 8 (Visit 4) visit date – 21 days	Week 8 (Visit 4) visit date – 15 days	
Week 5	Week 8 (Visit 4) visit date – 28 days	Week 8 (Visit 4) visit date – 22 days	
Week 4	Week 4 (Visit 3) visit date – 7 days	Week 4 (Visit 3) visit date – 1 day	

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
Week 3	Week 4 (Visit 3) visit date – 14 days	Week 4 (Visit 3) visit date – 8 days	If assessment falls into Week 3/Week 2/Week 1 and Baseline (Week 0) or Screening, assign assessment as Baseline (Week 0) or Screening.
Week 2	Week 4 (Visit 3) visit date – 21 days	Week 4 (Visit 3) visit date – 15 days	
Week 1	Week 4 (Visit 3) visit date – 28 days	Week 4 (Visit 3) visit date – 22 days	
Baseline (Week 0)	Date of first dose of study treatment – 7 days	Date of first dose of study treatment – 1 day	
Screening	N/A	Date of first dose of study treatment – 8 days	

6.2.4.2. Medication Assessment Windows

For the reporting of medication use and changes in medication use (e.g. change in OCS dose and change in immunosuppressive and/or cytotoxic HES therapy) will be assigned to a 4-weekly analysis time point according to the table below.

Table 4 Medication Assessment Windows

Reporting Period	First Day Included	Last Day Included
Pre-treatment	Medication is taken on the date of first dose of IP (Day 1)	
Weeks 0-4 (Baseline)	Day after day of first dose	28 days after day of first dose
Weeks 4-8	29 days after day of first dose	56 days after day of first dose
Weeks 8-12	57 days after day of first dose	84 days after day of first dose
Weeks 12-16	85 days after day of first dose	112 days after day of first dose
Weeks 16-20	113 days after day of first dose	140 days after day of first dose
Weeks 20-24	141 days after day of first dose	168 days after day of first dose
Weeks 24-28	169 days after day of first dose	196 days after day of first dose
Weeks 28-32	197 days after day of first dose	224 days after day of first dose
Weeks 32-36	225 days after day of first dose	252 days after day of first dose
Weeks 36-40	253 days after day of first dose	280 days after day of first dose
Weeks 40-44	281 days after day of first dose	308 days after day of first dose

Reporting Period	First Day Included	Last Day Included
Weeks 44-48	309 days after day of first dose	336 days after day of first dose
Weeks 48-52	337 days after day of first dose	364 days after day of first dose

6.2.5. Multiple measurements at One Analysis Time Point

In the case of any questionnaires or eCOA endpoint data which reflect multiple assessments or results on a single study day, the earliest date/time completed score on each given day (or analysis window) will be taken.

For ECG, if multiple assessments are recorded on the same day, the mean of the parameters recorded in the multiple assessments will be used in the derivation of any summary statistics for that ECG parameter. For spirometry measures, the best of the multiple assessments [as determined by the Spirometry vendor technician] will be used for summary statistics [identified within the SDTM datasets using SUPPRE.QVAL='Y' where QNAM='BERESFL']. For all other measurements, unless specified, if there are multiple assessments are taken at a single visit the first assessment will be used in any derivation of summary statistics. All values will be presented in listings.

For laboratory tests, if more than one assessment is taken on the same day, the test from a central laboratory will be taken over the test from a local laboratory. Participants having both High and Low values for Normal Ranges at any post-baseline visits 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, if applicable.

6.2.6. Handling of Partial Dates

Element	Reporting Detail
General	○ 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).
HES Flare and Adverse Events	○ Any partial dates for HES flare and adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if this imputation results in a date prior to the first dose of study treatment and the event could possibly have occurred during treatment from the partial information, then the date of the first dose of study treatment will be assumed to be the start date.

Element	Reporting Detail
	○ The event will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. ○ Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. The recorded partial date will be displayed in listings.
Concomitant Medications	○ Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. The recorded partial date will be displayed in listings.

6.2.7. Laboratory Parameters

If a laboratory value which is expected to have a numeric value for summary purposes has a non-detectable level reported in the database, where the numeric value is missing, but instead a character value starting with '<x' or >x' (or indicated as less than x or greater than x in the comment field) is present, a numeric value will be imputed; the number of significant digits in the observed value will be used to determine how much to add or subtract to impute the corresponding numeric value:

- Example 1: 2 significant digits = '< x' imputed as x – 0.01
- Example 2: 1 significant digit = '> x' imputed as x + 0.1
- Example 3: 0 significant digits = '< x' imputed as x -1

Laboratory values with missing values due to being below the limit of quantification (BLQ) for that parameter will have a value imputed as half the lower limit of quantification for that measure (i.e. the lowest observed value for that measure within the entire study database).

6.3. Appendix 3: Electronic Clinical Outcome Assessment (eCOA) Compliance

6.3.1. Study Level (Overall) Compliance

The overall compliance across all eCOAs within the study will be assessed over all study days and scheduled clinic visits between the date of the Screening visit through to the day of the participant's study completion or study withdrawal. An eCOA is considered complete if there is no missing data within the assessment.

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

$$\frac{Total\ number\ of\ complete\ eCOAs}{Sum\ of\ expected\ number\ of\ complete\ eCOAs\ per\ participant} \times 100$$

The eCOAs considered within this Overall eCOA compliance calculation will include:

– BFI Item 3 in participants aged ≥12 years (expected daily)

CCI

CCI

CCI

CCI

CCI

The target overall compliance for the study is 80%. The overall study eCOA compliance will be reported for each treatment group and overall.

A participant is considered to be compliant with their eCOAs if at least 80% of their eCOAs are complete (have no missing data), i.e, a participant is eCOA compliant if they meet the following criteria:

$$\frac{Total\ number\ of\ complete\ eCOAs}{Expected\ number\ of\ complete\ eCOAs} \times 100 \geq 80\%$$

The number of participants who are <50% compliant, 50-<80% compliant and ≥80% compliant with eCOA assessments will be summarised.

In the case of any questionnaires or eCOA endpoint data which reflect multiple assessments or results collected on a single study day, each eCOA assessment will only be counted once on each given day to avoid double-counting of any duplicate or repeated eCOA assessments.

6.4. Appendix 4: Adverse Events of Special Interest

Adverse events of special interest (AESI) in the mepolizumab clinical development program are described in the mepolizumab BRMP/DRMP. The methods by which these events will be identified within this study reporting are detailed in this section. Section 6.4.7 details the displays to be generated to aid in the review of this data.

6.4.1. Systemic Allergic (Type I Hypersensitivity) and Other Systemic Reactions

Systemic reactions will be collected via a targeted eCRF and each participant with such an adverse event are required to be assessed against Sampson's diagnostic criteria for anaphylaxis [Sampson, 2006].

Events reported on the eCRF as systemic reactions will be further categorized by the investigator as an 'allergic (type I hypersensitivity) reaction' or 'systemic other' reaction. Investigators are instructed to report systemic reactions with the best diagnosis/event term that describes the event.

6.4.2. Alterations in immune response (infections)

All infections and serious infections will be reported under the MedDRA system organ class of 'Infections and Infestations'.

Specific events of interest are Opportunistic Infections which will be identified through matching of collected adverse event preferred terms with those from:

- Opportunistic infections standard MedDRA query (SMQ) (narrow terms)
- Herpes zoster preferred term

6.4.3. Alterations in immune response (malignancies)

All neoplasms will be reported under the MedDRA system organ class of 'Neoplasms, benign, malignant and unspecified (including cysts and polyps)'.

Specific events of interest are Malignancies which will be identified through two differing methods by matching of collected adverse event preferred terms with those from:

Method 1: Sub-SMQs under the Malignancies SMQ

- Malignant tumours sub-SMQ (narrow terms)
- Tumours of unspecified malignancy sub-SMQ (narrow terms)

Method 2: Sub-SMQs under the Malignancies SMQ

- Malignant tumours sub-SMQ (narrow terms)

- Tumours of unspecified malignancy sub-SMQ (narrow terms)
- Malignancy-related conditions sub-SMQ (narrow terms)

6.4.4. Alterations in cardiovascular safety

Cardiac disorders and serious cardiac disorders will be reported under the MedDRA system organ class of 'Cardiac Disorders'.

Specific events of interest are Serious cardiac, vascular and thromboembolic (CVT) events and Ischemic events. Serious CVT events will be identified as all serious adverse events classified under the MedDRA system organ classes of 'Cardiac Disorders' or 'Vascular Disorders', and thromboembolic events will be identified through matching of collected adverse event preferred terms with those from:

Sub-SMQs under the Embolic and thrombotic events SMQ

- Embolic and thrombotic events, arterial sub-SMQ (narrow terms)
- Embolic and thrombotic events, venous sub-SMQ (narrow terms)
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous sub-SMQ (narrow terms)

Sub-SMQs under the Ischaemic Heart Disease SMQ

- Myocardial infarction sub-SMQ (narrow terms)
- Other Ischaemic heart disease sub-SMQ (narrow terms)

Sub-SMQs under the Central Nervous System Vascular Disorders SMQ

- Ischaemic central nervous system vascular conditions sub-SMQ (narrow terms)
- Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic sub-SMQ (narrow terms)

Serious Ischemic adverse events will be a subset of the Serious CVT events identified above through matching of collected adverse event preferred terms with those from:

Sub-SMQs under the Ischaemic Heart Disease SMQ

- Myocardial infarction sub-SMQ (narrow terms)
- Other Ischaemic heart disease sub-SMQ (narrow terms)

Sub-SMQs under the Central Nervous System Vascular Disorders SMQ

- Ischaemic central nervous system vascular conditions sub-SMQ (narrow terms)
- Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic sub-SMQ (narrow terms)

6.4.5. Local Injection Site Reactions

Local injection site reactions will be collected via a targeted eCRF.

6.4.6. Identifying Adverse Events of Special Interest

For the AESIs of Opportunistic Infections, Malignancies, Serious CVT events and Serious Ischemic events, relevant adverse event preferred terms will be identified as specified in Sections 6.4.1 to 6.4.5. SMQs and sub-SMQs will be based on the version of the MedDRA dictionary which is current at the time of analysis.

A list of the relevant adverse event preferred terms will be maintained within a project level reference dataset and will be applicable across indications. This project level reference dataset will be used to identify the AESIs within the analysis of this study.

6.4.7. Analysis of Adverse Events of Special Interest

For all of the AESIs stated in Sections 6.4.1 to 6.4.5 individual summaries showing the number and percent of subjects identified as having an AESI, broken down by adverse event preferred term, will be produced. In addition, an AESI profile summary table will be created for each AESI summarising the number of subjects with the AESI, serious AESI, drug related AESI together with summaries by maximum severity and separately by outcome. Infections, serious infections, neoplasms, cardiac disorders and serious cardiac disorders will be reported as part of the standard AE tables.

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7. REFERENCES

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