Statistical Analysis Plan Amendment 2

Study ID: 206713

Official Title of Study: A 52-week, randomised, double-blind, placebo-controlled, parallelgroup, multi-centre study of the efficacy and safety of GSK3511294 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: 206713

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-1

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-22	Amendment 02 Approval Date: 08-APR 2022	1. Section 1.1.2 Estimand: updated intercurrent event strategy for change in maintenance therapy	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. Section 3 Analysis Sets: Updated text related to enrolled, randomised, full analysis set, and safety population. Added China sub-population.	2. Revision of Analysis sets based on the new SAP template description. To included China reporting into this analysis plan.
			3. Section 4.3.2: updated model checking method	3. Correct the checking method
			4. Section 4.4.9: removed statistical analysis of CCI [redacted] endpoints	4. Only need summary
			5. Section 4.4.10 ADSD/ANSD: CCI [redacted]	5. Clarification
			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.	6. Clarification
			7. Section 4.6.3.3: adding two visits for ECG reporting and modified wording for categories to be reported	7. Update due to protocol amendment
			8. Section 4.9: Added CCI [redacted] blinded analysis for validation of questionaries	8. Update due to protocol amendment
			9. Section 4.10: removed that Table of 'Changes to Protocol Defined Analyses'.	9. Update due to protocol amendment
			10. Section 4.4.15: added a summary of systemic corticosteroids use associated with clinically significant exacerbations	10. Update in order to include all type of corticosteroids use

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:updated for the endpoints with descriptive summaries, CCI [redacted]. And removed safety endpoints from the table. 3. Section 3 updated FAS and Safety 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 6. Section 4.2.3.2 removed condition for performing CCI [redacted] 7. Section 4.4.10.2. Added analysis for responder based ADSD/ANSD 8. Section 4.4.13. Added a CCI plot 9. Section 4.4.15. Removed the CCI [redacted] 10. Section 4.9 added the section for 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 4.10 added clarification for analyses on China subpopulation 13. Section 4.1.1 added clarification for covaiates	1. CCI [redacted] 2. Clarification. 3. To exclude patients from the site that had GCP non-compliance for the main analyses. 4. Clarification 5. This covariate is not needed because >95% subjects were not on maintenance OCS therapy at baseline. 6. CCI [redacted] 7. CCI [redacted] 8. CCI [redacted] 9. CCI [redacted] 10. additional plot required for CSR 11. Clarification 12. Clarification 13. Clarification

			14. Section 4.3.3 added condition for performing analysis	14. Clarification

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 206713. 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 exacerbations[a] 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 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	
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

Objectives	Endpoints
CCI [redacted]	
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
CCI [redacted]	

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic

Objectives	Endpoints
	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: CCI [redacted] • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted] • Change in maintenance therapy (not important PDs):	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		CCI [redacted] • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): CCI [redacted]	
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	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: CCI [redacted] • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: CCI [redacted]	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-bronchodilator FEV_1 at Week

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	d) Change from baseline in ADSD/ ANSD weekly mean score at Week 52 e) Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks	• Change in maintenance therapy (not important PDs): CCI [redacted] • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): CCI [redacted]	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
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

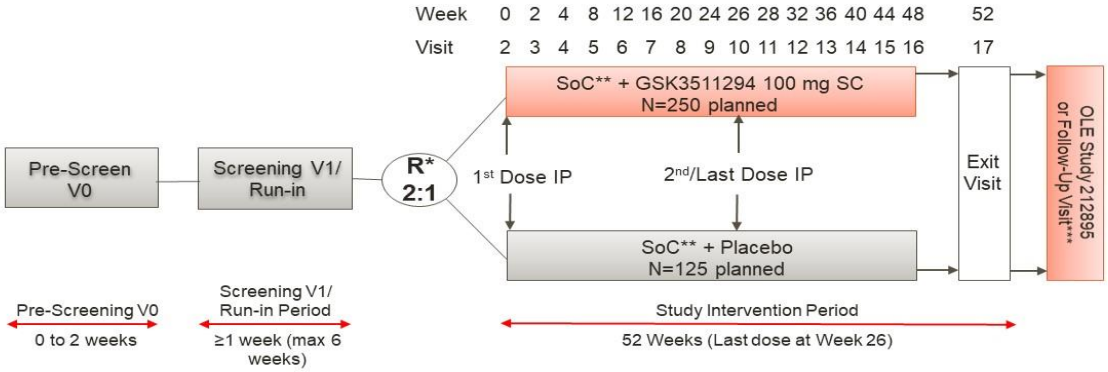
Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			
CCI [redacted]			

Objectives	Estimand		
	Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
CCI [redacted]			

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

Overview of Study Design and Key Features	
	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.
CCI [redacted]	• CCI [redacted] • A blinded data analysis is also planned to complete a psychometric analysis of the ADSD/ANSD and CCI [redacted]. • Regular IDMC reviews 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.	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 intervention in the study.	Study Population
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention excluding participants from Site PPD Data will be analysed according to randomised treatment arm.	• Study Population • Efficacy • Immunogenicity • PD • CCI
CCI		
FAS-ADSD/ANSD	All participants in the FAS population for whom at least one ADSD/ANSD questionnaire were administered	• Efficacy (ADSD/ANSD)
FAS-China	All participants in the FAS population who are enrolled from China	• Study Population • Efficacy •
CCI		

Analysis Set	Definition / Criteria	Analyses Evaluated
Safety	All randomised participants who receive at least one dose of study intervention excluding participants from Site PPD 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-China	All participants in the Safety population who are enrolled from China	• Safety •
CCI CCI	[redacted]	
FAS-Modified	All participants in the FAS population plus randomised participants from Site PPD 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 Site PPD who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a	• Key Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
	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.	
FAS-ADSD/ANSD-Modified	All participants in the FAS-ADSD/ANSD population plus randomised participants from Site PPD who receive at least one dose of study intervention.	• Efficacy (ADSD/ANSD)

Note: GCP non-compliance/significant data integrity concern at Site PPD 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-China, Safety-China and PK-China will be used for China 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 CCI 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
CCI [redacted]			
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)
CCI [redacted]			

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
CCI [redacted]			
CCI [redacted]			
CCI [redacted]			
CCI [redacted]			
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
CCI [redacted]			
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
CCI [redacted]			

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Other			
CCI [redacted]			
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 assement 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, Germany, Italy, Ireland, Poland, Spain, UK)
- US
- Rest of World (Canada, China, Russia)

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

4.2. Primary Endpoint 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
CCI [redacted]
Subgroup Analysis
• By baseline ICS dose (medium, high) subgroup analysis will be performed. • Separate model will be fitted for each subgroup.
Additional Analysis
• The same primary endpoint analysis will be performed using FAS-modified analysis set

CCI [redacted]

CCI

CCI

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 FEV1 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, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit • Continuous: baseline (SGRQ Total score, or ACQ-5 score, baseline pre-bronchodilator % predicted FEV1) • 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 assessments 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, 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 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
• CCI [redacted]

Secondary Endpoints Analyses
CCI [redacted]
Additional Analysis
The same secondary endpoint analyses will be performed using FAS-modified analysis set

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

CCI [redacted]

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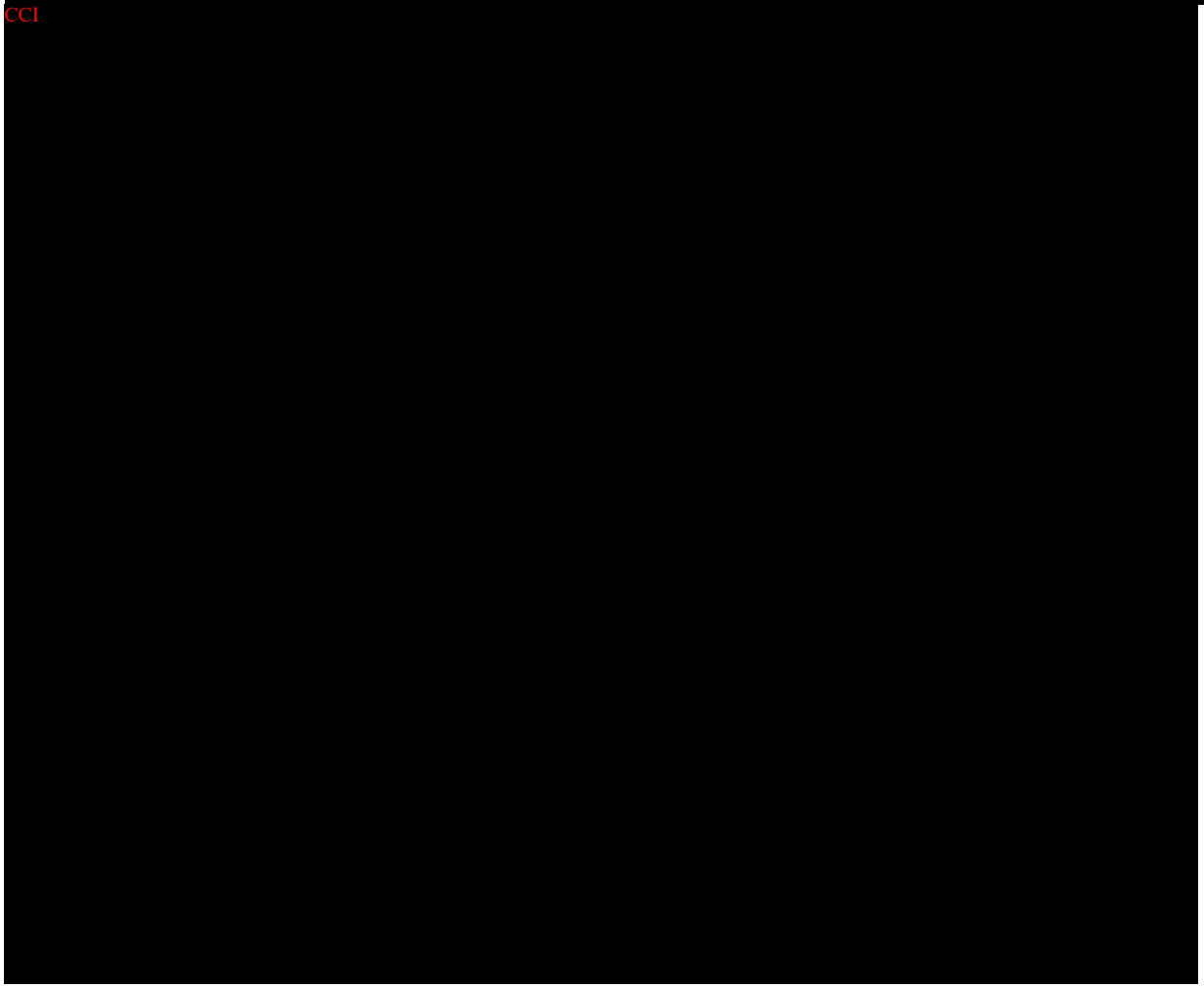

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4.5. CLINICAL PHARMACOLOGY DATA ANALYSES

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[redacted]

CCI

[redacted]

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%) 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.

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 CCI [redacted], 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.

CCI [redacted].

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 summarised by visits.

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

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

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

CCI

[redacted]

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 site PPD
- Summary of on-treatment serious adverse events and adverse events of special interest: incidence, relative risk and risk difference (including sites PPD
- Listing of all adverse events from site PPD

4.7. Immunogenicity Analysis

CCI

[redacted]

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.:

- CCI

[redacted]

- 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.

4.9. 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 4.6.2.1for 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 China Subpopulation

The key study population, efficacy, safety and PK analyses and some exploratory analyses will be repeated in the following subpopulations (as defined in Section 3, Analysis Sets) respectively:

FAS-China： All participants in the FAS population who are enrolled from China.

Safety-China: All participants in the Safety population who are enrolled from China.

PK-China: All participants in the PK population who are enrolled from China.

The subpopulation analyses will employ the same model as the overall population analyses. For MMRM analyses, once the model cannot converge from original settings (including repeated visits and covariates in the models), those will be adjusted to ensure model convergence and obtain stable estimations. For secondary endpoint ACQ-5 including 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.

4.11. CCI [redacted]

CCI [redacted]. 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 (this study), 213744 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).

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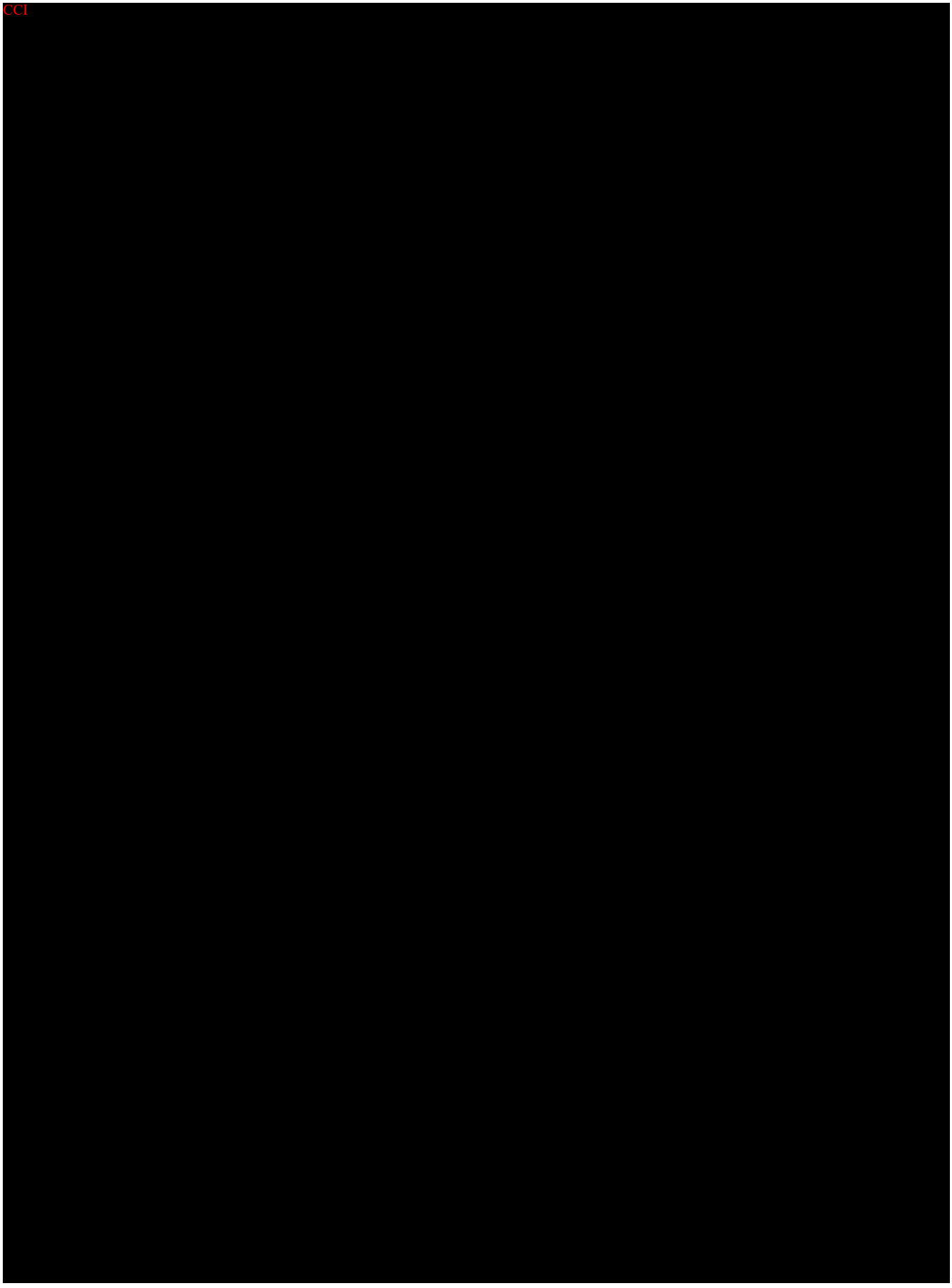

CCI
[redacted]

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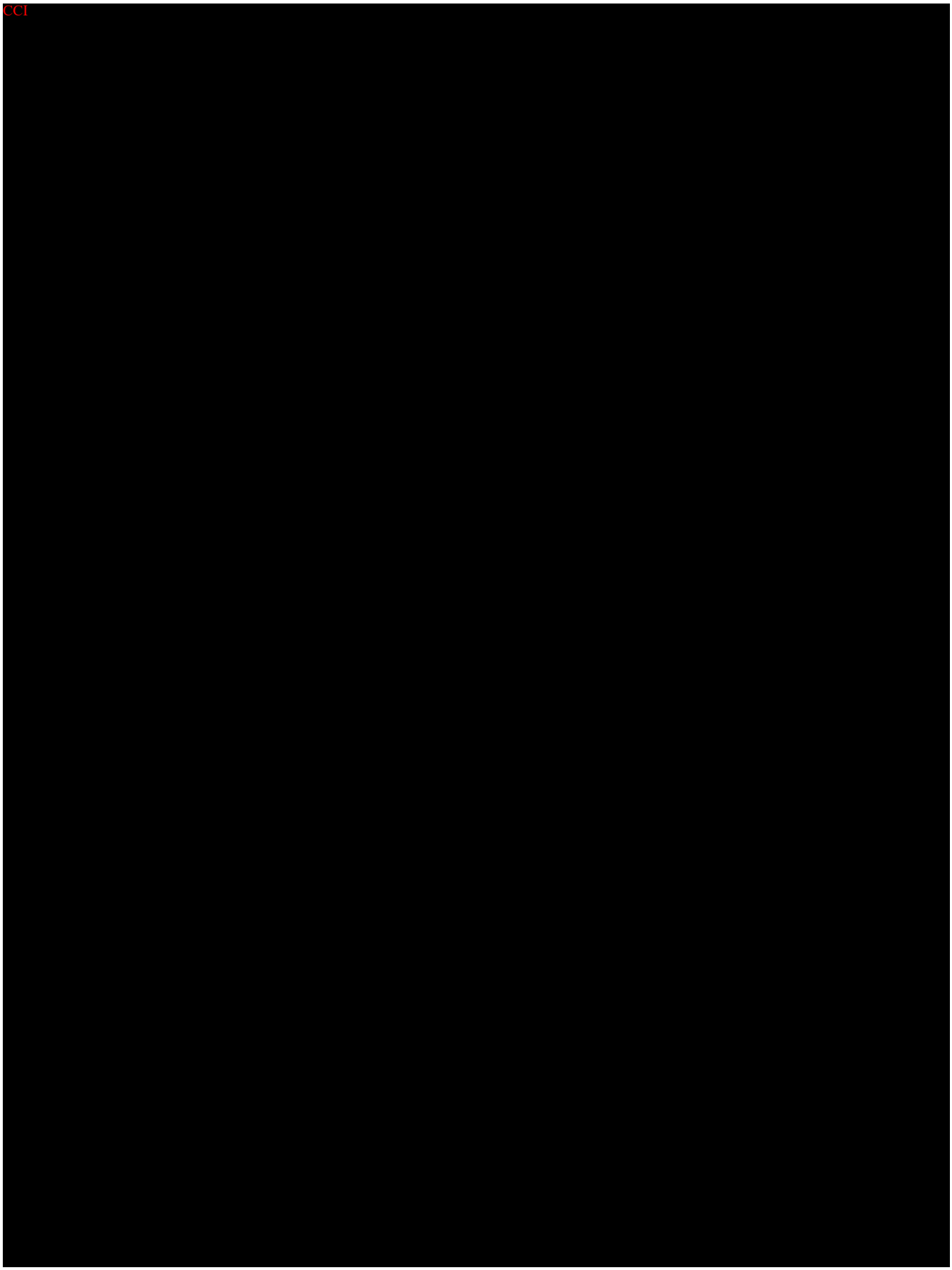

CCI [redacted]

5. SAMPLE SIZE DETERMINATION

Approximately CCI participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of CCI participants in a CCI ratio to GSK3511294 CCI and matching placebo CCI .

5.1. Sample Size Assumptions

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

5.1.1. Primary Endpoint

CCI [redacted]

CCI

[redacted]

5.1.2. Secondary Endpoints

Table 5 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 5 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
CCI			

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 5 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 5 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
CCI	CCI

5.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than CCI 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

CCI

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
ANSD	Asthma Nightly Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
LOS	Length of Stay
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
LS Mean	Adjusted mean for the treatment group
LS Mean Change	Adjusted mean change from baseline for the treatment group
MAR	Missing at Random
MNAR	Missing Not at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities
Min	Minimum
FAS	Full Analysis Set
Mg	Milligram
MMRM	Mixed Models Repeated Measures
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey

Abbreviation	Description
OCS	Oral corticosteroids
OPS	Output and Programming Specification
OR	Odds ratio
PD	Pharmacodynamics
PEF	Peak expiratory flow
PT	Preferred Term
CCI	[redacted]
PK	Pharmacokinetics
PRO	Patient-reported outcomes
CCI	[redacted]
QTcF	QTc corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
CCI	[redacted]
SoC	Standard of care
SOC	System Organ Class

6.2.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

7. REFERENCES

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