Statistical Analysis Plan Amendment 3

Study ID: 213744

Official Title of Study: A 52-week, randomised, double-blind, placebo-controlled, parallelgroup, multi-centre study of the efficacy and safety of GSK3511294 (Depemokimab) adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

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TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 (Depemokimab) adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number:213744

Compound Number: GSK3511294

Short Title: Placebo-controlled efficacy and safety study of GSK3511294 (Depemokimab) in participants with severe asthma with an eosinophilic phenotype

Acronym: SWIFT-2

Sponsor Name: GlaxoSmithKline Research & Development Limited

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	22-Jan-2021	Version 01 Approval Date: 01-OCT-2020	Not Applicable	Original version
Amendment 01	02-Aug-2022	Amendment 02 Approval Date: 05-APR 2022	1. Section 1.1.2 Estimand: updated intercurrent event strategy for change in maintenance therapy 2. Section 3 Analysis Sets: Updated text related to enrolled, randomised, full analysis set, and safety population. Added Japan sub-population. 3. Section 4.3.2: updated model checking method 4. Section 4.4.9: removed statistical analysis of PGI-P/PGI-C endpoints 5. Section 4.4.10 ADSD/ANSD: added study 217640 6. Section 4.5.2: updated imputation method for non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification. 7. Section 4.6.3.3: adding two visits for ECG reporting and modified wording for categories to be reported 8. Section 4.9: Added unblinded interim analysis for futility and blinded analysis for validation of questionaries 9. Section 4.10:	1. Different strategies to be applied to intercurrent event of change in maintence therapy and use of prohibited medication for PD endpoint. Also added clarification for this intercurrent event. 2. Revision of Analysis sets based on the new SAP template description. To included Japan reporting into this analysis plan. 3. Correct the checking method 4. Only need summary 5. Clarification 6. Clarification 7. Update due to protocol amendment 8. Update due to protocol amendment 9. Update due to protocol amendment 10. Update in order to include all type of corticosteroids use

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			removed that table of 'Changes to Protocol Defined Analyses'. 10. Section 4.4.15: added a summary of systemic corticosteroids use associated with clinically significant exacerbations	
Amendment 02	14-dec-2023	Amendment 02 Approval Date: 05-APR 2022	1. Section 1.1.1 Endpoints and Section 2.1 Multiplicity Adjustment 2. Section 1.1.2 Estimands: updated for the endpoints with descriptive summaries, changed from 'while on treatment strategy' to 'hypothetical strategy. And removed safety endpoints from the table. 3. Section 3 Analysis Sets: updated FAS and Safe analysis sets . Added FAS-modified and Safety-modifitied analysis sets. 4. Section 4.1.2 Baseline Definition: changed from 'Day -7 to Day 1' to 'Day -6 to Day 1' 5. Section 4.2.2, 4.3.2, 4.4, Main Analytical Approach, removed the covariate of ' baseline maintenance OCS therapy (OCS vs. no OCS)' from the analysis model	1. Based on FDA's feedback that for ADSD/ANSD measures to be considered for inclusion in the label they should be elevated in the hierarchy (as secondary endpoints). 2. Clarification. 3. To exclude patients from the sites that had GCP non-compliance/ significant data integrity concern for the main analyses. 4. Clarification 5. This coveraite is not needed because >95% subjects were not on maintenance OCS therapy at baseline. 6. Tipping point analysis will be performed regardless proportion of missing data 7. as planned since MCID for ADSD/ANSD becomes available 8. a figure is needed

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			6. Section 4.2.3.2 removed condition for performing tipping point sensitivity analysis 7. Section 4.4.10.2. Added analysis for responder based ADSD/ANSD 8. Section 4.4.13. Added a PEF plot 9. Section 4.4.15. Removed the sentences regarding summary of number of days with systemic corticosteroids (including OCS, IV and IM) use 10. Section 4.9 Risk Benefit Analysis: added the section to describe planned Risk Benefit forest plot 11. Section 4.3.2, 4.4.3, 4.4.10 added suggestion for how to exclude timepoints from analysis when the model does not converge. 12. Section 4.1.1 added clarification for covaiates 13. Section 4.3.3 added condition for performing analysis	for CSR. 9. Conconmitant medication data shows there is very limited number of IV or IM systemic corticosteroids usage 10. additional plot required for CSR 11. Clarification 12. Clarification 13. Clarification

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
Amendment 03	03 Apr 2024	Amendment 02 Approval Date: 05-APR 2022	1. Section 3, modified Screened population 2. Section 4.1.4 and Section 4.2 & 4.3 Added subgroup definitions and subgroup analyses 3. Section 4.2.3.2 added a condition for performing Tipping Point analysis 4. Section 4.5.2 added summary of AE by subgroups	1. clarification 2. identified new subgroups of interest 3. clarification 4. per EMA feedback to add subgroup summary for safety

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213744. Details of the planned final analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbationsa over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbationa • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS)

Objectives	Endpoints
	Fatigue items score at discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • ADSD responder status (responder defined as achieving ≥1.2 point reduction from baseline) over the 52-week period • ANSD responder status (responder defined as achieving ≥1.5 point reduction from baseline) over the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294

Objectives	Endpoints
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

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. Estimands

Table 2 Estimands

The following two attributes apply to all estimands:

- Treatment comparison: GSK3511294 + SoC compared with placebo + SoC
- Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary objective: To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	Annualised rate of clinically significant exacerbations over 52 weeks	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Secondary objective: to evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	a. Change from baseline in SGRQ total score at Week 52 b. Change from baseline in ACQ-5 score at Week 52 c. Change from baseline in pre-bronchodilator FEV_1 at Week 52 d. Change from baseline in ADSD/ ANSD weekly mean score at Week 52	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be	a. Difference in mean change from baseline in SGRQ total score at Week 52 between GSK3511294 + SoC and placebo + SoC b. Difference in mean change from baseline in ACQ-5 score at Week 52 between GSK3511294 + SoC and placebo + SoC c. Difference in mean change from baseline in pre-

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	e. Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks	handled with a hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	bronchodilator FEV_1 at Week 52 between GSK3511294 + SoC and placebo + SoC d. Difference in mean change from baseline in ADSD/ ANSD weekly mean score at Week 52 between GSK3511294 + SoC and placebo + SoC e. Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of	a. Time to first clinically significant exacerbation b. Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event	a. Hazard ratio of first clinically significant exacerbation between GSK3511294 + SoC and placebo + SoC b. Hazard ratio of first

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
existing asthma therapy	c. Change from baseline in SGRQ total score at discrete timepoints during the 52-week period d. Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period e. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period f. Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period g. Change from baseline in ADSD/ANSD weekly mean score at specified timepoints during the 52-week period	occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	clinically significant exacerbation requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC c. Difference in mean change from baseline in SGRQ total score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC d. Difference in mean change from baseline in ACQ-5 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC e. Difference in mean change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period between GSK3511294 +

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
			SoC and placebo + SoC f. Difference in mean change from baseline SNOT-22 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC g. Difference in mean change from baseline in ADSD/ ANSD weekly mean score between GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a. SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) b. ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) c. ADSD responder status (responder defined as	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic:	a. Odds ratio in SGRQ total score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC b. Odds ratio in ACQ-5 score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC c. Odds ratio in ADSD responder status over 52 weeks between

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	achieving ≥1.2 point reduction from baseline) over the 52-week period d. ANSD responder status (responder defined as achieving ≥1.5 point reduction from baseline) over the 52-week period	hypothetical strategy i.e. had the intercurrent event not occurred. Status following IE will be set as missing. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	GSK3511294 + SoC and placebo + SoC d. Odds ratio in ANSD responder status over 52 weeks between GSK3511294 + SoC and placebo + SoC
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation	a. Change from baseline in PROMIS Fatigue items score at discrete timepoints during the 52-week period b. Change from baseline in	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy	a. Descriptive summary of change from baseline in PROMIS Fatigue items score by treatment group and by visit

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean c. Change from baseline in morning peak expiratory flow (PEF) 2-week mean d. Change from baseline in daily asthma symptom scores 2-week mean e. Change from baseline in mean number of occasions of rescue medication use/day 2 week mean f. Mean number of days with oral corticosteroids (OCS) usage over 52 weeks	i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the	b. Descriptive summary of change from baseline in 2-weekly mean awakenings at night due to asthma symptoms requiring rescue medication use by treatment group and by time interval c. Descriptive summary of change from baseline in 2-week mean morning PEF by treatment group and by time interval d. Descriptive summary of change from baseline in daily asthma symptom scores 2-week mean by treatment group and by time interval e. Descriptive summary of change from baseline in 2 week mean number of occasions of rescue medication use/day by treatment group and by

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		intercurrent event occurring •	visit and time interval f. Descriptive summary of mean number of days OCS usage over 52 weeks by treatment group
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy	a. Patient-rated response to therapy at discrete timepoints during the 52-week period b. Clinician-rated response to therapy at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important	Descriptive summary of (by treatment group) a. Patient-rated response to therapy at discrete timepoints during the 52-week period b. Clinician-rated response to therapy at discrete timepoints during the 52-week period

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event. occurring. Summary will include all on and off treatment data.	
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on patient global impression of asthma severity and its change from baseline	a. Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period b. Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring	Descriptive summary of (by treatment group) a. PGI-S of asthma at discrete timepoints during the 52-week period b. PGI-C from baseline of asthma severity at discrete

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	the 52-week period	• Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	timepoints during the 52-week period
Other objective: to investigate the PD effects of GSK3511294	Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the	• Study intervention discontinuation due to reasons unrelated to the	Ratio in absolute blood eosinophil count GSK3511294

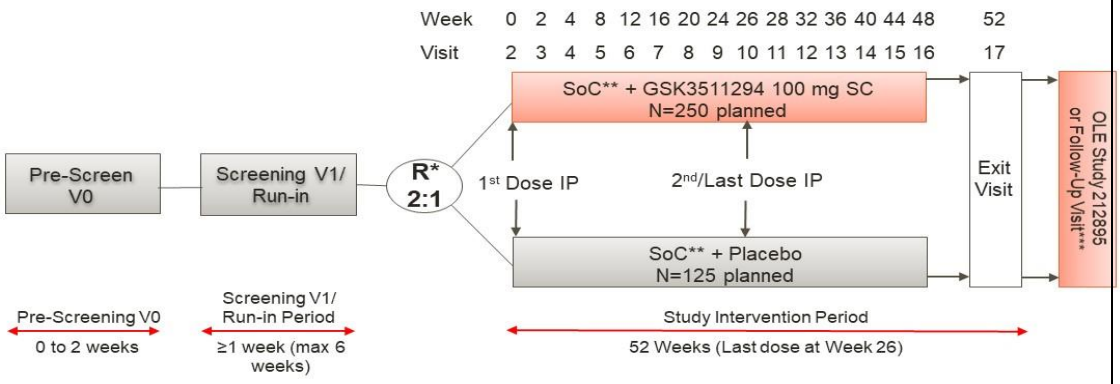
Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	52-week period	COVID 19 pandemic: while on treatment strategy i.e. only data collected while participant was on-treatment will be used on the analysis. Blood eosinophil counts taken more than 26 weeks following last dose will not be included in the analysis. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: same as above • Change in maintenance therapy(not important PDs): same as above • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): hypothetical strategy i.e. had the intercurrent event	+ SoC vs. placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		not occurred.	
Other objective: to investigate the PK of GSK3511294	GSK3511294 plasma concentration at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy(not important PDs): same as above • Concomitant medication important PDs (change in	Descriptive summarise of GSK3511294 plasma concentration by visit. (GSK3511294 + SoC arm only)

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		maintenance therapy or use of prohibited medications): hypothetical strategy i.e. had the intercurrent event not occurred.	
Health Resource Use: To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	Healthcare utilisation for asthma including hospitalisation (including ICU admissions and Length of Stay-LOS), ED, and physician office/clinic visits (scheduled and unscheduled)	Same strategy as per primary endpoint	Descriptive summary of healthcare utilisation

1.2. Study Design

Overview of Study Design and Key Features



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

Design Features	• Phase 3A • 52-week treatment period • Randomised • Double-blind • Placebo-controlled • Parallel group • Multi-centre • Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125). • A sample size of 375 randomised will provide 99% power to demonstrate superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC in annualised rate of clinically significant exacerbations over 52 weeks, based on the true annualised rate of exacerbations in the placebo arm being 1.18 , an assumed true treatment difference of a 50% reduction and at a 5% two-sided significance level. • Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks.
Study intervention and Study intervention Assignment	The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11, Exit Visit 17, and WS Visit (if applicable). Participants will remain on their existing stable maintenance asthma therapy throughout the study.
Interim Analysis	• An unblinded interim analysis for futility is planned • Regular IDMC review of safety data are planned.

2. STATISTICAL HYPOTHESES

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

2.1. Multiplicity Adjustment

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Change from baseline in ANSD at Week 52
6. Change from baseline in ADSD at Week 52
7. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who sign the ICF (not including subjects who failed at pre-screening).	• Study Population
Enrolled	All participants who entered the study. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Randomised	All participants who were randomly assigned to study	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
	intervention in the study.	
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention excluding participants from sites 250085 & 250523. Data will be analysed according to randomised treatment arm.	• Study Population • Efficacy • Immunogenicity • PD • Health Resource Use
FAS-PROMIS	All participants in the FAS population for whom at least one PROMIS fatigue items were administered	• Efficacy (PROMIS)
FAS-ADSD/ANSD	All participants in the FAS population for whom at least one ADSD/ANSD questionnaire were administered	• Efficacy (ADSD/ANSD)
FAS-Japan	All participants in the FAS population who are enrolled from Japan and with Japanese heritage only	• Study Population • Efficacy • PD
FAS-Non-Japan	All participants in the FAS population who are not in FAS-Japan analysis set	• PD
Safety	All randomised participants who receive at least one dose of study intervention excluding participants from sites 250085 & 250523. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received. This population will serve as the primary population for analyses of safety endpoints.	• Safety
Safety-Japan	All participants in the Safety population who are enrolled from Japan and with Japanese heritage only	• Safety
Safety-Non-Japan	All participants in the Safety population who are not in Safety-Japan analysis set	• Not planned in this SAP but flagged for future analysis
PK	All participants in the FAS population for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	• PK
PK-Japan	All participants in the PK population who are enrolled from Japan and with Japanese heritage only	• PK
PK-Non-Japan	All participants in the PK population who are not in PK- Japan analysis set	• PK
FAS-Modified	All participants in the FAS population plus randomised particiants from sites 250085 & 250523 who receive at least one dose of study intervention.	• Efficacy (Primary and Secondary)
Safety-Modified	All participants in the Safety population plus randomised particiants from sites 250085 & 250523 who received at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received.	• Key Safety
FAS-ADSD/ANSD-Modified	All participants in the FAS-ADSD/ANSD population plus randomised participants from sites 250085 & 250523 who receive at least one dose of study intervention.	• Efficacy (ADSD/ANSD)

Note: GCP non-compliance/significant data integrity concern at Sites 250085 & 250523 was identified.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Full Analysis Set (FAS) will be used for all Study Population, Efficacy, Immunogenicity and PD analyses, unless otherwise stated. The Safety analysis set will be used for safety analyses, unless otherwise stated. PK analysis sets will be used for PK data analysis. FAS-Japan, Safety-Japan and PK-Japan will be used for Japan outputs. The Output and Programming Specification (OPS) document will provide more details.

Confidence intervals will use 95% confidence intervals (CI) 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.

For endpoints that are formally modelled, summary statistics will be provided. In the statistical analysis where covariates are included in the modelling, the following approach will be applied:

- The covariate of exacerbation history is classified as 2, 3, 4+. In the event that exacerbation history is <2, it will be included in the category of '2'.
- For the covariate of baseline pre-bronchodilator % predicted FEV1, screening pre-bronchodilator % predicted FEV1 will be used if baseline value is missing. If both sreeening and baseline pre-bronchodilator % predicted FEV1 are missing, a missing value will be assigned for this covariate.

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

Randomisation is stratified based on baseline ICS dose (medium or high). All statistical models will include this stratum as a covariate. In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the CRF, not the assigned stratum at randomization.

Assessments collected at withdrawal visit will be included in summary tables but won't be included in any statistical analysis.

4.1.2. Baseline Definition

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

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

Table 3 Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy, Health Outcomes and Other			
SGRQ total and domain scores		X	Day 1 pre-dose
ACQ-5		X	Day 1 pre-dose
Pre-bronchodilator FEV_1	X	X	Day 1 pre-dose
Post-bronchodilator FEV_1	X	X	Day 1 pre-dose
PROMIS Fatigue items score		X	Day 1 pre-dose
ADSD/ANSD weekly mean score	X (daily following Screening)		Average of measurements from Day -7 to Day -1 inclusive (at least 4 days must be non-missing)
Awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day -1 inclusive (at least 4 days must be non-missing)
Morning PEF 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
Daily asthma symptom scores 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
Mean number of occasions of rescue medication use/day 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
SNOT-22 score		X	Day 1 pre-dose
PGI-S	X	X	Day 1 pre-dose
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
Clinical Chemistry	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
Hematology with differential (including eosinophil count)	X	X	Most recent individual value prior to first dose of study treatment
Other			
Complement C3 and C4		X	Day 1 pre-dose
Immunogenicity		X	Day 1 pre-dose

NOTES :

- Only records that have been assigned a treatment phase of 'pre-treatment' will be considered as baseline assessments.
- ADSD is to be completed before going to bed and refers to asthma symptoms during the day. Day 1 assessment of ADSD will not be pre-dose. Therefore an average of measurements from Day -7 to Day -1 is defined as the baseline for ADSD/ANSD.
- Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

4.1.3. Multicenter Studies

For the purposes of covariate adjustment in the statistical analysis, countries will be grouped into regions. The following regions are defined:

- European (Czechia, France, Hungary, Italy, Poland, Spain)
- US
- Rest of World (Australia, Canada, Puerto Rico, Japan, Taiwan)

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

4.1.4. Subgroups of Interest

Table 4 specifies the subgroups of interest to be used in summary or analyses and the subgroup categories.

Table 4 Subgroups of Interest

Subgroup	Category
Age 1	12-17, 18-64, >=65
Age 2	12-17, >=18
Age 3	12-17, 18-64, 65-74, >=75
Gender	Male, Female
Weight	4 categories determined by quartiles of weight at baseline from the study data
Race	American Indian or Alaska Native, Asian , Black or African American, Native Hawaian or Other Pacific Islander, White, Mixed
Region	European (Czechia, France, Hungary, Italy, Poland, Spain), US, Rest of the World (Australia, Canada, Puerto Rico, Japan, Taiwan)
Baseline ICS Dose	Medium, High
Baseline Eosinophil Supgroup 1	<0.15, >=0.15 cells/uL
Baseline Eosinophil Subgroup 2	<0.30, >=0.30 cells/uL
Baseline ACQ-5	<1.5, >=1.5

Sample size may be small for some subgroup analyses. All sub-group statistical analysis results should be interpreted with caution, especially those with small sample size. If the number of participants is too small (ie. <20) within a category of a subgroup, then the categories may be refined or only summary statistics will be produced.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint

The primary endpoint is the annualized rate of clinically significant exacerbations over the 52 weeks following randomisation.

Clinically significant exacerbations of asthma are defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see protocol Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

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

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

4.2.2. Main analytical approach

Primary Statistical 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, exacerbation history (variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region
  • Continuous: baseline pre-bronchodilator % predicted FEV_1
  • Offset: Log_e(total time in the 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
• Treatment group model estimated annualized exacerbation rates and associated 95% CI • pairwise treatment rate ratios and associated p-value and 95% CI. • pairwise treatment percent reductions in annual exacerbation rate and associated 95% CI
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, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy).
Subgroup Analysis
• By baseline ICS dose (medium, high), by baseline eosinophil subgroup 1 (<0.15, >=0.15), by baseline eosinophil subgroup 2 (<0.30, >=0.30) and by baseline ACQ-5 (<1.5, >=1.5) subgroup analyses will be performed for FAS analysis set. • For subgroup analysis, subgroup, subgroup*treatment group and subgroup*visit*treatment group terms will be included in each of subgroup analysis model.

Primary Statistical Analyses
• In the event the subgroup analysis model fails to converge, model simplification methods may be addressed (i.e. adjusting covariate structure, streamlining timepoints, combining subgroups, running model separately for subgroup). • A forest plot will be produced to present estimated treatment differences and 95% CIs at week 52 • including all subgroups (including P-value for subgroup*treatment group interaction) • Annualized rate of clinically significant exacerbations over each of 13 week interval will also be performed.
Additional Analysis
The same primary endpoint analysis will be performed using FAS-modified analysis set

4.2.3. Sensitivity analyses

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

4.2.3.1. Sensitivity Analysis 1 (MNAR Based on off-treatment Data)

This sensitivity analysis will be performed where subjects who withdrew from the study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on the off-treatment data collected from subjects who continued in the study following discontinuation of randomised intervention. Multiple imputation methods will be used with results combined across imputations using Rubin's method [Roger, 2018].

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.2.3.2. Sensitivity Analysis 2 (Tipping Point Analysis)

Tipping point analysis will explore the impact of missing data by using differing assumptions regarding the exacerbation rate in subjects who withdraw from the study. Subjects who withdrew from study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on a range of values for the rate of exacerbations per year following study withdrawal. The values to be investigated will be based on increases relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates will vary independently for the active and placebo arms, and will include scenarios where subjects in the active arm have worse outcomes following early withdrawal from the study than subjects in the placebo arm. The tipping point multiple imputation method will be based on pattern mixture models [Keene, 2014]. The results from the analyses of each sample are combined using Rubin's method.
If the test for the endpoint is not significant at the two-sided 5% level, then the sensitivity analysis for the endpoint will not be performed.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoint(s)

The secondary endpoints are:

- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Change from baseline in ANSD at Week 52 (see Section 4.4.10)
- Change from baseline in ADSD at Week 52 (see Section 4.4.10)
- Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

4.3.2. Main analytical approach for SGRQ total score, ACQ-5 score and pre-bronchodilator FEV_1

Secondary Endpoints Analyses
Endpoint(s)
• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • Terms in the model: **Response**: SGRQ Total score or ACQ-5 score or pre-bronchodilator FEV1 at each visit. **Categorical**: treatment group, exacerbation, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit **Continuous**: baseline (SGRQ Total score, or ACQ-5 score,or baseline pre-bronchodilator FEV1), baseline pre-bronchodilator % predicted FEV1 (for SGRQ total score and ACQ-5 endpoints only) **Interaction**: baseline*visit, treatment group*visit **Repeated**: visit • The MMRM analysis for SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. • The MMRM analysis for ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 8, 48, 24, 28. • The MMRM analysis for pre-bronchodilator FEV1 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 • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence

Secondary Endpoints Analyses
that the model assumptions are reasonable.
Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each visit will be presented. • The LS mean treatment differences (and associated 95% CIs) for all visits will also be presented graphically. • SGRQ total scores, ACQ-5 score and pre-bronchodilator FEV1 (absolute value and changes from baseline) will also be summarised by treatment group 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, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).
Additional Analysis
The same secondary endpoint analyses will be performed using FAS-modified analysis set
Subgroup Analysis
• by baseline eosinophil subgroup 1 (<0.15, >=0.15), by baseline eosinophil subgroup 2 (<0.30, >=0.30) and by baseline ACQ-5 (<1.5, >=1.5) subgroup analyses will be performed for FAS analysis set . • For subgroup analysis, subgroup, subgroup*treatment group and subgroup*visit*treatment group terms will be included in each of subgroup analysis model. • In the event the subgroup analysis model fails to converge, model simplification methods may be addressed (i.e. adjusting covariate structure, streamlining timepoints, combining subgroups, running model separately for subgroup). • A forest plot will be produced to present estimated treatment differences and 95% CIs at week 52 including all subgroups (including P-value for subgroup*treatment group interaction)

4.3.3. Main analytical approach for annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be analysed using a negative binomial generalised linear model, as described for the primary endpoint, Section 4.2.2 for details. This endpoint would only be analysed in the event that a total of 20 or more exacerbations requiring hospitalisation and/or ED visit occurred in the study.

4.3.4. Sensitivity analyses

The sensitivity analyses for the primary endpoint as described in Section 4.2.3 will also be performed for the secondary endpoints.

4.4. Other Endpoints Analyses

4.4.1. Time to first clinically significant exacerbation and Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Endpoint(s)
• Time to first clinically significant exacerbation • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Model Specification
• Cox's proportional hazards model • Terms in the model: **Response**: time to first clinically significant exacerbation or first clinically significant exacerbation requiring hospitalization and/or ED visit **Categorical**: treatment group, exacerbation exacerbation history (variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region **Continuous**: baseline pre-bronchodilator % predicted FEV_1 • The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead. • Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln (-ln[S(t)]) plot will be produced.
Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure.
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, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.2. Change from baseline in SGRQ total score and in ACQ-5 score at discrete timepoints during the 52-week period

Analytic approach for change from baseline in SGRQ total score and change from baseline in ACQ-5 score at discrete timepoints during the 52-week period has been included in the secondary endpoints analyse, see Section 4.3.2 for details.

4.4.3. SGRQ total score responder status at Week 52 and ACQ-5 score responder status at Week 52

Other Endpoints Analyses
Endpoint(s)
• Proportion of responders according to SGRQ total score (responder defined as achieving ≥4-point reduction from baseline) • Proportion of responders according to ACQ-5 score (responder defined as achieving ≥0.5-point reduction from baseline)
Model Specification
• Generalized linear mixed model • Terms in the model: **Dependent**: response (yes/no) **Categorical**: treatment group, exacerbation baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline (SGRQ Total score, or ACQ-5 score), baseline pre-bronchodilator % predicted FEV1 **Interaction**: baseline (SGRQ Total score, or ACQ-5 score)*visit, treatment group*visit The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed.

• Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. • The analysis of responder based on ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 8, 48, 24, 28.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit • Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
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, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.4. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1

Analytic approach for change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period has been included in the secondary endpoint analysis of change from baseline in pre-bronchodilator FEV_1 at Week 52, see Section 4.3.2 for details.

Change from baseline in post-bronchodilator FEV_1 at discrete timepoints during the 52-week period will be analyzed in the same approach as for change from baseline in pre-bronchodilator FEV_1.

4.4.5. PROMIS Fatigue items score

PROMIS Fatigue items score and change from baseline in PROMIS Fatigue items score will be summaried by treatment group and visit.

4.4.6. SNOT-22 score

The SNOT-22 questionnaire is administered (post randomisation) at Week 26 and 52. The 22 questions of the SNOT-22 are each graded on a 6-point scale ranging from 0 = 'no symptoms' to 5 = 'as bad as things could be'. The scores for each of the questions are summed to derive the total score which ranges from 0 to 110, with higher scores representing worse quality of life.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in SNOT-22 total score at Week 26 and Week 52
Model Specification, Model Checking & Diagnostics
• See Model Specification, Model Checking & Diagnostics for secondary endpoints statistical analyses • analysis will include data collected at Weeks 26 and 52.
Model Results Presentation
• See Model Results Presentation for secondary endpoints statistical analyses (figures will not be presented) • SNOT-22 score (absolute value and changes from baseline) will also be summarised by treatment group and visit.

Other Endpoints Analyses
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, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.7. Patient-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the participant at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse
Patients rated response to therapy will be summarised by treatment group and visit.

4.4.8. Clinician-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the investigator at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse
Clinician rated response to therapy will be summarised by treatment group and visit.

4.4.9. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at the visits: Randomisation and Screening, Day 1, Week 12, 20, 26, 40, 52. This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at Week 12, 20, 26, 40 and 52. The single question will ask participants to rate the overall

change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

PGI-S and PGI-C responses will be summarised by treatment group and visit.

4.4.10. ADSD/ANSD

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective which received qualification from the FDA in March 2019 supporting use in drug development as an exploratory measure.

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

4.4.10.1. ADSD/ANSD Change from Baseline

Secondary and Other Endpoints Analyses
Endpoint(s)
• Change from baseline in Asthma Daily Symptom Diary (ADSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit) • Change from baseline in Asthma Nightly Symptom Diary (ANSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit)
Model Specification, Model Checking & Diagnostics
• Similar to model specification, model checking and diagnostics detailed in Section 4.3.2 • Response variable: weekly mean scores • Baseline score is defined in Section 4.1.2 • In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is every other week prior to week 16. If the model still does not converge, then drop week 44, 20, 36, 32, 48, 24, 28.
Model Results Presentation
• LS means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each Week will be presented. • The LS mean treatment differences (and associated 95% CIs) for all weeks will also be presented graphically.

• ADSD and ANSD weekly mean absolute score and changes from baseline will also be summarised by treatment group and visit. Summary will include weekly mean score at all visits (including all weeks prior to week 16). .
Handling of missing data and data excluded due to intercurrent events
Same approach as described in Section 4.3.2
Additional Analysis
The same secondary endpoint analyses will be performed using FAS-ADSD/ANSD-modified analysis set

4.4.10.2. Responder Based on ADSD/ANSD

Endpoint(s)
• Proportion of responders according to ADSD weekly mean score (responder defined as achieving ≥1.2 point reduction from baseline) • Proportion of responders according to ANSD weekly mean score (responder defined as achieving ≥1.5 point reduction from baseline)
Model Specification
Generalized linear mixed model • Terms in the model: **Dependent**: response (yes/no) **Categorical**: treatment group, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline weekly mean score (ADSD/ANSD) **Interaction**: baseline weekly mean score (ADSD/ANSD)*visit, treatment group*visit • The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include ADSD/ANSD weekly mean score at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. • In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is every other week prior to week 16. If the model still does not converge, then drop week 44, 20, 36, 32, 48, 24, 28.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
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, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.11. Mean number of occasions of rescue medication per day

Daily diary data for rescue medication (salbutamol/albuterol) use will be aggregated over 2-week periods, then the mean daily usage, excluding days with missing data, will be calculated for each 2-week period (Weeks 1-2, 3-4,…, 51-52). Data for each 2-week period, and change from baseline for each 2-week period will be summarised by treatment group and visit. For definition of baseline see Section 4.1.2.

4.4.12. Awakenings at night due to asthma symptoms requiring rescue medication use

Awakening at night due to asthma symptoms requiring rescue medication use will be summarised as for rescue medication use, see Section 4.4.11.

4.4.13. Morning peak expiratory flow (PEF)

Morning PEF will be summarised as for rescue medication use, see Section 4.4.11.

The summaries will be for :

1. all data included as per FAS population
2. excluding data where asthma medication was taken within 6 hours prior to PEF assessment

The mean change from baseline and associated 95% CIs in morning PEF at all timepoints for the treatment groups will also be presented graphically (for all data).

4.4.14. Daily asthma symptom scores

Daily asthma symptom score will be summarised as for rescue medication use, see Section 4.4.11.

4.4.15. Number of days with oral corticosteroids

Total number of days of oral corticosteroids (OCS) use over 52 weeks that are associated with clinically significant exacerbations per subject will be summarised by treatment group. Also, number of clinically significant exacerbations, number of clinically significant exacerbations treated with OCS, and mean number of days using OCS per clinically significant exacerbations treated with OCS will be summarised by treatment group.

Number of subjects on maintenance OCS at screening, total number of days of maintenance OCS use over 52 weeks and mean number of days of maintenance OCS use per subject will also be summarised by treatment group.

4.5. CLINICAL PHARMACOLOGY DATA ANALYSES

4.5.1. Pharmacokinetic Analyses

In this study, GSK3511294 plasma concentration are collected at discrete timepoints during the 52-week treatment period. GSK3511294 plasma concentration will be summarised by visit. (GSK3511294 + SoC arm only).

The PK data from this study will be included in a meta-analysis of the PK and PKPD data across all GSK3511294 studies. Details of meta-analysis will be in a separate CPMS analysis plan.

4.5.2. Pharmacodynamic Analyses - Blood Eosinophils

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

Ratio to baseline during W52 will be analysed using a MMRM analysis. Model specification, model checking and diagnostics are the same as described for secondary endpoints statistical analyses, see Section 4.3.1. Analysis will include data from all visits that blood eosinophils data is collected. LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group will be presented. Mean treatment ratio and 95% CI for GSK3511294 vs placebo will also be presented.

Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary.

4.6. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set unless otherwise specified. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), laboratory data, vital signs, and ECGs will be included in data displays in the form of frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

4.6.1. Extent of Exposure

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

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

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

Subject years exposure is calculated as follow:

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).

4.6.2. 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.

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. These summaries will also be produced by age subgroup (12-17, 18-64, ≥65).

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

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

Common (>=3%) on treatment 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. The summary table will be displayed in descending order by SOC and PT.

AE will also be summarised by subgroups of age 1, age 2, age 3, gender, race and region by SOC and PT.

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

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

4.6.2.1. 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.

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

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

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

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

A summary of the incidence of serious adverse events and adverse events of special interest (excluding QTc prolongation) will be produced displaying the relative risk and risk difference and their 95% CIs between and GSK3511294 and placebo.

AESI of QTc prolongation will be summarised as detailed in Section 4.6.3.3 ECG.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

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

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

The details of the planned displays will be in OPS.

4.6.3.2. 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.

4.6.3.3. 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 summariesd by visit.

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.

4.6.3.4. Complement

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

4.6.4. Additional Safety Analyses

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

- Overview of all adverse events (including sites 250085 & 250523)
- Summary of on-treatment serious adverse events and adverse events of special interest: incidence, relative risk and risk difference (including sites 250085 & 250523)
- Listing of all adverse events from sites 250085 & 250523

4.7. Immunogenicity Analyses

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.

All participants' baseline immunogenicity samples will be analysed. Post-baseline immunogenicity samples will only be analysed for participants receiving GSK3511294 100 mg SC.

The following descriptive summaries will be presented for GSK3511294 100 mg SC group by visit using FAS 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 binding antibody results for participants without positive result prior to dosing: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). 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 results. 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

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

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

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

4.8. Healthcare Resource Utilization

The total number of visits per participant for each type of healthcare contact: non inpatient (home visits [day], home visits [night], physician office/clinic visits, urgent care/outpatient clinic visits, emergency room visits, telephone calls, telemedicine

consultations) and inpatient admissions (intensive care unit and general hospital wards) will be presented by summarising the respective visits and number of days (Length of Stay-LOS). This will also be summarised for each contact type (asthma-exacerbations, other healthcare contact).

4.9. Risk Benefit Analyses

A forest plot will be produced to display efficacy and safety data from analyses in adjacent panels using Full Analysis Set.

The efficacy results will include primary endpoint (and its associated endpoint), i.e. clinically significant exacerbations (and exacerbations requiring hospitalisation and/or ED visit). The AE results will be obtained from the analyses as described in Section 4.6.2.1 for the following categories of AEs:

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

4.10. Analyses on Japan Subpopulation

A set of key study population, efficacy, safety, immunogenicity, PD and PK analyses will be repeated in the Japan subpopulations (as defined in Section 3, Analysis Sets). Details are provided in the OPS.

4.11. Interim Analyses

There will be one unblinded interim analysis for futility. Periodic review of safety data by an independent data monitoring committee (IDMC) will also be performed. Other than the emergency unblinding procedures described in the protocol, all personnel having direct responsibility for the conduct of the study will remain blinded to treatment groups for all data until the database is frozen.

4.11.1. IDMC Safety Review

IDMC will periodically review unblinded safety data from the three Phase III studies in the severe asthma program: 206713, 213744 (this study) and 206785, in accordance with the IDMC Charter. IDMC will also review safety data from study 212895, an open-label extension study including participants who were previously enrolled in study 206713 or 213744 when sufficient data is collected.

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. The safety data analyses for the IDMC reviews will be performed by an independent Statistical Data Analysis Centre (SDAC).

4.11.2. Unblinded Interim Analysis for Futility

An unblinded interim analysis for futility will be conducted by an independent SDAC in conjunction with an IDMC to maintain study integrity.

The futility analysis will evaluate efficacy based on the primary endpoint of annualised rate of clinically significant exacerbations using interim data from Phase III studies 206713 and 213744 (this study) when approximately 675 participants are randomised across both studies. The stopping rule is binding, i.e. if the stopping criteria is met then the recommendation will be to stop, conditional on the IDMC deeming that there is no delayed onset of clinical efficacy. Should it be judged that there is delayed onset then this may invalidate an assumption of the interim analysis that the pre-interim data is reflective of post-interim data which could result in inflation of type 2 error. In such a situation, the IDMC will use their expert judgment in determining their recommendation.

Recruitment into the study will continue whilst the futility analysis is taking place. Any communication to the sites regarding the decision will only take place if a decision to stop the study is made. Should the studies be stopped, all on-going participants will complete their follow-up period but will not receive any further doses whilst no further participants will be recruited into the study.

The full details of the process are included in IDMC Charter.

4.11.2.1. Decision Rule

The interim analysis will be based on the predictive probability of meeting the end of study (program) success criteria (defined as statistical significance at a two-sided 5% alpha level in **both** studies 206713 and 213744). Should the predictive probability of success be less than or equal to 0.25 then the studies will be stopped for futility.

The futility rule:

Futility	**Continue**
Predictive probability (statistical significance two-sided 5%) in **both** 206713 & 213744) ≤ 0.25	Predictive probability (statistical significance two-sided 5%) in **both** 206713 & 213744) > 0.25

4.11.2.2. Methodology

Predictive probability of success will be used to determine the decision of futility or continue. The methodology involves predicting the remainder of the data on the primary endpoint for participants that have not yet completed or yet to be randomised into the study. The primary analysis is then performed separately for each study on this "complete" dataset, i.e. comprising of observed pre-interim data and predicted post-interim data. The success criteria is applied at this stage. To account for uncertainty attached to parameters at the interim, and therefore uncertainty in the predicted remaining

data (due to the limited data), this step is performed 1000s of times. The proportion of iterations that meet the success criteria (statistical significance in both studies) gives the predictive probability of success. If this is low (≤0.25), the studies will stop for futility Specific steps on the methodology are given below.

1. Data on the primary endpoint (number of clinically significant exacerbations) will be pooled across the two pivotal studies (206713, 213744) for the purposes of predicting post-interim data. Pooling allows for a more precise estimate of the overall treatment effect resulting in improved operating characteristics. Since these are replicate studies the pooling is deemed appropriate. Participants with at least one month of time in the study since randomisation will be included in the interim analysis (the negative binomial model accounts for varying follow-up time across participants).
2. The primary analysis with pooled data across both studies will be fitted (plus an additional fixed term for study) in a Bayesian framework (non-informative priors on all model parameters). Posterior distributions for the β model parameters and k dispersion parameter will be obtained with 1000s of sets of samples (iterations) taken from these posterior distributions which will be shown in the steps below to be used to predict exacerbations in the post-interim period.
3. For each iteration the expected number of exacerbations pre and post-interim is calculated as $\hat{y}_{i,1}$ and $\hat{y}_{i,2}$, respectively, for each participant, i. The predictions for post-interim data will be based on the interim posterior distribution. To calculate $\hat{y}_{i,1}$ and $\hat{y}_{i,2}$, the steps are as follows:
    1. The design matrix (Z) is multiplied with the set of posterior β samples and then back-transformed (exponentiated) to give expected annualised exacerbation rate for each participant (μ_i) based on the interim data. Note: for participants yet to be randomised, and therefore without values observed for baseline covariates, bootstrapping from already randomised participants will be performed.
    2. The expected exacerbation rate for the pre-interim and post-interim periods are calculated by multiplying μ_i by the pre-interim and post-interim times in the study for the participant: $\hat{y}_{i,1} = \mu_i \times t_{i,1}$ and $\hat{y}_{i,2} = \mu_i \times t_{i,2}$.
    3. For the two periods (pre and post-interim), the number of exacerbations within each period is negative binomial. The distribution of one period conditional upon the other, within a participant, is also negative binomial [Keene, 2014]. The negative binomial parameters for the post-interim period are calculated for each participant and set of posteriors samples (iteration):

$$p_{i,2} = \frac{\frac{1}{k} + \hat{y}_{i,1}}{\frac{1}{k} + \hat{y}_{i,1} + \hat{y}_{i,2}}$$

$$k_{i,2} = k_1 + count_{i,1}$$

Where k_1 is the sampled dispersion parameter, $count_{i,1}$ is the number of exacerbations for participant *i* in period 1 (pre-interim), *i* is the participant and *j*=1,2 is the period (pre, post-interim).

Using these parameters, simulate a participant's number of clinically significant exacerbations for post-interim data for each set of posterior samples

4. The pre-interim observed data (one set) will be combined with each set of post-interim data (1000s of sets) to create 1000s of end of study datasets
    1. Each participant's exacerbation count will be the summation of pre-interim observed count (if the participant was randomised at least one month before the interim data cut) plus the post-interim simulated exacerbation count (if the participant did not complete before the interim).
    2. Each participant's length of time in the study will now be the assumed average length of time in the study, which is set at 0.86 years.
5. The primary analysis model is applied to each iteration (dataset), each study separately. The p-value for the treatment effect (rate ratio) will be calculated. For each iteration, if the success criteria (statistical significance at 5% two-sided level for both studies) is met then the iteration is marked as success (flag as 1), or if not then fail (flag as 0).
6. The mean of these success flags in step 7 is calculated to give the predictive probability of success.
7. If the predictive probability of success is ≤0.25 then the futility criteria has been met.

4.11.2.3. Timing and Operating Characteristics

The proposed timing of the futility analysis is when approximately 675 participants have been randomised across the studies. At this time it is estimated that approximately 200 participants will have completed the studies and 500 received both doses (i.e. at least 6 months worth of data). The median follow-up time in the interim analysis is estimated to be 9 months with the information fraction for the primary endpoint estimated to be 60%, where information fraction is calculated as:

$$Information\ fraction = \frac{\sum_{i=1}^{n(interim)} length\ of\ time\ in\ study\ \boldsymbol{at\ interim}_i}{\sum_{i=1}^{750} length\ of\ time\ expected\ \boldsymbol{in\ complete\ study}_i}$$

Table 5 shows operating characteristics of the futility analysis for a range assumed true treatment effects when approximately 725 participants have been randomised (proposed interim timing). Operating characteristics were obtained by simulating 5,000 studies and following the steps in Section 4.11.2.2 for each simulated study. Operating characteristics are obtained from the aggregate of these simulations.

As this is a futility analysis and there is no opportunity to stop for efficacy the type 1 error (calculated under the null hypothesis of assumed rate ratio = 1) is controlled well below the 5% level. The power of each study is approximately 99%, compared with >99% in the scenario where there is no futility analysis (as described in the protocol). The

expected observed rate ratio at the interim to trigger futility is expected to be approximately 0.70.

Table 5 Operating Characteristics of Futility Analysis

Assumed treatment effect (rate ratio depemokimab vs. placebo)	Probability of success (statistical significance in both studies)	Power[1]: 206713	Power[1]: 213744	Probability of futility
1	<0.01	<0.01	<0.01	0.98
0.9	0.01	0.04	0.02	0.94
0.8	0.08	0.18	0.13	0.76
0.7	0.37	0.50	0.44	0.42
0.6	0.78	0.85	0.82	0.11
0.5	0.98	0.98	0.98	0.01

[1] at two-sided 5% significance level for end of study test and incorporating the possibility of futility

4.11.2.4. Outputs

- An interim analysis-specific output presenting the predicted probability of success at the interim
- An interim analysis-specific output presenting model-adjusted annualised exacerbation rate ratio for depemokimab compared to placebo by time period (< 3 months since randomisation, 3 – 6, 6 – 9, 9 – 12)
- Kaplan-Meier plot of time to first clinically significant exacerbation
- Primary analysis summary table for each study. The primary analysis will be conducted on the interim data and provide model-adjusted estimates as a supportive output.
- Summary of Subject Disposition and Reasons for Study Withdrawal
- Summary of Demographic Characteristics
- Summary of Time in Study

4.11.2.5. Decision Making

The outputs from the interim analysis will be forwarded from the SDAC to the IDMC. As the stopping rule is binding, the decision will be communicated from the SDAC to the IDMC and then to GSK following agreement from the IDMC.

4.12. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol amendment 2 (Dated: 08-APR-2022) and its rationale are summarised as below.

Substantial validation work has been conducted on the ADSD/ANSD PRO measures since the original protocol and SAP were finalised. These measures will provide additional treatment benefit information and could be included in the label for treatment

decision making. Consequently, and following additional regulatory agency feedback, ADSD/ANSD change from baseline at week 52 endpoints have been added as secondary endpoints and into the hierarchy. In addition, ADSD and ANSD responders have been added as other endpoints.

5. SAMPLE SIZE DETERMINATION

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

5.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

5.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

5.1.2. Secondary Endpoints

Table 6 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 6 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

5.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 7 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 7 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

5.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than 375 participants in the study. This is due to local country requests or requirements, for example, the local health authority specifying a minimum number to be enrolled. The primary analysis and clinical study report (CSR) will be based on the initial target enrolment. If the study target enrolment is reached before a local country enrolment requirement is met, then recruitment in that country may continue. Participants from those countries, who have already been enrolled at the time of reaching the target enrolment, will be included in the primary analysis. All data (pre- and post-target enrolment) will be analysed together but reported later in a supplement to the study report. Inferences will be drawn on the original study report based on the target enrolment.

6. SUPPORTING DOCUMENTATION

6.1. Early PK Access Key Activities

Designated representative(s) may be unblinded for performing population PK, PKPD dataset preparation and draft PK, PKPD model development using scrambled (random reassignment of subject identification numbers) PK, PKPD unblinded datasets. The PK and PKPD datasets will include information on PK concentration, actual dosing information, demographics (including race and ethnicity), vital signs, concomitant medications, antidrug antibodies, biomarkers (e.g. eosinophils and IL5 concentration) and laboratory information. No information on adverse event and efficacy will be included.

6.2. Appendix 1 Abbreviations and Trademarks

6.2.1. List of Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADSD	Asthma Daily Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANSD	Asthma Nightly Symptom Diary
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FAS	Full Analysis Set
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids

Abbreviation	Description
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
LOS	Length of Stay
LS Mean	Adjusted mean for the treatment group
LS Mean Change	Adjusted mean change from baseline for the treatment group
MAR	Missing at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities
Mg	Milligram
Min	Minimum
MMRM	Mixed Models Repeated Measures
MNAR	Missing Not at Random
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
OCS	Oral corticosteroids
OPS	Output and Programming Specification
OR	Odds ratio
PD	Pharmacodynamics
PEF	Peak expiratory flow

Abbreviation	Description
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
PT	Preferred Term
QTcF	QTc corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SNOT-22	Sino-nasal Outcomes Test-22
SoC	Standard of care
SOC	System Organ Class

6.2.2. Trademarks

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7. REFERENCES

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