Statistical Analysis Plan Amendment 2

Study ID: 212895

Official Title of Study: A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744

NCT number: NCT05243680

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TITLE PAGE

Protocol Title: A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744

Study Number: 212895

Compound Number: GSK3511294

Abbreviated Title:

Acronym AGILE

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND	**146742**
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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
01	23 Feb 2022	01(30-JUL-2021)	Not Applicable	Original version
02	23 Jul 2024	01(30-JUL-2021)	Update to analysis sets in Section 3. Inclusion of additional analyses on the Safety-modified analysis set.	Minor modification to Japan subset and update to account for site with GCP non-compliance.
			Update categories for region in Section 4.1.3	To be consistent with study 206713 and 213744.
			Additional sentence added at end of 4.5.2	Reference to additional AE display for broad SMQ 'Torsade de pointes/QT Prolongation'
			Removal of a immunogenicity data summary in Section 4.6	Not required for this extension study
			Update in Section 4.7	Update of imputation for limit of quantification
03		01(30-JUL-2021)	Adding appendix 3	Per GSK new guidance adding eCOA Compliance

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the interim and final Clinical Study Reports(CSR) for Study 212895. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary (Safety)	
• To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12 month open label extension phase	• Incidence of AEs/SAEs over 52 weeks • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294 over 52 weeks
Secondary (Efficacy)	
• To evaluate the effects of long-term dosing of GSK3511294 100 mg (SC) every 26 weeks on a range of clinical markers of asthma control and additional efficacy assessments on top of existing asthma therapy over a 12 month open label extension phase	• Annualized rate of clinically significant exacerbations[a] over 52 weeks • Change from Baseline in Asthma Control Questionnaire-5 (ACQ-5) score at discrete timepoints during the 52 week period • Change from Baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 26 and Week 52. • Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52
Other	

• To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12 month open label extension phase	• ECG assessments at discrete timepoints during the 52 week period
	  • Change from baseline in ECG values
	  • Maximum QTc values post baseline
	  • Maximum increase in QTc values post baseline
	  • ECG findings
	• Change from baseline in vital signs including blood pressure (BP), body temperature, and pulse rate at discrete timepoints during the 52 week period

Objectives	Endpoints
	• Change from baseline in laboratory parameters (including haematological, clinical chemistry) and hepatobiliary laboratory abnormalities, at discrete timepoints during the 52 week period
CCI [redacted]	
Pharmacodynamic (PD)	
CCI [redacted]	

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit. 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. Estimand

The following two attributes apply to all estimands:

- Population: Adult and adolescent participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy

- Treatment: GSK3511294 100 mg (SC) given every 26 weeks on top of SoC.
  - ✓ open-label GSK3511294 + SoC and on GSK3511294 + SoC in previous study
  - ✓ open-label GSK3511294 + SoC and on placebo + SoC in previous study

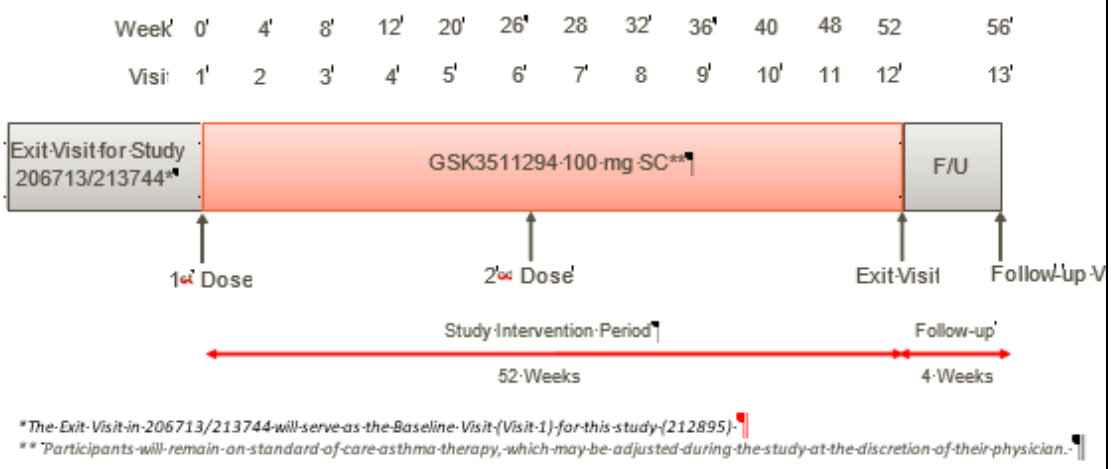
Estimand		
Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary objective (Safety): To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12 month open label extension phase		
a) Incidence of AEs/SAEs over 52 weeks	• Study intervention discontinuation due to reasons unrelated to the	a) Number and percentage of participants with any

Estimand		
b) Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294 over 52 weeks	COVID 19 pandemic: while on-treatment strategy i.e. using data up until 26 weeks after last dose of GSK3511294. This strategy is to summarise the events while the participants are exposed to the treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on-treatment strategy i.e. using data up until 26 weeks after last dose of GSK3511294 • Change in maintenance therapy or use of prohibited medications: CCI [redacted]	AEs and incidence rate of AEs over 52 weeks b) Number and percentage of participants with incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294 and mean titre results over 52 weeks
Secondary Objective (Efficacy): To evaluate the effects of long-term dosing of GSK3511294 100 mg (SC) every 26 weeks on a range of clinical markers of asthma control and additional efficacy assessments on top of existing asthma therapy over a 12-month open label extension phase		
a) Annualized rate of Clinically significant exacerbations over 52 weeks b) Change from Baseline in Asthma Control Questionnaire-5 (ACQ-5) score at discrete timepoints during the 52-week period c) Change from Baseline in St. George's Respiratory Questionnaire (SGRQ)	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment CCI [redacted] This strategy reflects the ITT principle. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted]	a) Annualised rate of clinically significant exacerbations over 52 weeks b) Mean Change from Baseline in ACQ-5 score during the 52-weeks period c) Mean Change from Baseline in SGRQ total score at Week 26 and Week 52

Estimand		
total score at Week 26 and Week 52. d) Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52	CCI [redacted] • Change in maintenance therapy or use of prohibited medications: CCI [redacted]	d) Mean Change from Baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52
Other Objective: To describe the long-term safety profile of GSK3511294 100 mg (SC) every 26 weeks in participants with severe asthma with an eosinophilic phenotype on top of existing asthma therapy over a 12-month open label extension phase		
a) ECG assessments during the 52-week period • Change from baseline in ECG values • Maximum QTc values post baseline • Maximum increase in QTc values post baseline • ECG findings b) Change from baseline in vital signs including blood pressure (BP), body temperature, and pulse rate during the 52-week period c) Change from baseline in laboratory parameters and hepatobiliary laboratory abnormalities during the 52-week period	Same intercurrent event strategies as for the primary (safety) endpoint	a) Descriptive summary for change from baseline in ECG values, maximum QTc value post baseline, maximum increase in QTc value post baseline and ECG finding over the 52-week period b) Descriptive summary for change from baseline in vital signs including blood pressure (BP), body temperature, and pulse rate over 52-week period c) Descriptive summary for change from baseline in laboratory parameters and hepatobiliary laboratory abnormalities over the 52-week period
Other Objective: To evaluate the effects of long-term dosing of GSK3511294 on patient global impression of asthma severity		
CCI [redacted]		

Estimand
CCI [redacted]

1.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• multicentre, single-arm, open-label 12- month extension study • 52-week treatment period • Participants who completed either study 206713 or 213744 will have the opportunity to participate in this study, regardless of which treatment they were previously randomized. • The total number of participants enrolled in this trial will not be greater than the combined number randomised into Studies 206713 and 213744. • Participants meeting all the inclusion criteria and none of the exclusion criteria will receive their first open-label dose of GSK3511294 SC at Visit 1 (baseline visit). Participants will receive a second open-label dose of GSK3511294 SC at 26 weeks after Visit 1, providing up to 52 weeks of treatment.
Study intervention	GSK3511294 100 mg SC
Study intervention Assignment	All Participants will receive open label GSK3511294 100 mg SC
Interim Analysis	• As the study will be still ongoing at the time of regulatory submission, interim analyses will be performed in order to provide open-label safety and efficacy data in an interim Clinical Study Report (CSR) to inform the risk-benefit assessment of GSK3511294 in asthma with an eosinophilic phenotype. • An independent data monitoring committee (IDMC) review of Study 212895 safety data is planned as part of the IDMC review of overall safety for studies 206713 and 213744. Study 212895 is not governed by an IDMC.

2. STATISTICAL HYPOTHESES

Because the study has a single treatment arm, statistical analyses of treatment effect will not be performed. Therefore, no hypotheses have been defined for this study.

2.1. Multiplicity Adjustment

This is a single arm study. There will be no treatment comparison. Therefore, multiplicity adjustment is not applicable.

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 received study intervention or underwent a post screening study procedure). Note screening failures 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
Safety	All participants who receive at least one dose of open-label GSK3511294 excluding participants from sites 250190, 250085 and 250523	• Study Population • Safety • Efficacy • Immunogenicity • PD
Safety-Japan	All participants in the Safety population who are enrolled from Japan and with Japanese heritage only	• Study Population • Safety • Efficacy • Immunogenicity • PD
Safety-Non-Japan	All participants in the Safety population who are not in Safety-Japan analysis set	• PD
Safety-Modified	All participants in the Safety population plus enrolled participants from sites 250190, 250085 and 250523 who received at least one dose of study intervention.	• Key Safety

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Safety Analysis Set will be used for all Study Population, Efficacy, Safety, Immunogenicity and PD analyses, unless otherwise stated. The Output and Programming Specification (OPS) document will provide more details.

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

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

A subset of Study Population, Efficacy, Safety, Immunogenicity and PD outputs will be produced for Safety-Japan (and Safety-Non-Japan) analysis sets. A list of these outputs will be included in the OPS.

Additional output(s) will be produced for Safety-Modified analysis set, see OPS for details.

4.1.2. Baseline Definition

For participants whose Exit Visit in 206713 or 213744 was on the same day, or within 7 days of Visit 1 in this study (212895), the assessments collected at Exit Visit in 206713 or 213744 will be copied over to this study's database at the time of reporting. These assessments will be labelled as a subject's baseline values. For participants whose Visit 1 in this study is performed greater than 7 days after the Exit Visit in 206713 or 213744, the assessments will be performed pre-dose at Visit 1 in this study and will be used as baseline values. For participants whose assessments are done at both Exit Visit in 206713 or 213744 and Visit 1, the assessments performed pre-dose at Visit 1 in this study will be used as baseline values. The assessments refer to ECG, vital signs, laboratory, immunogenicity, complement C3 and C4, spirometry, ACQ-5, SGRQ and PGI-S assessments.

Generally, change from baseline will be defined as the difference between the value of the endpoint at the time point of interest and the baseline value. However, if stated below, a change from baseline analysis may be performed on the ratio scale and change from baseline will be the ratio: time point of interest value/baseline value.

4.1.3. Multicentre Studies

The following regions are defined:

- Europe (Czechia, France, Italy, Poland, Spain, UK, Germany, Hungary, Ireland)
- US

- Rest of World (Japan, China, Taiwan, Australia, Canada)

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

4.2. Primary Endpoint(s) Analyses

The primary endpoints are incidence of AEs/SAEs and incidence of immunogenicity measured by the presence of ADA/NAb to GSK3511294 over 52 weeks. The estimands for the primary endpoints are provided in Section 1.1.

The main analysis approach for incidence of AEs/SAEs is described in Section 4.5.2 while the analysis approach for incidence of immunogenicity measured by the presence of ADA/NAb to GSK3511294 is described in Section 4.6.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Secondary endpoint(s)

4.3.1.1. Definition of endpoints

The secondary endpoints are:

- Annualized rate of clinically significant exacerbations over 52 weeks
- Change from baseline in ACQ-5 score at discrete timepoints during 52-week period
- Change from baseline in SGRQ total score at Week 26 and Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52

4.3.1.2. Main analytical approach

Secondary Endpoints Analyses
Endpoint(s)
• Annualized rate of clinically significant exacerbations over 52 weeks
Model Specification

• Generalized linear model assuming a negative binomial distribution
• Terms in the model:
  ◦ **Response**: number of recorded clinically significant exacerbations experienced per subject.
  ◦ **Categorical**: treatment group during study 206713 or 213744 and geographical region
  ◦ **Continuous**: % predicted pre-bronchodilator FEV1 from the baseline measurement of 206713 or 213744
  ◦ **Offset**: Log_e(total time in this study in years)

Model Checking & Diagnostics
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.
Results Presentation
• model estimated annualized exacerbation rates and associated 95% CI for: ◦ open-label GSK3511294

Secondary Endpoints Analyses
○ open-label GSK3511294 and on GSK3511294 in previous study ○ open-label GSK3511294 and on placebo in previous study
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, CCI [redacted] • For participants that withdraw from the study, preventing assessment of the endpoint, CCI [redacted]

Secondary Endpoints Analyses
Endpoint(s)
• Change from baseline in SGRQ total score at Week 26 and Week 52 • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • Change from baseline in pre-bronchodilator FEV_1 at Week 26 and Week 52
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • Terms in the model: **Response:** Change from baseline in SGRQ Total score or Change from baseline in ACQ-5 score or Change from baseline in pre-bronchodilator FEV1 at each visit. **Categorical:** treatment group during 206713 or 213744, geographical region, and visit **Continuous**: baseline (SGRQ Total score, or ACQ-5 score, or pre-bronchodilator FEV1), and % predicted pre-bronchodilator FEV1 from the baseline measurement of 206713 or 213744 (for SGRQ total score and ACQ-5 score endpoints only) **Interaction:** treatment group*visit **Repeated:** visit • The MMRM analysis for SGRQ total scores will include data collected at Weeks 26 and 52. The MMRM analysis for ACQ-5 score will include data collected at Weeks 4, 8, 12, 20, 24, 26, 28, 32, 40 and 52. The MMRM analysis for pre-bronchodilator FEV_1 will include data collected at Weeks 26 and 52. • The model will be fit with an unstructured variance-covariance matrix. • The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead. In the event the model fails to run using residual method and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints/intervals of most interest. • Baseline is defined in Section 4.1.2.
Model Checking & Diagnostics
• The fit of the regression models will be examined using “Q-Q” plots of the standardized residuals.
Results Presentation
• Least-square (LS) mean change from baseline values will be presented with their associated standard errors as well as 95% CIs for: ○ open-label GSK3511294 ○ open-label GSK3511294 and on GSK3511294 in previous study ○ open-label GSK3511294 and on placebo in previous study

Secondary Endpoints Analyses
• The LS mean and associated 95% CIs for all visits will also be presented graphically. • SGRQ total scores, ACQ-5 score and pre-bronchodilator FEV_1 (absolute value and changes from baseline) will also be summarised by treatment group during 206713 or 213744 and visit.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, CCI [redacted] • For participants that withdraw from the study, preventing assessment of CCI [redacted]

4.4. Other Endpoints Analyses

CCI [redacted]

4.5. Safety Analyses

All safety summaries and listings will be produced for the Safety Analysis Set unless otherwise specified. All safety summaries will be presented overall and by the treatment in the previous study.

4.5.1. Extent of Exposure

Two doses of open-label study treatment will be administered during treatment period: Visit 1 (Day1/Week 0) and the second at Visit 6 (Week 26). Each dose is viewed as providing therapeutic coverage for 26 weeks (182 days). The number of treatments administered and the number of days exposure in this study will be summarised descriptively and listed. Total subject-year exposure in this study will also be presented.

Number of days of exposure to study treatment in this study will be calculated as follows:

Duration of Exposure in Days = (Date of Final Dose) – (Date of First Dose) + 182

Subject years exposure in this study is calculated as follows:

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

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

4.5.2. Adverse Events

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

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

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 permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced.

A summary of number and percentage of participants with any adverse events by maximum severity will be produced.

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). 2) in descending order by PT only.
Common (>=3%) AEs will be summarised by overall frequency and summarised by time to onset.

A separate 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.

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 in descending order by System Organ Class (SOC) and Preferred Term (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.

AE/study intervention related AE/SAE/etc will be summarised separately according to study treatment phases.

Summary table	Pre-treatment	On Treatment	On and Post treatment	Pre, on and Post treatment
AEs by SOC and PT		✓	✓	
Common AEs (>=3%) by overall frequency		✓		

Summary table	Pre-treatment	On Treatment	On and Post treatment	Pre, on and Post treatment
Drug related AE by SOC and PT		✓	✓	
SAE by SOC and PT	✓	✓	✓	
Drug related SAE by SOC and PT			✓	
Drug related SAE by overall frequency			✓	
Drug related fatal by SOC and PT			✓	
Drug related non-serious AE by overall frequency			✓	
Adverse Events of Special Interest (AESI)		✓	✓ Only single summary	
Summary of Deaths				✓
COVID-19 AEs		✓		

Note: study treatment phases are defined in Section 6.2.2.

4.5.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK3511294 program include:

- Allergic (Type 1 hypersensitivity) 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]

- 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 PT 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.

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

Additionally, AESI of QTc prolongation will be summarised using the MedDRA SMQ Broad "Torsade de pointes/QT Prolongation" by overall and by the treatment in the previous study, for the program level analysis. The display will include both an "Any Event" row and the individual PTs.

4.5.2.2. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The overall incidence of AEs and SAEs of COVID-19, COVID-19 AEs leading to study intervention discontinuation and COVID-19 AEs leading to study withdrawal will be summarised. The incidence of these events at individual PT level can be obtained from the standard AE/SAE summaries.

4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

The impact of the COVID-19 pandemic on the safety results will be assessed. Subject status and subject disposition for the study conclusion record by relationship to COVID-19 pandemic, treatment status and reasons for discontinuation of study treatment by relationship to COVID-19 pandemic, important COVID-19 related protocol deviations, visits impacted by COVID-19 pandemic will be summarised.

COVID-19-related adverse events by System Organ Class and Preferred Term, COVID-19 assessments for subjects with COVID-19 adverse events will be summarised.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst-case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for haematology, and chemistry laboratory tests will be produced. Liver function laboratory tests will be included with chemistry lab tests.

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above. Possible Hy's law cases are defined as any elevated alanine aminotransferase (ALT)>3×upper limit of normal (ULN), total bilirubin≥2×ULN and alkaline phosphatase (ALP)<3×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. ALP<3×ULN/missing means it is satisfied unless the ALP is ≥3xULN at the time of bilirubin elevation. The summary will be produced for worst case post baseline only.

An e-DISH plot of maximum post baseline total bilirubin versus maximum post baseline ALT will be created.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody are collected at baseline visit of previous study (206713 or 213744) and if clinically indicated post baseline (in this study), analysed on as needed basis and will be summarised only for participants with data available.

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.

4.5.3.3. ECG

Change from baseline (for post-baseline timepoints) values for QTc(F), and heart rate will be summarised by treatment for Baseline, Week 2, Week 26, Week 28, and Week 52. ECG findings will be summarised by visits.

Individual maximum QTc(F) values will also 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 <= 450, increase to 450 < to <= 480, increase to 480 < to <= 500, increase to 500< to <=530 and increase to > 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.

4.5.4. Additional Safety Analyses

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

- Overview of all adverse events (including sites 250190, 250085 and 250523)
- Listing of all adverse events from sites 250190, 250085 and 250523

4.6. Immunogenicity Analysis

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

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti-GSK3511294 antibodies.

The following descriptive summaries will be presented by visit using Safety population

- 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 neutralizing antibody assay results: it will summarise the neutralising antibody assay results for participants with a positive binding antibody confirmatory assay result. Neutralising antibody assay results will be categorised as positive or negative. It will also summarise the highest post-baseline neutralizing antibody assay result obtained.

- Summary of AE by highest post-baseline binding antibody confirmatory assay result

Note: Visits will include baseline visit (V1) 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 subcategories: 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.

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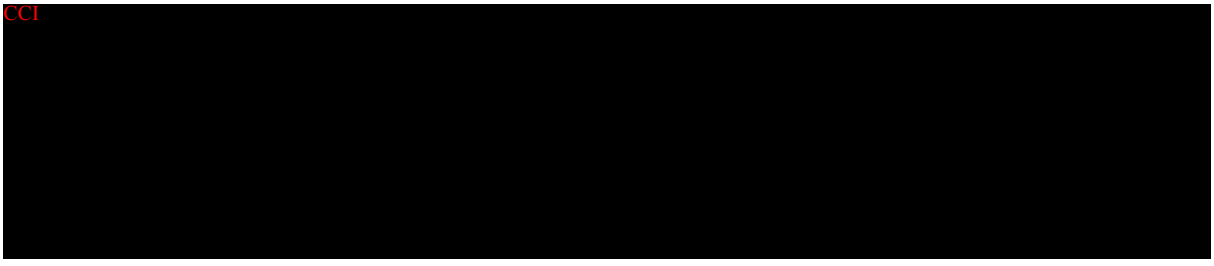

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4.9. Interim Analyses

4.9.1. Interim Analysis for Regulatory Submission

As the study will be still ongoing at the time of regulatory submission, interim analyses will be performed in order to provide open-label safety and efficacy data in an interim Clinical Study Report (CSR) to inform the risk-benefit assessment of GSK3511294 in asthma with an eosinophilic phenotype..

At interim a 'cut' will be made in the data, where any data collected beyond a prespecified cut-off date will not be included within the datasets to be reported. The interim analysis will include the analyses specified in this analysis plan. The details of the outputs are in the OPS.

4.9.2. IDMC

IDMC will periodically review safety data from the study 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.

Data from Study 212895 is being provided for information to the IDMC as potential supporting data for the overall assessment of safety for use of GSK3511294 in the 206713, 213744 and 206785 study population. The IDMC will not issue recommendations for the conduct of Study 212895.

4.10. Changes to Protocol Defined Analyses

None.

5. SAMPLE SIZE DETERMINATION

There is no sample size calculation for this study since this is an estimation study with the primary aim to estimate long-term safety outcomes. The sample size will be determined by the number of available participants who were randomised into Study 206713 and Study 213744 and are eligible for the current study based on inclusion and exclusion criteria.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

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

In this multicentre global study, enrolment will be presented by country and site.

All summaries will be presented overall and by previous treatment groups.

6.1.1. Participant Disposition

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 summarised. For those who have neither completed nor withdrawn, they will be categorized as on study intervention or in follow up.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, are ongoing with study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarised with descriptive statistics. In addition, the following age categories will be summarised: 12-17, 18-64 and >=65 based on the Enrolled Analysis Set.

History of tobacco use will be summarised (i.e., Never, Current, Former).

A summary of baseline cardiovascular family history assessment will be presented. The number of participants who report a family history of cardiovascular risk factors will be summarised.

Past medical conditions and current medical conditions as of Baseline will be summarised respectively. Past medical conditions are those conditions which were considered no longer present at each participant's baseline visit. Current medical conditions are those conditions which were considered present/ongoing at each participant's baseline visit.

Lung function, pre bronchodilator FEV_1, FVC, percent predicted FEV_1, and FEV_1/FVC at baseline visit 1 will be summarised.

The following data will be summarized using baseline data from previous study 206713 or 213744 where ICS dose at baseline refers to baseline in previous study:

- Summary of Asthma History and Baseline Disease Characteristics

- Summary of Asthma Exacerbation History

6.1.3. Protocol Deviations

Important protocol deviations will be summarised.

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

6.1.4. 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 show the number and percentage of participants taking concomitant medications by Ingredient. Multi-ingredient products will be summarised by their separate ingredients rather than as a combination of ingredients. Summaries will be split into asthma and non-asthma concomitant medications. Summaries for asthma medication will be categorised by Respiratory Medication Class (RMC) dictionary. Anatomical Therapeutic Chemical (ATC) classifications will appear in the summary for non-asthma medication.

The summary of concomitant medications will include:

- Summary of Asthma Concomitant Medications Taken During Treatment by Respiratory Medication Class Group
- Summary of Exacerbation Concomitant Medications Taken for an Exacerbation During Treatment by Respiratory Medication Class Group
- Summary of Non-Asthma Concomitant Medications Taken During Treatment

Note: ‘during treatment’ refers to on treatment period in this study (212895).

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

The following criteria will be used to flag potential clinical importance:

Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
CCI [redacted]				

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

Liver Function			
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**
			High Flag (>x)
ALT/SGPT	U/L	High	3 x ULN
AST/SGOT	U/L	High	3 x ULN
AlkPhos	U/L	High	3 x ULN
T Bilirubin	µmol/L	High	34.2
ALT, Bilirubin	U/L		ALT ≥ 3xULN and Bilirubin ≥ 2xULN (>35% direct)
ALT, INR			ALT ≥ 3xULN and INR > 1.5

6.2.2. Study Phases

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

6.2.2.1. Study Phases in General (unless specified in Section 6.2.2.2 to Section 6.2.2.3)

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

Study Phase	Definition
Pre-Treatment	Assessment/Event Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Assessment/Event Date ≤ Date of Last Dose of Study Treatment + 182 days
Post-Treatment	Assessment/Event Date > Date of Last Dose of Study Treatment + 182 days

6.2.2.2. Study Phases for Concomitant Medication

Study Phase	Definition
Pre-Treatment	Concomitant medication (CM) start date < Study Treatment start date
On-Treatment	If CM start date < Study Treatment start date and CM stop date ≥Study Treatment start date or If Study Treatment start date < CM start Date < Last Dose of Study Treatment date + 182 days
Post-Treatment	If CM start date < Last Dose of Study Treatment date +182 days and CM stop date ≥ Last Dose of Study Treatment date +182 days Or If CM start Date > Last Dose of Study Treatment date +182 days

6.2.2.3. Study Treatment Flag for Adverse Events

Study Phase	Definition
Pre-Treatment	AE start date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ AE start date ≤ Date of Last Dose + 182 days
Post-Treatment	AE start date > Date of Last Dose + 182 days

NOTES:

- If the AE start date is on or after study treatment start date and the study treatment stop date is missing, then the AE will be considered as on-treatment.
- Time of study Treatment dosing and start/stop time of AEs should be considered, if collected.

6.2.3. Study Day and Reference Dates

The reference date is the study intervention start date and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations. It will also be used to calculate study day for safety measures

The study day is calculated as below:

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

6.2.4. Assessment Window

Not applicable for this study.

6.2.5. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. Triplicate ECG assessment refers to the repeated ECG assessment performed on the same day at the visit. In the case that there are only two repeated ECG assessments performed on the same day, mean of the two measurements will be calculated and used for calculating summary statistics. This will apply to both baseline and post baseline assessments. The individual triplicate ECG assessment will be included in the determination of worst-case on study treatment/post-baseline. The mean of the triplicate assessments will not be used in the determination of worst-case.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.2.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table><tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

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

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

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

6.3. Appendix 3 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.

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

6.3.1. 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).

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.

The study-level compliance will be summarized at the participant level by pre-defined ranges for compliance (<40%, 40-<60%, 60-<80% >=80%).

6.3.2. Endpoint-Level Compliance

For endpoint-level compliance, 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.

Trademarks

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None

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MedDRA
SAS

7. REFERENCES

Protocol: A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744

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