Statistical Analysis Plan Amendment 3

Study ID: 219538

Official Title of Study: A Phase 2b, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Dose Finding study toevaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of GSK1070806 SC injection in Adult Participants with Moderate to Severe Atopic Dermatitis

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TITLE PAGE

Protocol Title:	A Phase 2b, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Dose Finding study to evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of GSK1070806 SC injection in Adult Participants with Moderate to Severe Atopic Dermatitis
Study Number:	219538
Compound Number:	GSK1070806
Acronym:	AtDventure

Sponsor Name: GlaxoSmithKline Research & Development Limited

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	02 November 2023	03 August 2023	Not Applicable	Original version
SAP Amendment 1	29 August 2024	07 June 2024	Minor typos corrected and abbreviations aligned	
			Removal of CFB IGA endpoint and addition of SP-NRS4 endpoint at each scheduled visit	IGA is an ordinal endpoint. Descriptive statistics will be calculated and analysis of the binary endpoint of IGA0/1 will remain.
			Addition of ACQ-5 endpoint at [redacted] Primary Analysis	It is clinically important to have this endpoint analyzed at the [redacted] Primary Analysis in addition to the Week 28 analysis.
			Update handling of use of rescue ICE for continuous endpoints to composite strategy.	Answers clinical question of interest more appropriately.
			Treatment conditions (all active doses and placebo) added to in new primary estimand	To make the estimand clearer and reflect planned comparisons
			Removal of estimands on PP-NRS4 endpoint on the population of participants with baseline PP-NRS score of ≥5	Limited clinical interest in this population subset.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Handling strategies for treatment discontinuation ICE and use of rescue therapy ICE in the dose response estimand updated to hypothetical.	Answers clinical question of interest more appropriately.
			Addition of how to handle remaining missing data. Continuous data will be imputed under MAR assumption and binary data will be imputed as non-responder.	Aligns with clinical thinking.
			Discontinuation ICE by visit indicator removed from binary model table	Bayesian logistic regression performed at each week separately, so this indicator is inappropriate
			Additional detail given on subgroup analysis categories and models.	Provide clearer information on intended statistical and descriptive approach.
			Scope of PK early access updated.	Aligns with new recommended approach.
			Clarification of data included at each planned analysis.	Added clarity.
			Addition of conditional per protocol analysis set.	Sensitivity analyses using this population may be performed if deemed necessary.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Definition of baseline and approach to duplicate records updated.	Added clarity.
			Addition of sensitivity analysis on actual treatment.	Reflects study requirements.
			Clarification of adverse event and immunogenicity tables.	Reflects study requirements.
			Addition of eCOA compliance section.	Aligns with new requirement.
			Addition of specific timepoint for dose response endpoint 'PCFB in the EASI to [redacted]'	Reflects more accurately the reporting intention of this endpoint.
			Updated to case-by-case approach to assigning actual treatment if dose(s) were not in line with any protocol defined regimens (Table removed).	Reflects complexity of potential scenarios.
			Addition of technical appendix to describe the primary analysis approach in more detail.	Reflects need for additional information due to complexity of approach.
SAP Amendment 2	24 October 2024	07 June 2024	Addition of Japan subpopulation analysis and regional subgroup analysis on additional estimands	Reflects need for additional analysis due to higher-than-expected use of

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				rescue medication in Japan
			Update to priors for logistic regression	To ensure logistic regression models can run when proportion of responders is zero
			Update to per protocol analysis set	To exclude any participant from any site with a serious breach
			Update to the ICE date for treatment discontinuation	Aligns with clinical thinking. Taking last dose plus [redacted] to account for the half life meant the ICE could not be experienced before primary timepoint
			Removed main effects from subgroup (interaction) models	Little statistical impact and allows for simpler interpretation of model and calculation of observed margins
			Updated how prior and concomitant medications are summarized	To align with new GSK standard
			Addition of approach to handling remaining missing binary data.	Conditional approach given there is possibly higher

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				than expected study withdrawals
			Updated the region subgroups categories and comparisons.	To clarify analyses may be conducted on East Asia vs Rest of World and Japan vs Rest of World (which would include China)
			Updated extent of exposure summary.	Given participants can only receive 1 or 2 doses, summary statistics on days of exposure were inappropriate.
			Clinical efficacy baseline definition to include Day 1 post-dose if Day 1 pre-dose assessment missing	Allow flexibility with no clinical impact
SAP Amendment 3	16 Jun 2025	07 June 2024	All reporting will be performed at the final analysis. Statistical analysis of only the primary and key secondary endpoints will be produced, limited to the primary/secondary efficacy estimands; descriptive statistics will be produced for the remaining secondary endpoints. Previous treatment experience and reason for stopping previous	Only described analyses are required given the study has been terminated.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			treatment subgroup analyses, as well as analyses excluding Japan, will be performed on the primary endpoint and IGA0/1. The immunogenicity and PK analyses will be more limited in scope. The summary of overall eCOA compliance will be produced. Safety analyses will remain but will be limited to the primary safety estimand only. All other analyses will not be produced.	
			Addition of modified full analysis set.	The primary analysis will now be based on the modified full analysis set given the study has been terminated.
			Clarification on the binary analysis model to only include the CCI dose and placebo treatments.	To limit the chance of proportion of responders being zero in the intermediate doses so the logistic regression models can run.
			Addition of repeating analysis of PCFB EASI and IGA0/1	Clinical interest given high use of

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			excluding Japan participants.	persistent rescue in Japan.
			Key laboratory parameters have been defined.	To clarify the secondary objective.
			Addition of assessment window for POEM endpoint.	Previously unintentionally omitted.
			Addition of futility assessment in the bio-IR population as part of interim analysis 2.	Reflecting what was planned prospectively and carried out since SAP Amendment 2.
			Details of the D-E-R modelling and further PK/PD analyses will be provided in a separate document.	Only analyses described are required for the CSR given the study has been terminated.

1. INTRODUCTION

This SAP has been updated after the decision to terminate the study.

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 219538. Details of the planned interim analysis, as well as the final analyses, are provided.

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

The objectives and endpoints stated below are taken directly from the Protocol. Note that the exploratory objectives are no longer being assessed, except for the potential for ADA formation, given the study termination decision.

Objectives	Endpoints
Primary	
To evaluate the efficacy of GSK1070806 CCI versus placebo in adults with moderate to severe AtD.	PCFB in the EASI to [redacted]
Secondary	
To evaluate the efficacy of GSK1070806 across the dose range versus placebo by characterizing the longitudinal dose-response relationship in adults with moderate to severe AtD.	PCFB in the EASI to [redacted]
To further evaluate the impact of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	• Achieving EASI Reduction of ≥75% from Baseline (EASI75) at [redacted] • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points (IGA0/1) at [redacted] • CFB in PP-NRS at [redacted] • Achieving PP-NRS Reduction of ≥4 points from Baseline (PP-NRS4) at [redacted]
To further evaluate the efficacy of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	Achieving EASI Reduction of ≥50%/90%/100% from Baseline (EASI50/90/100) at [redacted] Achieving SCORAD Reduction of ≥50%/75% from Baseline (SCORAD50/75) at [redacted]. CFB to [redacted] for the following measures: • BSA • SCORAD
To assess the impact of GSK1070806 CCI and across the dose range versus placebo on Health Related-Quality of Life (HR-QoL), depression and anxiety, fatigue, sleep, WPAI and pain as measured by a range of PROs in adults with moderate to severe AtD.	CFB to [redacted] for the following PRO measures: • SP-NRS • PROMIS-Sleep disturbance 8b

Objectives	Endpoints
	• FACIT-Fatigue • BFI-item 3 • POEM • DLQI • HADS • WPAI-AD
To assess the safety of GSK1070806 CCI and across the dose range in adults with moderate to severe AtD.	• Occurrence of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) • Change from baseline in key laboratory parameters. • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities.
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

1.1.1. Estimand Strategy for Efficacy Objectives

Table 1 Primary Estimand

Estimand 1 – Primary estimand	
Clinical question of interest	What is the treatment difference for GSK1070806 CCI [redacted] vs. placebo with or without use of non-medicated background treatments as measured by PCFB in the EASI score to [redacted] in participants with moderate to severe AtD (either biologic naïve or experienced); regardless of discontinuation of investigational treatment for any reason but where use of rescue therapy for AtD before [redacted] is considered a negative outcome? Rationale: This clinical question of interest is designed to evaluate the difference in treatment response of GSK1070806 CCI [redacted] vs. placebo with or without use of non-medicated background treatments where the use of rescue therapy for AtD results in a negative outcome, irrespective of permanent intervention discontinuation for any reason. The composite strategy explicitly recognizes that use of rescue therapy constitutes a failure of the treatment to manage the participant's disease and avoids reporting results reflecting use of an additional medicated treatment rather than a placebo.
Treatment Condition	SC GSK1070806 CCI [redacted] vs. placebo administered once every [redacted] with or without use of non-medicated background treatments regardless of permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoint	PCFB to [redacted] in EASI where any use of rescue medication is considered an unfavorable outcome.
Population	Participants with moderate to severe AtD (either biologic naïve or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy.
Strategy for ICEs	• ICE: permanent treatment discontinuation before [redacted] Strategy: treatment policy

Estimand 1 – Primary estimand	
	• ICE: use of rescue therapy for AtD before [redacted] Strategy: composite; use of rescue therapy is considered a negative outcome, and post-ICE assessments are imputed as the participant's worst observation (from baseline or post-baseline assessments) • ICE: treatment discontinuation due to extreme administrative and operational disruptions (e.g., situations such as pandemic illness, or war causing lockdown or site closure and restricting access to the study medication) Strategy: hypothetical
Population-level summary	Difference (GSK1070806 CCI [redacted] with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in mean percent change between treatment conditions.

Additional Estimand For The Primary Efficacy Objective

One additional estimand for the primary objective will be defined (estimand 2). The attributes follow the primary estimand (estimand 1) except for the endpoint definition and the strategy for ICE of use of rescue therapy.

Table 2 Additional Estimand to the Primary

Estimand 2 – Additional Estimand to the Primary	
Endpoint	PCFB to [redacted] in EASI
Strategy for ICEs	• ICE: use of rescue therapy for AtD before [redacted] Strategy: treatment policy

Rationale: This additional estimand is designed to evaluate the treatment effect attributable to GSK1070806 CCI [redacted] with or without use of non-medicated background treatments, irrespective of permanent treatment discontinuation or use of rescue therapy before [redacted]. This provides evidence of efficacy regardless of whether participants took the drug as per the protocol and is most closely reflective of usual clinical practice.

1.1.2. Estimand Strategy for Secondary Dose Response Objective

Table 3 Estimands for the Dose-Response Objective

Estimands for the dose- response objective	
Clinical question of interest	What is the longitudinal dose-exposure response for GSK1070806 across the dose range vs. placebo with or without use of non-medicated background treatments as measured by PCFB in the EASI score at each time point in participants with moderate to severe AtD (either biologic naive or experienced); had discontinuation of investigational treatment for any reason not occurred or had rescue therapy not been administered for AtD before [redacted]?
Treatment Condition	SC GSK1070806 across the dose range vs. placebo administered once every [redacted] with or without use of non-medicated background treatments.
Endpoint	PCFB at each scheduled timepoint in EASI.
Population	Participants with moderate to severe AtD (either biologic naive or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy.
Strategy for ICEs	• ICE: permanent treatment discontinuation before [redacted] • ICE: use of rescue therapy for AtD before [redacted] • ICE: treatment discontinuation due to extreme administrative and operational disruptions (e.g., situations such as pandemic illness, or war causing lockdown or site closure and restricting access to the study medication) Strategy: hypothetical Note: Observed PK/PD values will be used for modelling purposes.
Population-level summary	Difference (Each dose of GSK1070806 with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in mean percent change between treatment conditions.

1.1.3. Estimand Strategy for Secondary Efficacy Objectives

Continuous secondary efficacy objectives

These estimands (continuous) for the secondary efficacy objectives follow the attributes, including the handling strategies for all ICEs, of the primary estimand (estimand 1) except for the treatment condition, endpoints, and population-level summary, as described below.

Table 4 Estimands (Continuous) for the Secondary Efficacy Objectives

Estimands (Continuous) for secondary efficacy objectives	
Treatment Condition	SC GSK1070806 CCI [redacted] and across the dose range vs. placebo administered once every [redacted] with or without use of non-medicated background treatments regardless of permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoints	CFB to [redacted] in: • PP-NRS • BSA • SCORAD • SP-NRS • PROMIS-Sleep disturbance 8b • FACIT-Fatigue • BFI-item 3 • POEM • DLQI • HADS • WPAI-AD where any use of rescue medication before [redacted] is considered an unfavorable outcome.
Population-level summary	Difference (Each dose of GSK1070806 with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in mean change between treatment conditions.

Binary secondary efficacy objectives

These estimands are applicable to the binary secondary efficacy objectives. The treatment condition, endpoints, strategy for handling use of rescue therapy ICE and population-level summary differ from the primary estimand (estimand 1) and are detailed below.

Table 5 Estimands (Binary) for Secondary Efficacy Objectives

Estimands (binary) for secondary efficacy objectives	
Treatment Condition	SC GSK1070806 CCI and across the dose range vs. placebo administered once every [redacted] with or without use of non-medicated background treatments regardless of permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoints	At [redacted]: • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points without use of rescue therapy for AtD • Achieving EASI reduction of ≥ 50%/75%/90%/100% from baseline without use of rescue therapy for AtD • Achieving PP-NRS reduction of ≥ 4 points from baseline without use of rescue therapy for AtD • Achieving SCORAD reduction of ≥ 50%/75% from baseline without use of rescue therapy for AtD
Strategy for ICEs	• ICE: use of rescue therapy for AtD before [redacted] Strategy: composite; use of rescue therapy is considered a negative outcome, and post-ICE assessments are imputed as non-responder
Population-level summary	Difference (Each dose of GSK1070806 with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in proportions between treatment conditions.

These additional estimands will follow the attributes of the estimands for binary secondary efficacy objectives except for endpoints and the strategy for ICE of use of rescue therapy.

Table 6 Additional Estimands (Binary) for Secondary Efficacy Estimands

Additional estimands (binary) for secondary efficacy objectives	
Endpoints	At [redacted]: • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points • Achieving EASI reduction of ≥ 75 from baseline • Achieving PP-NRS reduction of ≥ 4 points from baseline
Strategy for ICEs	• ICE: use of rescue therapy for AtD before [redacted] Strategy: treatment policy

Note: Population for endpoints 'achieving PP-NRS reduction of ≥ 4 points from baseline' and 'achieving SP-NRS reduction of ≥ 4 points from baseline' will include only the subset of participants with a PP-NRS/SP-NRS ≥4 points at baseline respectively.

1.1.4. Estimand Strategy for Safety Objectives

Table 7 Estimands for Safety Objectives

Estimands for safety objectives	
Clinical question of interest	What is the difference in safety for GSK1070806 CCI and across the dose range vs. placebo with or without use of non-medicated background treatments as measured by occurrence of AEs, SAEs, AESIs, and grade ≥3 hematological/clinical chemistry abnormalities, as well as change from baseline in key laboratory parameters in participants with moderate to severe AtD (either biologic naive or experienced); regardless of discontinuation of investigational treatment for any reason or use of rescue therapy for AtD before [redacted]? Rationale: This clinical question of interest is designed to evaluate the safety of GSK1070806 CCI and across the dose range vs placebo with or without use of non-medicated background treatments, irrespective of permanent treatment discontinuation or use of rescue therapy for AtD before [redacted]. This provides comparison of safety regardless of whether participants took the drug as per the protocol and is most closely reflective of usual clinical practice.
Treatment Condition	SC GSK1070806 CCI and across the dose range vs placebo administered once every [redacted] with or without use of non-medicated background treatments regardless of use of rescue therapy for AtD before [redacted] or permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoints	• Occurrence of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) • Change from baseline in key laboratory parameters • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities.
Population	• Participants with moderate to severe AtD (either biologic naive or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy.
Strategy for ICEs	• ICE: permanent treatment discontinuation before [redacted] • ICE: use of rescue therapy for AtD before [redacted]

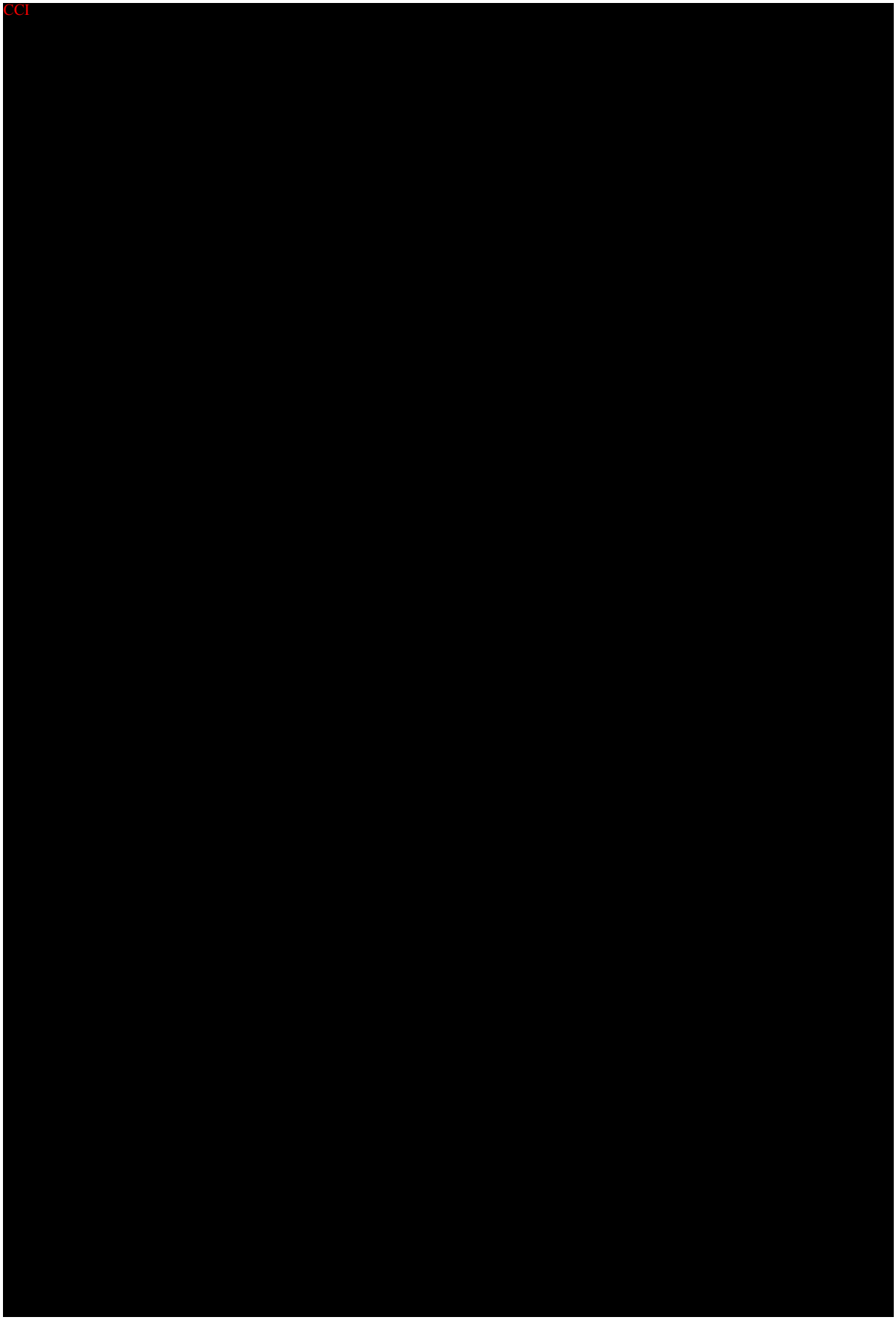
Estimands for safety objectives	
	• ICE: treatment discontinuation due to extreme administrative and operational disruptions (e.g., situations such as pandemic illness, or war causing lockdown or site closure and restricting access to the study medication) Strategy: treatment policy
Population-level summary	• AEs, SAEs: number and % of participants with at least 1 event by System Organ Class and Preferred Term for each treatment arm • CFB in key laboratory parameters: mean for each treatment arm and timepoint

Additional estimands for safety objectives

For key safety endpoints, overall AEs and overall SAEs only, these estimands will use the "while on treatment" approach, i.e. any safety events which occur post discontinuation of study intervention which are not classified as treatment emergent will be excluded. Treatment emergent events are events which occur up to [redacted] after a participant's last dose as per the definition given in Section 4.1.3.

1.2. Study Design

CCI



2. STATISTICAL HYPOTHESES

An estimation approach with no hypothesis testing will be used to address the primary objective. For the primary estimand, a Bayesian analysis will be utilized with a non-informative prior for the true treatment difference. It is assumed that the PCFB EASI follows a normal distribution with a non-informative prior for the true treatment difference. The primary assessments of interest are the point estimates of the treatment difference in PCFB EASI and 95% credible intervals; in addition, posterior probabilities that the true treatment difference in each active treatment arm versus placebo is greater than a range of clinically meaningful differences given the observed differences will be provided. Comparisons relative to the key secondary/exploratory objectives will be assessed using probability inference approaches.

2.1. Multiplicity Adjustment

An estimation approach with no hypothesis testing will be performed and therefore multiplicity adjustments are not applicable.

3. ANALYSIS SETS

No analyses will be conducted using the per protocol and actigraphy analysis sets given the study has been terminated.

Table 8 Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study. • This population will be based on the treatment the participant was randomized to. • All participants who receive a treatment randomization number will be considered to have been randomized.	Study Population
Safety	• All participants who received at least 1 dose of study intervention. • This population will be based on the treatment the participant actually received. In the situation where 2 different treatments were	Efficacy Safety Biomarker PD

Analysis Set	Definition / Criteria	Analyses Evaluated
	received; the participant's actual treatment will be assigned on a case-by-case basis. • Note: Participants who were not randomized but received at least 1 dose of study treatment should be listed.	
Full Analysis Set (FAS)	• All randomized participants who received at least 1 dose of study treatment. • This population will be based on the treatment the participant was randomized to.	Study Population Efficacy
Modified FAS	• All randomized participants who received at least 1 dose of study treatment, were randomized at least [redacted] before the study termination decision, and attended a [redacted] or early withdrawal visit prior to the study termination decision. • This population will be based on the treatment the participant was randomized to.	Study Population Efficacy
Per-Protocol (PP)	• All participants in the FAS population except: • Participants at any site with a serious breach identified. • Participants with a protocol deviation relating to incorrect treatment/dosing errors or violation of one or more of the following: ○ Inclusion criteria 4, 5, 7 ○ Exclusion criteria 16, 17. PP analysis will be conditional on FAS results. This population will be based on the treatment the participant was randomized to.	Efficacy
PK	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	Efficacy PK
Immunogenicity	• All participants in the Safety analysis set who had at least 1 Immunogenicity sample collected with analysis result.	Immunogenicity
CCI [redacted]		

The term "Analysis Set" will be referred to as "Population" in the displays.

For any analyses using the safety analysis set, i.e. actual treatment, if a participant did not receive dose(s) in line with any of the protocol defined treatment arms, the treatment arm with which to combine participant(s) will be evaluated on a case-by-case basis.

4. STATISTICAL ANALYSES

4.1. General Considerations

Given the study has been terminated early, the final study analysis and reporting will be conducted when all ongoing randomized participants at the time of study termination have completed the safety follow up period, [redacted] after their last dose (or early withdrawn).

The statistical analysis will be performed according to the Analysis Sets (Table 8) in the Analysis Sets Section 3, unless specified otherwise.

Randomized treatment will be used for the analyses except safety, PK/PD and immunogenicity, which will use actual treatment received. Sensitivity analyses will also be described.

Participants who prematurely withdrew from study will not be replaced. In the case of incorrect stratification (i.e., biologic-naïve vs biologic-experienced) assignment at the time of randomization, the analyses will be performed based on the actual/correct stratum per data collected in the CRF.

Credible Intervals (CrI) of the posterior distribution as well as Confidence Intervals (CI) will use 95% confidence levels unless otherwise specified.

Handling of values below lower limit of quantification: Non-quantifiable [NQ] values will be considered as non-missing values.

All analyses conducted by biostatistics will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely accepted statistical or graphical software as required. Data will be presented in listings, tables, and figures. Unless otherwise specified, summary tables will provide the following descriptive statistics as a minimum:

- Continuous data: n, mean, standard deviation, minimum and maximum.
- Continuous data (log-normally distributed): n, geometric mean, %CVb, minimum, maximum
- Categorical data: number and percentage of participants in each category.

For descriptive summaries of continuous data, an intercurrent event strategy will not be applied unless otherwise specified. In other words, data impacted by an intercurrent event will not be discarded or imputed for continuous descriptive summary displays that have no statistical model involved.

It is anticipated that participant accrual will be spread thinly across centers and summaries of data by center would unlikely be informative. If this is not the case and there are appreciable numbers of participants at a particular center, an exploration of the heterogeneity of treatment effect across centers may be graphically explored providing a positive treatment effect is demonstrated in the overall study population.

Baseline disease severity (IGA score, categorical: 3 = Moderate, 4= Severe) will be included as a covariate in all statistical analyses of efficacy except for analyses of EASI (PCFB EASI as well as EASI75). The randomization stratification parameters of region and previous treatment experience will also be included as covariates in all statistical analyses of efficacy. If there are insufficient participants in a region for the planned statistical analysis, further combining of regions will be considered.

4.1.1. Bayesian Inference

The main statistical analyses will be carried out in the Bayesian framework. Models will be fitted by Monte Carlo Markov Chain (MCMC) simulations.

Prior distributions are given in the analysis sections below.

Posterior distributions for each arm and for the treatment difference between arms will be summarized using posterior median, 95% equal-tailed credible intervals (CrI), and posterior probabilities of the true treatment difference being greater than pre-specified thresholds. All models for continuous endpoints will be run without an intercept and all logistic regression models for binary endpoints will be run with an intercept.

The inference will be carried out as follows:

- 2 chains will be run, with different (over-dispersed) initial values in order to assess convergence. Posterior summaries will use only 1 chain.
- A minimum burn-in period of 1,000 MCMC samples (for each chain) will be used, and this may be updated by assessing worm plots and computation time.
- Number of samples (for each chain) will be set as appropriate based on worm plots and computational time to generate samples of the posterior distribution.
- A thinning sample may be used to improve convergence. If k is the thinning ratio, the number of MCMC samples will be minimum $k \times 10{,}000$.

To assess convergence (MCMC), the following will be used:

- Ratio of Monte Carlo error/posterior SD should be as small as to ensure that only a fraction of the posterior variability is due to simulation error.

  The final MCMC samples will be such that this ratio for the key parameters in the model is ≤ 0.01.

- Diagnostic plots and visual inspection:
  - Trace plots (the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant)
  - Autocorrelation plots (provide information on how slow or fast the Markov chain converges)

All the diagnostic outputs and alternative models fitted (where applicable) will be stored in the relevant reporting efforts.

4.1.2. Baseline Definition and Duplicate Records

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day 1 pre-dose) based on date and time of the assessment and the treatment.

For clinical efficacy only, as per SoA, if day 1 pre-dose assessment is missing, baseline may be considered as the following criteria, given in order of preference:

- Day 1 post-dose
- Pre-dose up to Day -7. Given the large time gap between screening and Day 1, pre-dose assessments before Day -7 will not be considered.

If none of the criteria are met, baseline will remain missing.

For PP-NRS, SP-NRS and BFI-Item 3 baseline, the baseline score will be averaged from daily values from Day -7 to Day -1 if ≥ 4 (out of 7) days are not missing. If only ≤ 3 days (out of 7) are available, baseline is set to missing.

For all eCOA endpoints, if there are multiple assessments of the same type collected at the same scheduled time (including baseline visit), the earliest of these assessments will be used as the value for that endpoint. For all other types of assessments, if there are multiple assessments of the same type collected at the same scheduled time, the average of these assessments will be used.

4.1.3. Treatment Discontinuation Definition

The date of treatment discontinuation will be defined as [redacted] after the date of the last dose of study intervention (i.e., date of last dose of study intervention + [redacted]). This is driven by the half-life of GSK1070806 in participants with atopic dermatitis.

In the event a participant withdraws from the study, their treatment discontinuation date will be defined as the date of the last dose of study intervention + [redacted]. If the withdrawal from the study is after [redacted] IMP dosing, the participant will be considered to have completed treatment.

4.1.4. Intercurrent Events

4.1.4.1. Treatment Discontinuation before [redacted]

Given the nature of this ICE, only participants who decide not to receive any further study treatment (including participants who withdraw from the study) prior to their [redacted] dose can experience this ICE. The date of this ICE will align with the date the participant decided not to have any further study treatment, as collected in the eCRF. In all efficacy estimands in Section 1.1, this ICE is handled with the treatment policy strategy.

Following this ICE under the treatment policy strategy, all data collected will be used. Handling of missing outcomes is detailed in Section 4.1.5.

In the dose-response estimands in Section 1.1, this ICE is handled with the hypothetical strategy. Following this ICE under the hypothetical strategy, any data collected after the ICE is not relevant and all data collected after the ICE will be set to missing. The outcomes set to missing will be imputed using an extended MAR assumption that, had the ICE not occurred, the outcomes would be consistent with observed patients who had not experienced this ICE with similar baseline characteristics and outcome of previous visits.

4.1.4.2. Treatment discontinuation due to extreme administrative and operational disruptions

In all efficacy and dose-response estimands in Section 1.1, this ICE is handled with the hypothetical strategy. Following this ICE under the hypothetical strategy, any data collected after the ICE is not relevant and all data collected after the ICE will be set to missing. The outcomes and ICE status set to missing will be imputed using an extended MAR assumption that, had the ICE not occurred, the outcomes would be consistent with observed patients who had not experienced this ICE with similar baseline characteristics and outcome of previous visits.

4.1.4.3. Use of Rescue Therapy for AtD before [redacted]

For the dose-response estimand, following this ICE under the hypothetical strategy, refer to Section 4.1.4.1.

For the efficacy estimands, following this ICE under the composite strategy:

- For binary endpoints: participants will be classed as non-responders at all scheduled visits from the date of the ICE onwards.
- For continuous endpoints: participants will have all outcomes at all scheduled visits from the date of the ICE onwards set to missing. Their worst observation will be calculated as their worst observation across all their observations (baseline and post-baseline) prior to the ICE for use in the modelling. For participants who withdraw from the study prior to this ICE being observed, the risk of having this ICE post withdrawal before [redacted] will be modelled (see Section 4.2.2).

Following this ICE under the treatment policy strategy, the same approach as the one outlined in Section 4.1.4.1 will be followed.

Following this ICE under the hypothetical strategy the same approach as the one outlined in Section 4.1.4.1 will be followed.

Investigators are allowed to rescue participants who are experiencing unacceptable or worsening symptoms of AtD at any time if absolutely required. Prior to initiating rescue, it is recommended to increase the frequency of non-medicated treatments such as emollient at least twice a day in an effort to control symptoms.

If not controlled, investigators may consider the addition of low/moderate potency TCS (e.g., triamcinolone acetonide 0.1% cream, hydrocortisone 1% cream). Investigators may also select to use TCIs and/or crisaborole where approved.

In participants who do not improve sufficiently with the provided rescue topical therapy after 7 days, a higher potency TCS may be used.

If topical rescue therapy as described above fails to sufficiently control AtD symptoms, then oral systemic medications may be used as rescue (e.g., corticosteroids, cyclosporine, methotrexate); however, the investigational product will be required to be permanently discontinued for the remainder of the study duration.

Only persistent use of rescue therapy will be categorized as an intercurrent event. Definition of persistent use is detailed in Table 9. The intercurrent event date of persistent use of rescue therapy will be defined as the date the rescue therapy use is first classified as persistent use (for example, the seventh day of using a moderate potency TCS). If this date coincides exactly with a visit date, the composite (hypothetical for dose response estimand) handling strategy will be implemented immediately. If the date of ICE start is in between visits, the handling strategies will only be implemented at the next visit.

Table 9 Definition of Persistent Use of Rescue Therapy for AtD

Type	Definition of Persistent Use
Low/moderate potency TCS (e.g., triamcinolone acetonide 0.1% cream, hydrocortisone 1% cream)	7 or more continuous days
High potency TCS	7 or more continuous days
Oral systemic immunosuppressant medications (e.g., corticosteroids, cyclosporine, methotrexate but excluding JAK inhibitor)	21 or more continuous days
Oral JAK inhibitor	7 or more continuous days
Topical JAK inhibitor	7 or more continuous days

After [redacted], all TCS are permitted per protocol and any use, including persistent use, will not be classified as ICE. Systemic medications of any kind remain prohibited per protocol, however, use will not be classified as rescue medication and will not constitute an ICE. For TCS use after [redacted] the definition of persistent use remains and will be

used in the context of dose response modelling.

4.1.5. Remaining Missing Data

If there are any missing data after the handling strategies for ICEs have been implemented, continuous endpoints will be imputed under a MAR assumption (implicit). Binary endpoints will be imputed as non-responder except when both of the following conditions are met:

- Intermittent missing data (missing data with completed visits before and after); and
- Participant is a responder at the visits immediately before and immediately after the missing visit.

For this case, binary endpoints will be imputed as a responder.

The additional approach to remaining missing data will no longer be applicable, given the study has been terminated.

An additional approach to remaining missing binary data may be used as sensitivity analysis for key secondary endpoints (IGA0/1, EASI75, PP-NRS4) on the main estimands for secondary binary endpoints. Further details on the outputs will be given in the OPS.

If there are any missing data after the handling strategies for ICEs have been implemented, binary endpoints with corresponding continuous endpoints will be multiply imputed using Markov Chain Monte Carlo multiple imputation. The MI will be run 25 times using the model specified in Table 10 for the imputation of PCFB EASI corresponding to EASI75 and the model specified in Section 4.3.2.2 will be used for the imputation of CFB PPNRS and IGA corresponding to PP-NRS4 and IGA0/1. Normality assumptions will be checked and if violated, alternative models may be considered.

For EASI and PPNRS endpoints, the imputed values will not be rounded. The imputed values will be compared to the observed baseline to determine if response was achieved. For IGA, the imputed values will be rounded to the nearest integer and the imputed values will be compared to response criteria to determine if response was achieved.

Each imputed dataset will be analyzed as per Table 13 with results combined using Rubin's rules.

4.2. Primary Endpoints Analyses

The primary objective is to evaluate the efficacy of GSK1070806 CCI [redacted] versus placebo in adults with moderate to severe AtD, using PCFB in the EASI score measured at [redacted]. The intermediate doses of GSK1070806 will also be included in the model and presented in the output. The primary inference with respect to the intermediate doses will come from the D-E-R modelling which is detailed in Section 4.3.1.

Descriptive statistics on the raw data will be presented.

A Bayesian repeated measures linear model will be fitted to the PCFB in EASI at Weeks 1, 2, 4, 6, 8, 10, 12, 14 and 16, including baseline EASI score, region (China versus Japan versus Rest of World), prior treatment experience (biologic naive versus biologic experienced), week (categorical) and treatment as well as interactions for treatment-by-week, and baseline EASI score-by-week unstructured covariance matrix to handle repeated measures.

The treatment difference for GSK1070806 CCI from placebo at [redacted] as well as each intermediate dose of GSK1070806 from placebo at [redacted], from this model will be summarized as Median and 95% credible interval (CrI) of the posterior distribution.

4.2.1. Definition of EASI

EASI is a clinician assessed endpoint comprising an assessment of the percentage of body area affected as well as the severity of four key signs [Hanifin, 2001].

The body is partitioned into four regions:

- Head and neck
- Upper extremities
- Trunk
- Lower extremities

The area within each region with inflammation is estimated as a percentage of the total area of that region. The estimated percentage is categorized:

0 = none, 1 = <10%, 2 = 10% - 29%, 3 = 30% - 49%, 4 = 50% - 69%, 5 = 70% - 89%, 6 = > 89%.

The average severity of erythema, induration/papulation/edema, excoriations, and lichenification are categorized individually:

0 = none, 1 = mild, 2 = moderate, 3 = severe (half steps are allowed).

For each body region separately, the average severity for each of the four signs is summed and then multiplied by the categorized percentage of inflammation. This score is multiplied by the following:

0.1 for head and neck, 0.2 for upper extremities, 0.3 for trunk, 0.4 for lower extremities.

The overall EASI score is the sum of all the individual body region scores. The score is in the range of 0 to 72 with higher scores indicating more severe atopic dermatitis.

A listing of EASI data detailing the individual components of the EASI score will be described in the OPS.

4.2.2. Main analytical approach

The analysis will be based on the modified full analysis set given the study has been terminated. Participants will be analyzed according to the treatment they are randomized to.

To account for potentially unobserved use of rescue after study withdrawal, Bayesian models are described in Section 6.1 and summarized briefly below, under the following assumptions:

- If a participant withdraws from the study (after treatment discontinuation or otherwise) and use of rescue has not yet been observed, the participant is still at risk of using rescue therapy up to [redacted]. This drives the requirement of the joint modelling approach given the use of rescue therapy is handled with the composite strategy (WOCF) in the primary estimand.
- Given the long PD effect ([redacted] half-life), it is reasonable to assume that missing values due to study withdrawal (after treatment discontinuation or otherwise) would be similar to all other participants within that treatment group and for the purpose of this analysis could be considered on-treatment. There is no requirement to distinguish whether participants are on or off treatment due to the long PD effect.

Scenario	Data
• Participant withdraws from the study. • No ICE of use of rescue is observed before participant withdraws from study.	• Data up to study withdrawal: use as observed. • After study withdrawal: assume data are at risk of use of rescue ICE up to [redacted]
• Participant withdraws from the study. • ICE of use of rescue is observed before treatment discontinuation and/or study withdrawal.	• Data are used as observed up to the date of use of rescue ICE. • Data after use of rescue ICE are set to missing. The WOCF is implicitly used in the estimate of the marginal treatment effect.

The approach will jointly model the use of rescue ICE for any withdrawn participant with no actual observation of rescue before withdrawal and the outcome of PCFB EASI. The MCMC will impute missing ICE rescue status using a geometric distribution to determine the visit at which rescue is first used. If this value is before [redacted], the participant will be treated as experiencing the ICE of use of rescue. If the value is after [redacted], the participant will be treated as not experiencing this ICE.

The effects of interest (treatment difference: GSK1070806 CCI [redacted] – placebo, as well as each intermediate dose of GSK1070806 – placebo) will be constructed as functions of the posterior parameters to obtain expected PCFB EASI values when no rescue is taken and raw averages of worst pre-rescue PCFB EASI score for each treatment when rescue was taken. See Section 6.1.7 in the technical appendix for further detail.

Table 10 presents the analysis method and model specification that will be used.

Table 10 Primary Analysis Model

Endpoint(s)	
PCFB to [redacted] in EASI	
Analysis Method	
Bayesian repeated measures model	
Model Specification	
Outcome	Percent change from baseline in the EASI Assumption: normally distributed
Predictors	• Baseline EASI score (continuous) • Region (categorical, China vs Japan vs Rest of World, reference: Rest of the World) • Prior treatment experience (categorical, biologic naïve vs biologic experienced, reference: naive) • Treatment (categorical, all doses) • Week (categorical, weeks 1, 2, 4, 6, 8, 10, 12, 14 and 16, reference: [redacted]) • Treatment*week interaction • Baseline EASI*week interaction
Model	Linear model of Outcome by Predictors
Prior distributions for parameters associated with the predictors	• All parameters: vague prior Normal (0, SD=10^6)
Prior distribution for residual covariance matrix	• Σ: unstructured residual covariance matrix of dimension 9×9 ~ Inverse Wishart (J, S), with J = number of visits (degree of freedom), S = identity matrix • If convergence issues occur, an alternative covariance matrix structure may be used, for example a compound symmetric structure, to help improve convergence.
Model Checking & Diagnostics	
See Section 4.1.1	
Results Presentation	
• Adjusted posterior median, and 95% CrI for each treatment by timepoint interaction (table). • Posterior median treatment differences (Final: each active dose – placebo) and associated 95% CrI for each timepoint (table and figure). • Probabilities that the true treatment difference (Final: each active dose – placebo) at each visit is < 0%, -20%, -25%, -30%, -35% and -40% (table) • Outputs will include results for earlier timepoints in addition to the objective specified timepoint of [redacted]	

If convergence issues persist after considering alternative covariance matrix structures or variance of the priors, a simpler model may be fitted.

4.2.3. Sensitivity analyses

The analysis of PCFB EASI will be repeated excluding all Japan participants.

The following analyses will no longer be performed given the study has been terminated.

This analysis may be repeated using actual treatment received. Refer to the OPS for further details. If deemed necessary, this analysis will be repeated using the per-protocol analysis set as defined in Section 3.

4.2.4. Additional estimands

These analyses will no longer be performed given the study has been terminated.

One additional estimand for the primary objective is described in Section 1.1.1. The key difference is in the strategy for ICE attribute for the use of rescue therapy for AtD before [redacted] The strategies for handling the remaining intercurrent events remain unchanged from the primary estimand.

Refer to Section 4.1.4 for detail on how the ICEs will be handled for these estimands.

Refer to Section 4.2.2 for more detail on the analysis method; the statistical analysis will be performed according to the plan outlined in Table 10.

4.3. Secondary Endpoints Analyses

This section will detail the analysis approaches for the secondary efficacy endpoints. The section will be split to firstly address the objective to evaluate the efficacy of GSK1070806 across the dose range by characterizing the longitudinal dose-response relationship before addressing the objectives to further evaluate the efficacy and impact of GSK1070806.

4.3.1. Characterizing the Longitudinal Dose-response Relationship

All analysis will be based on the PK analysis set. PK, PD or TE, demographic and efficacy data from other studies and databases may be integrated into the analysis to inform D-E-R relationships, if required.

4.3.1.1. Definition of clinical endpoint

PCFB in the EASI at each time point.

4.3.1.2. Main analytical approach

This approach will assess the efficacy across the dose range versus placebo by characterizing the longitudinal dose-response relationship.

An integrated longitudinal mixed effects D-E-R model will be fitted to total GSK1070806 and the individual EASI response data from all treatment arms and all time points, including follow-up period, with the possible inclusion of target engagement data (predicted free IL-18) in the model. Details of this analysis will be described in a separate SAP. The model predicted difference from placebo in EASI, along with 95% confidence intervals, will be reported at [redacted] for each dose regimen. All modelling details may be reported separately.

The primary inference with respect to the intermediate doses will come from this analysis. However, for completeness, results from the intermediate doses from the pairwise comparison as described in Section 4.2.2 will also be provided.

The above analyses are planned to be conducted according to the estimand for the dose response objective, but other approaches may be evaluated. Potential differences in strategies to handle the ICEs, as compared to the estimand, will be documented in the CSR.

4.3.1.3. Software

All data manipulation, summary statistics (mean, median, standard deviation (sd), and other measures, as appropriate), and graphical presentation will be performed using R (version 3.2.5 or higher) (https://www.R-project.org/). R scripts used for data manipulation, final analyses and outputs will be archived. The population PK/TE/PD analysis will be conducted via nonlinear mixed effects modelling with NONMEM software, Version VI or higher (Beal, 1989-2013). The platform(s), operating system(s), Fortran compiler and any other software used will be documented.

4.3.2. Further Evaluating the Efficacy and Impact of GSK1070806

4.3.2.1. Definition of endpoints

For PP-NRS, SP-NRS and BFI-Item 3, the daily scores will be averaged over the 7 days prior to the scheduled visit to create a weekly measurement. The weekly score will be averaged from daily values from Day -7 to Day -1 for baseline, Day 1 to Day 7 for first week, Day 8 to Day 14 for second week, and so on.

Further details on endpoints and derivation are discussed in Appendix 4 (Section 6.4) Data Derivation Rules as well as the OPS.

Table 11 Definition of Secondary Efficacy Endpoints

Clinical Efficacy Endpoints
Continuous
CFB to [redacted] in: • BSA • SCORAD
Binary
Achieving at [redacted]: • EASI75 • EASI50/90/100 • SCORAD50/75 • IGA0/1
Patient Reported Outcomes
Continuous
CFB to [redacted]: • PP-NRS • SP-NRS • PROMIS-Sleep disturbance 8b • FACIT-Fatigue • BFI-item 3 • POEM • DLQI • HADS • WPAI-AD
Binary
Achieving at [redacted]: • PP-NRS4

For HADS, the depression score and anxiety score are calculated and analyzed separately. Refer to the OPS for further details.

For WPAI-AD, the four scores: work time missed due to health, impairment while working due to heath, activity impairment due to health, overall work impairment due to health are calculated and analyzed separately. Refer to the OPS for further details.

4.3.2.2. Main analytical approach

All analysis will be based on the modified full analysis set. Participants will be analyzed according to the treatment they were randomized to.

Statistical analysis of secondary efficacy endpoints will be limited to IGA0/1, EASI75 and PP-NRS4 and will compare the CCI [redacted] and placebo treatment arms as per the attributes of estimands (binary) for secondary efficacy objectives (Table 5) . Intermediate dose arms will not be included in the statistical analysis as sample size in these arms is expected to be too small to allow for robust estimation, due to the study being terminated early. Descriptive statistics will be provided for all other secondary endpoints and for all treatment arms without statistical modelling. No analyses will be conducted using the

additional estimand.

Continuous Endpoints

The following analysis will not be performed given the study has been terminated.

The attributes of the estimands (continuous) for secondary efficacy objectives (Table 4) will be applied to all continuous endpoints in Table 11.

The analysis of all the continuous endpoints (clinical and PROs) listed in Table 11 will follow the method outlined in Section 4.2.2 with the model specified in Table 10 except with the update of including all treatments CCI [redacted], [redacted]: each vs placebo, reference: placebo), respective baseline scores and baseline*visit interaction as well as the addition of baseline disease severity (IGA score, categorical, reference: IGA3) for all analyses except PCFB EASI as stated in the primary analysis. The weeks included in the model will reflect the schedule of activities in the protocol. The vague prior for all treatment groups will be Normal (0, SD=10^6). The difference from each GSK1070806 dose to placebo at [redacted] from this model will be summarized as Median and 95% credible interval of the posterior distribution.

For endpoints for which thresholds of clinical interest are agreed, the results presentation will also include probabilities that the true treatment difference (each GSK1070806 dose–placebo) is greater than endpoint specific thresholds as detailed in Table 12.

Table 12 Thresholds of Clinical Interest (secondary continuous endpoints)

	Thresholds of Clinical Interest
Clinical Efficacy Endpoints	**Change from baseline**
SCORAD	0 and 8.7 points
Patient Reported Outcomes	
PP-NRS	0 point change and 4 point improvement
SP-NRS	0 point change and 4 point improvement

Binary endpoints

Details of the estimands for the secondary efficacy endpoints are described in Section 1.1.1 The attributes of estimands (binary) for secondary efficacy objectives (Table 5) will be applied to all binary endpoints (clinical and PROs) in Table 11 The additional estimands (binary) for secondary efficacy objectives (Table 6) will be applied to IGA0/1, EASI75, and PP-NRS4.

Binary endpoints will be analyzed using Bayesian logistic regression with more details on the model given in Table 13. Only efficacy data up to and including [redacted] will be used, as detailed in Section 1.2. The 95% credible interval of the posterior distribution will be presented as well as posterior median and 95% credible intervals for the true difference in proportion of responders (GSK1070806 [redacted] – placebo), adjusted posterior median and 95% credible intervals of the true response rate for each treatment group using the back-transformation of the logit using observed margins, and frequency counts and proportions of responders after handling ICEs and missing data.

Table 13 describes the analysis method and model specification for binary endpoints.

Table 13 Binary Analysis Model

Binary Endpoints	
• Achieving EASI75 response at [redacted] • Achieving EASI50/90/100 response at [redacted] • Achieving SCORAD50/75 response at [redacted] • Achieving IGA0/1 response at [redacted] • Achieving PP-NRS4 response at [redacted]	
Baseline	
Baseline score will be centered around its observed mean prior to inclusion in the model. • Baseline IGA value (categorical) will be used in the model for analysis of IGA0/1, this will be equivalent to baseline disease severity (IGA value) so this will not appear twice. • Baseline EASI value will be used in the model for analysis of EASI50/75/90/100, baseline disease severity IGA value) will not be used in these analyses.) • Baseline SCORAD value will be used in the model for analysis of SCORAD. • Baseline PP-NRS value will be used in the model for analysis of PP-NRS4.	
Analysis Method	
Bayesian Logistic Regression	
Model Specification	
Outcome	Response (0/1) at [redacted]
Predictors	• Treatment (categorical, reference: placebo) • Respective baseline score (IGA0/1: categorical, reference: IGA3. All other endpoints: continuous) • Prior treatment experience (categorical, biologic naïve vs biologic experienced, reference: naive) • Baseline disease severity (categorical, reference: IGA3), for analyses of SCORAD50/75 and PP-NRS4
Model	Logistic regression of Outcome by Predictors
Prior distributions for coefficients (**β**)	β = parameters associated to predictors • All parameters: weakly informative prior N(0, SD=10^2)
Model Checking & Diagnostics	
See Section 4.1.1. If the number of responders at individual weeks does not allow the model to run or the model does not converge, a simpler model may be fitted, or a smaller SD will be used for the prior of the model parameters, or results may not be presented.	

Results Presentation
• Adjusted posterior median and 95% CrI of true response rate for each treatment group, using the back-transformation of the logit. Posterior median estimates and associated inferences will be based on the marginal standardization median for each treatment group at each time point (see Section 6.5 for more details). • Posterior median and 95% CrI for the true difference in proportion of responders (each GSK1070806 dose W16 – placebo W16). • Probabilities that the true treatment difference is greater than thresholds specified in Table 14. • A separate Bayesian model is fitted to each timepoint. Outputs will summarize results for earlier timepoints in addition to the objective specified timepoint of [redacted] into one table.

Posterior probabilities that the true treatment difference (GSK1070806 [redacted] – placebo) at each visit is greater than various thresholds of clinical interest will be presented. Table 14 specifies the thresholds of clinical interest for binary endpoints; posterior probabilities will not be calculated for endpoints with no thresholds defined. Posterior probabilities for all thresholds of clinical interest may not be presented; if deemed appropriate the number of thresholds included in displays may be decreased.

Table 14 Thresholds of Clinical Interest (binary endpoints)

	Thresholds of Clinical Interest
Clinical Efficacy Endpoints	
EASI Reduction of ≥75% from Baseline	0%, 15%, 30%, 35%, 40%, 45%, 50%
EASI Reduction of ≥50% from Baseline	0%, 15%, 30%, 35%, 40%, 45%, 50%, 60%
EASI Reduction of ≥90% from Baseline	0%, 10%, 20%, 25%, 30%, 40%
EASI Reduction of 100% from Baseline	0%, 15%, 30%, 35%, 40%
SCORAD Reduction of ≥50% from Baseline	0%, 15%, 30%, 40%, 50%, 60%
SCORAD Reduction of ≥75% from Baseline	0%, 15%, 30%, 40%, 50%
IGA score of 0 or 1	0%, 15%, 30%, 35%, 40%
Patient Reported Outcomes	
PP-NRS Reduction of ≥4 points from Baseline	0%, 15%, 20%, 30%, 35%, 40%

4.3.2.3. Sensitivity analyses

The analysis of IGA0/1 will be repeated excluding all Japan participants.

Analysis of secondary endpoints described in Table 11, limited to EASI-75, IGA0/1, PP-NRS4 may be repeated using actual treatment received. Refer to the OPS for further details. These analyses may also be repeated using the additional approach to remaining missing data.

If deemed necessary, the analysis of these endpoints will be repeated using the per-protocol analysis set as defined in Section 3.

4.3.2.4. Additional estimands

Analyses in this section will not be performed given the study has been terminated.

The additional estimands (binary) for the secondary efficacy objectives will be applied to key endpoints as specified (Table 6). Only randomized treatment will be used.

4.4. Exploratory Endpoints Analyses

CCI

4.4.1. Clinical Exploratory Endpoints

4.4.1.1. Definition of Endpoints

Table 15 Clinical Exploratory Endpoints

Endpoint	Summary measure	Timepoints	Analysis
CCI			

Endpoint	Summary measure	Timepoints	Analysis
CCI [redacted]			

4.4.1.2. Main Analytical Approaches

Continuous Endpoints

CCI [redacted]

CCI [redacted] For analyses conducted at 'each scheduled timepoint up to Week 28', the same Bayesian repeated measures model and model diagnostics as described in Section 4.2.2 will be used. However, the Week predictor (categorical) and baseline*week interaction will include Week 20, 24, and 28 (or the weeks reflecting the schedule of activities in the protocol) in addition to visits up to [redacted] (i.e., all the efficacy data will be used). The reference for this predictor will be Week 28. The unstructured residual covariance matrix will be of dimension 12x12 to account for the additional weeks. If convergence issues occur, an alternative covariance matrix structure may be used, for example a compound symmetric structure, to help improve convergence.

If convergence issues persist after considering alternative covariance matrix structures, a simpler model may be fitted.

All results will be displayed in the associated tables and figures. Further details will be provided in the OPS.

In addition to any model-based analysis, descriptive statistics will be presented. Further details will be given in the OPS.

Binary Endpoints

The endpoints with timepoint as 'at each scheduled timepoint up to Week 28' will only be addressed at the end of study analysis. All efficacy data up to Week 28 will be included. The same approach as for binary secondary endpoints detailed in Section 4.3.2.2 and the same model diagnostics will be applied to the binary exploratory endpoints. If convergence issues arise, a simpler model may be fitted.

For the end of study analysis which will address any endpoints with an 'at each scheduled timepoint up to Week 28' timepoint, the results presentation will include:

- Adjusted posterior median and 95% CrI of true response rate for each treatment group, using the back-transformation of the logit (table).
- Posterior median and 95% CrI for the true difference in proportion of responders (each GSK1070806 dose – placebo) (table)
- Probabilities that the true treatment difference is greater than thresholds, as appropriate, specified in Table 14.
- A separate Bayesian model is fitted to each timepoint. Outputs will summarize results for all timepoints up to and including Week 28 into one table.

In addition to any model-based analysis, descriptive statistics will be presented. Frequency counts for participants achieving EASI50/75/90/100, SCORAD50/75, and IGA0/1 will be presented by treatment group for each visit up to [redacted] for the primary analysis (Section 4.3.2.2) and Week 28 for the end of study analysis. Descriptive statistics, as per Section 4.3.2 under binary endpoints, will be presented on this data.

Time to Event Endpoints

A Kaplan-Meier plot of time to event for each endpoint will be displayed by treatment group.

Cox proportional hazards model controlling for treatment arm, region and previous treatment experience will be fitted. Respective baseline values will be included for all endpoints except time to first use of rescue therapy. Baseline disease severity (IGA score) will be included for time to first use of rescue therapy.

If the Cox proportional hazards model fit is considered inadequate additional analysis may be conducted.

A table for each endpoint will present summary measures as per Table 16 by treatment group. Further details will be given in the OPS.

4.4.1.3. Sensitivity Analyses

CCI [redacted]
CCI [redacted]
CCI [redacted]

If deemed necessary, the analysis of these endpoints will be repeated using the per-protocol analysis set as defined in Section 3.

The analyses of EASI-75 and IGA0/1 may be repeated using the additional approach to remaining missing data.

4.4.2. Patient Reported Outcomes (PROs)

4.4.2.1. Definition of Endpoints

The same analysis strategies will be applied for continuous and binary endpoints as described in the Continuous Endpoint and Binary Endpoint sections (Section 4.4.1.2).

Table 16 Definition of PRO Measures

Endpoint	Summary measure	Timepoints	Analysis
Continuous			
PP-NRS	Mean change from baseline	Each scheduled timepoint up to Week 28	Bayesian repeated measures model as described in Section 4.2.2 (Table 10) and Section 4.3.2.2. Descriptive statistics, mean (SD), on the raw data will also be presented. The ACQ-5 will be assessed only in participants with known history of asthma.
SP-NRS			
PROMIS-Sleep disturbance 8b			
FACIT-Fatigue			
BFI- item 3			
POEM			
DLQI			
HADS			
WPAI-AD			
ACQ5		At [redacted] and each scheduled timepoint up to Week 28	
Binary			
Achieving PP-NRS reduction of ≥4 points from baseline	Proportion of participants achieving response	Each scheduled timepoint up to Week 28	Only participants with a PP-NRS/SP-NRS of ≥4 points at baseline will be analyzed. Bayesian logistic regression model as described in Section 4.3.2.2 (Table 13). Descriptive statistics as described in Section 4.3.2 will also be presented.
Achieving SP-NRS reduction of ≥4 points from baseline		At [redacted] and each scheduled timepoint up to Week 28	

4.4.2.2. Main analytical approach

Analyses will follow methods planned for the secondary endpoints as detailed in Section 4.3.2.2. Given all the endpoints in Table 16, other than ACQ5 and SP-NRS4, are 'at each scheduled timepoint', these analyses will only be conducted at the end of study analysis. CFB in ACQ5 to [redacted] and achieving SP-NRS reduction of ≥4 points from baseline will form part of the primary analysis.

4.4.2.3. Sensitivity Analyses

Analysis of PP-NRS4 as described in Table 16 may be repeated using actual treatment received. Refer to the OPS for further details. This analysis may be repeated using the additional approach to remaining missing data. If deemed necessary, the analysis may be repeated using the per-protocol analysis set as defined in Section 3.

4.4.3. Biomarker Analyses

CCI [redacted]

4.4.4. Actigraphy Sub-Study

CCI [redacted]

4.5. Safety Analyses

Some of the safety analyses will no longer be produced given the study has been terminated; details are provided in each subsection where appropriate. Overall, no analyses using the additional estimands for the safety objectives will be produced.

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified. Participants will be analyzed according to the treatment they received. All displays will be for the overall study duration rather than individually for the treatment and follow-up periods.

No formal statistical testing will be performed on Safety data.

As per the estimands for the safety objectives, all primary safety analysis will use the "treatment policy" approach, i.e. all safety events reported in the study will be included.

Additional estimands for the safety objectives will use "while on treatment approach" and will be performed on key safety outputs (AE and SAE related outputs only). Any safety events that happen after [redacted] after the last dose will be excluded. Missing safety data will not be imputed.

In the event of database lock occurring whilst there are any ongoing SAEs, the outcome of these events will be monitored. In the event of a significant update to an event,

information will be captured on a paper SAE form; this information will be reflected in the global safety database.

4.5.1. Extent of Exposure

Exposure to study treatment will be summarized by number and percentage of participants receiving no doses, 1 dose, or 2 doses. Participants who were randomized but do not have a treatment start date will be categorized as having 'no doses'.

4.5.2. Adverse Events

Adverse event (AE) analyses including the analysis of AEs, Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards. Adverse events will be mapped to system organ classes (SOC) and preferred terms (PT) using the latest version of the standard Medical Dictionary for Regulatory Activity (MedDRA dictionary). The definitions of AEs and SAEs are detailed in the protocol (Sections 10.3.1, 10.3.2). Any additional definitions may be listed in the OPS.

An AE is considered study intervention emergent if the AE onset date (and time if available) is on or after study intervention start date (and time). All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not.

A drug-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes" based on the assessment of causality as defined in the protocol, Section 10.3.5.3. 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. AEs with missing intensity will be considered unknown.

An overall summary of AEs, including counts and percentages of participants with any AE, drug-related AEs, SAEs, AEs leading to permanent discontinuation of study treatment will be produced.

Separate summaries of the number and percentage of participant with any AEs, drug-related AEs and AEs leading to permanent discontinuation of study treatment by system organ class (SOC) and preferred term (PT) will be produced. A summary of the number and percentage of participants with any AEs and drug-related AEs by maximum intensity will also be produced by SOC and PT. Both summaries relating to any AEs will be repeated for the estimands and additional estimands for safety objectives. A summary of AEs leading to permanent discontinuation of study treatment will also be produced by overall incidence.

A summary of all common AEs, that occurred in strictly 5% of the participants or above in any treatment group will be provided by PT and ordered by overall incidence (no rounding for the percentage will be used in terms of the 5% threshold, e.g., events with

4.9% incidence rate should not be included within this table). A summary of common non-serious adverse events by SOC and PT will also be produced, including both the number and percentage of participants with the AE as well as the number of occurrences of the AE.

A summary of non-serious drug-related AEs by PT will be produced ordered by overall incidence.

The following summaries will be provided for the SAEs:

- Overall summary of SAEs, including counts and percentages of participants with any SAE by SOC and PT (to be repeated for additional estimands for the safety objectives)
- Summary of SAEs by SOC and PT and maximum intensity (to be repeated for additional estimands for the safety objectives)
- Summary of SAEs by System Organ Class and Preferred Term (Number of Subjects and Occurrences)
- Summary of Serious Fatal and Non-Fatal Drug-Related Adverse Events by PT and ordered by Overall Incidence

A summary of AEs by ADA status (Positive (Treatment-induced or boosted participants) and Negative (Treatment-induced negative or treatment-unaffected participants) will only be produced if there is at least one participant who is ADA positive. If the ADAs have an impact on PK, efficacy, or safety, corresponding figures to these summaries will be produced.

All AE listings will be reported overall (i.e, not split by treatment phase/follow up) as defined in Section 6.4.2.

4.5.2.1. Adverse Events of Special Interest

The following will be considered AESIs:

- Serious infections
- Opportunistic infections
- Serious hypersensitivity reactions
- Injection site reactions

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

Serious infections will include all serious adverse events coded to the "Infections and infestations" SOC. The additional information for serious infections collected on the serious infections targeted eCRF will be summarized including infection type and origin.

Potential opportunistic infections will be derived using the list of events using the "Opportunistic infections" (Broad) SMQ. Potential events will be reviewed and adjudicated in a blinded fashion on an ongoing basis by the GSK1070806 SRT. Infections adjudicated as opportunistic by the SRT will be used in the summaries of this AESI. Opportunistic infections are further characterized by the Investigator on a targeted eCRF. The additional information for opportunistic infections collected on the targeted eCRF will be summarized for adjudicated events including infection type and origin.

Similarly, potential serious hypersensitivity reactions will be derived using the list of events using "Hypersensitivity" (Broad) SMQ, "Anaphylactic/anaphylactoid shock condition" (Broad SMQ), and "Anaphylactic reaction" (Broad) SMQ (with algorithmic approach applied), limiting to serious. Potential events will be reviewed and adjudicated in a blinded fashion on an ongoing basis by the GSK1070806 SRT. Serious AEs adjudicated as serious hypersensitivity reactions by the SRT will be used in the summaries of this AESI. Serious hypersensitivity reactions are also further characterized by the Investigator on the eCRF including symptoms/management data. These additional symptoms/management data collected on the targeted eCRF will be summarized for adjudicated events.

Injection site reactions (ISRs) will be derived using "injection site reactions" and "administration site reactions NEC" HLTs. Injection site reactions are also identified by the Investigator on the eCRF and symptoms of the ISRs are recorded. The symptoms data for the ISRs collected on the target eCRF for ISRs identified based on "injection site reactions" and "administration site reactions NEC" HLT terms will be summarized.

Further details on derivations will be described in the OPS.

The summaries of characteristics describing action taken will be provided for each AESI, respectively for each treatment arm:

- Summary of Characteristics of Serious Infections
- Summary of Characteristics of Opportunistic Infections
- Summary of Characteristics of Serious Hypersensitivity Reactions
- Summary of Characteristics of Injection Site Reactions

The summaries described above will include the number of subjects with the event, number of events, event characteristics (% based on all subjects), event characteristics (% based on subjects with the event), number of occurrences (% based on all subjects), number of occurrences (% based on all subjects with the Event), outcome (% based on all subjects), outcome (% based on subjects with the Event), maximum intensity (% based on all subjects), maximum intensity (% based on all subjects with the event), action taken (% based on all subjects), action taken (% based on all subjects with the event).

Additional tables providing summary and characteristics of the AESI based on the AESI-specific CRF will be provided for each treatment arm:

- Summary of Serious Infections
- Summary of Opportunistic Infections
- Summary of Serious Hypersensitivity Reactions
- Summary of Injection Site Reactions

The summaries described above will reflect summary of event-specific questions described in the CRF.

The percentage will be calculated with total number of participants as the denominator. The worst-case approach will be applied at participant level for the maximum severity, i.e., a participant will only be counted once as the worst case from all the events experienced by the participant. All actions taken with study intervention/treatment as collected on the eCRF will be used and clarified with footnotes accordingly.

An overall summary of AESIs, including counts and percentages of participants with any AESI will be produced.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Laboratory data will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards.

Separate summary tables for haematology, and chemistry laboratory tests as well as urine concentration parameters will be produced. Liver function laboratory tests will be included with chemistry lab tests.

Change from baseline in laboratory parameters will be presented for continuous variables, with a summary of baseline values included in the tables.

For purposes of disclosure, Table 17 lists the laboratory parameters that are prospectively defined as ‘key’. This was omitted in the secondary objective of the Protocol.

Table 17 Laboratory Parameters

Laboratory Assessments	Parameters			
Hematology	Platelet Count*	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils* Lymphocytes* Monocytes* Eosinophils* Basophils*	
	Red blood cell (RBC) Count*			
	White blood cell (WBC, absolute)*			
	Reticulocyte Count			
	Hemoglobin*			
	Hematocrit*			
Clinical Chemistry	Blood Urea Nitrogen (BUN)*	Potassium	Aspartate Aminotransferase (AST)*/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin*
	Creatinine*	Calcium	Alanine Aminotransferase (ALT)*/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose*	Alkaline phosphatase*	Gamma-Glutamyl Transferase (GGT)*	Albumin*
	Sodium			
	Estimated Creatinine Clearance/glomerular filtration rate (CKD-EPI[1])*			
Coagulation Profile	• International Normalized Ratio (INR)*, Activated Partial Thromboplastin Time (APTT), Fibrinogen			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood, protein, or leukocyte is abnormal)			

NOTES:

1. Chronic Kidney Disease Epidemiology Collaboration creatinine equation 2021 (CKD-EPI 2021) will be used for calculating and reporting eGFR. For participants from Japan sites, the Japanese coefficient (0.813) -modified CKD-EPI will be used for calculating and reporting eGFR.

* Key laboratory parameter. Key laboratory parameters will be disclosed as per secondary safety objective in Section 1.1 at each timepoint as per the schedule of assessments in the protocol.

Grade shift tables will be presented for all the variables where the grades are available. Uninalysis results of PCI (increase in protein or an increase in Occult blood results during the study, or if microscopy is performed) will be be presented in the standard listing. For the parameters that do not have grades available (e.g. hematocrit, BUN) any out of range values based on their normal range will be flagged and presented in the standard listing.

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in case of a liver event. Possible Hy's law cases are defined as any elevated alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and total bilirubin ≥2

× ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5. Total bilirubin ≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. All liver events will be summarized together.

4.5.3.2. Vital Signs

Vital signs data will be presented in tabular format and summarized descriptively according to GSK standards. Although not included in a static listing, normal/PCI ranges for the parameters will be added to the analysis data to allow out of range results to be identified in RAPIDO DV after SAC at end of study.

A summary table of change from baseline in vital signs will be produced, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, and temperature.

Grade shift tables will be produced for systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Summaries of grade increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 2 and increase to Grade 3 for the worst-case post-baseline only. The grade definitions for SBP and DBP are presented within Table 18.

Table 18 Grade Definitions for SBP and DBP

Grade	SBP	DBP
0	<120	<80
1	120-139	80-89
2	140-159	90-99
3	>=160	>=100

4.5.3.3. ECG

Summary of ECG findings and summary of change from baseline in ECG values will not be produced given the study has been terminated. The summary of maximum QTcF values post-baseline relative to baseline by grade and the summary of maximum increase in QTcF values post-baseline relative to baseline by category will still be produced.

A single ECG will be taken for the baseline value. However, in the case of triplicate ECG if QTc is prolonged, baseline is taken to be the mean of the triplicate values collected pre-dose Day 1.

The QTc data analysis will use the values based on Fridericia's formula. If the ECG machine does not automatically calculate the QTc interval according to Fridericia's formula (QTcF), site staff should use the below equation to manually calculate the QTcF and document the result in the participant's medical record.

- $QTcF = QT/\sqrt[3]{((60)/HR)}$ QTcF result in msec
  - QT in msec, HR in bpm

The QTc values based on Fridericia formula will be rounded to the nearest integer and the values will be categorized into the following CTCAE grade and ranges:

Table 19 Grade Definitions for QTc values

Grade	Maximum QTc values post-baseline relative to baseline
0	<450 msec
1	450-480 msec
2	481-500 msec
3	≥ 501 msec

The changes in QTc values will be categorized into the clinically important ranges which are specific to changes in QTc: >30-60 and > 60 msec.

The following summaries will be provided:

1. Summary of maximum QTc values post-baseline relative to baseline by grade
   - This summary will display the number and percentage of participants with any grade increase, increase to grade 2 and increase to grade 2 for the worst-case post-baseline only. Missing baseline grade will be assumed as grade 0.
2. Summary of maximum increase in QTc values post-baseline relative to baseline by range
   - A summary of change in QTc value will display the number and percentage of participants with a change within each range for the worst-case post-baseline only. Participants with missing baseline value will be excluded from this summary.
3. Summary of ECG findings (the clinical significance and interpretation of each planned ECG). In the case of triplicate ECG measurements, results will be presented separately by measurement number.
4. Summary of change from baseline in ECG values. In the case of triplicate ECG measurements, summaries will use the mean of the triplicate.

4.6. Other Analyses

4.6.1. Subgroup analyses

Given the study has been terminated, only two subgroups are of interest: previous treatment experience and reason for stopping previous biologic treatment or biologic

naïve. Only the CCI *and placebo treatment arms will be included. The remaining subgroup analyses will not be performed.*

The subgroups defined in Table 20 are of interest in this study. A separate exploratory analysis of the primary endpoint (PCFB EASI) and a subset of secondary efficacy endpoints (IGA0/1, EASI75, PP-NRS4) within each subgroup will be carried out at thefinal analysis. The subgroup analyses will focus on estimates and credible intervals for the treatment effects within the subgroups. Posterior probabilities will be presented using previously defined thresholds of clinical interest (Table 12 and Table 14).

Overall, subgroup analyses may not be performed, or subgroup categories may be collapsed or redefined prior to unblinding the study if there is a small number of participants in a treatment arm within a subgroup. In the case of combining subgroup categories, the terms of the model may also be reconsidered as appropriate.

Additionally, for analysis of the binary endpoints, if the number of responders at individual weeks either overall or within a subgroup does not allow the model to run or the model does not converge, a simpler model may be fitted, a smaller SD may be used for the prior of the model parameters, subgroup categories may be collapsed, or results may not be presented. Alternatively, a separate model for each subgroup category may be considered.

Table 20 Definition of Subgroups

Subgroup	Categories	Rationale
Region	• Japan • China • Rest of World	Interest lies in exploring whether there is a difference in treatment benefit between regions. These analyses will inform regulatory submissions in China/Japan for Phase 3.
	• Japan • Rest of World (Including China)	
Previous treatment experience	• Biologic-naïve • Biologic experienced	Interest lies in exploring whether there is a difference in treatment benefit between groups.
Baseline disease severity	• IGA 3 • IGA 4	
	• EASI Score < 21 • EASI Score ≥ 21	
	• PP-NRS < 7 • PP-NRS ≥ 7	
Reason for stopping previous biologic treatment or biologic naïve	• Biologic naïve • Biologic experienced – Reason for stopping previous treatment: inadequate responder (lack of efficacy or intolerance or AEs) • Biologic experienced – Reason for stopping previous treatment: cost or loss of access	

For reason for stopping previous biologic treatment: lack of efficacy and intolerance or AEs categories will be combined. If a participant is enrolled under the original global protocol, if reason is missing or categorized as 'other', participants will be assumed to be part of cost or loss of access category. Otherwise, participants will be assumed to be a part of the lack of efficacy category.

All binary subgroup analyses will use the estimands (binary) for the secondary efficacy objectives and will be based on the methods described in 4.3.2.2 for IGA0/1, EASI75, and PP-NRS4 with the addition of the interaction between treatment and the subgroup and removal of the subgroup main effect if previously present. If convergence issues occur, a simpler model may be fitted.

The continuous subgroup analyses of PCFB EASI will be based on methods described in Section 4.2.2. The analyses will follow the primary estimand. Given the study has been terminated, a simpler approach will be adopted; a separate model for each level of the

subgroup will be fitted, rather than using a treatment by subgroup interaction term. If convergence issues occur, an alternative covariance matrix structure may be used, for example a compound symmetric structure, to help improve convergence. If convergence issues persist after considering alternative covariance matrix structures, a simpler model may be fitted.

Details on the models are given in Table 21.

The following analyses using the additional estimand will not be produced given the study has been terminated.

Additionally, region subgroup of Japan vs Rest of World will be repeated on the additional estimand to the primary for PCFB EASI and on the additional estimands (binary) for the secondary efficacy objectives for IGA0/1, EASI75, and PP-NRS4, in which the use of rescue ICE is handled with a treatment policy strategy.

Table 21 Subgroup Analyses Models

Subgroup	Endpoint	Additional Predictors	Notes
Region	• PCFB EASI • EASI75 • IGA0/1 • PP-NRS4	Interaction: treatment and region PCFB: interaction of treatment, region, and week	Remove main effect of region
Previous treatment experience	• PCFB EASI • EASI75 • IGA0/1 • PP-NRS4	Interaction: treatment and previous treatment experience PCFB: separate model for each level of subgroup.	Remove main effect of previous treatment experience
Baseline disease severity: IGA3 vs IGA4	• PCFB EASI • EASI75	• Interaction: treatment and baseline disease severity PCFB: interaction of treatment, baseline disease severity, and week	• Remove main effect of baseline disease severity • Baseline EASI score retained in model.
	• IGA0/1 • PP-NRS4	Interaction: treatment and baseline disease severity	Remove main effect of baseline disease severity
Baseline disease severity: EASI < 21 vs EASI ≥ 21	• PCFB EASI • EASI75	• Interaction: treatment and baseline disease severity • PCFB: interaction of treatment, baseline	

Subgroup	Endpoint	Additional Predictors	Notes
		disease severity, and week	
Baseline disease severity: PP-NRS < 7 vs PP-NRS ≥ 7	PP-NRS4	• Interaction: treatment and baseline disease severity	
Reason for stopping previous biologic treatment	• PCFB EASI • EASI75 • IGA0/1 • PP-NRS4	• Interaction: treatment and reason for stopping previous biologic treatment or biologic naïve • PCFB: separate model for each level of subgroup.	Naïve participants will be included in this analysis. The subgroup will have 3 categories: biologic naïve vs biologic experienced cost or loss of access vs biologic experienced inadequate responder (lack of efficacy/intolerance or AE). Previous treatment experience covariate will be removed from this model.

In addition to statistical modelling, the following summaries will be repeated by previous treatment experience and by reason for stopping previous biologic treatment:

- Percent change from baseline in EASI
- Frequency counts of EASI50/75/90/100 response
- Frequency counts of IGA0/1 response
- Frequency counts of PP-NRS4 response
- Frequency counts of previous biologic treatments by reason for stopping previous biologic treatment

Only biologic experienced participants will be summarized in the repeats by reason for stopping previous biologic treatment (biologic naïve participants will be excluded which differs from the statistical modelling approach).

Given the study has been terminated, the following summaries will no longer be presented.

In addition to the statistical modelling for the region subgroup, the following summaries will be repeated by region:

- Baseline atopic dermatitis characteristics (Japan vs China vs RoW)
- Use of rescue before [redacted] (figure only, Japan vs China vs RoW)

4.6.1.1. Sensitivity Analyses

Analyses in this section will no longer be performed given the study has been terminated.

Statistical analyses and descriptive summaries of previous treatment experience subgroup and reason for stopping previous treatment subgroup in Table 20 may be repeated using actual treatment received. Refer to the OPS for further details.

If deemed necessary, the analysis of these endpoints for this subgroup only will be repeated using the per-protocol analysis set as defined in Section 3.

4.6.2. Analyses to Support Regional Submission

Analyses in this section will no longer be performed given the study has been terminated.

Since the study will be used to support China/Japan regulatory submission, the key population, efficacy, and safety analyses will be repeated for the following populations:

- China subpopulation: All participants of Chinese heritage enrolled at sites in China mainland.
- Japan subpopulation: All participants of Japanese heritage enrolled at sites in Japan.
- East Asia subpopulation: All participants of a relevant Asian heritage (Asian – Chinese Heritage, Asian – Japanese Heritage, and Asian – Korean Heritage) enrolled at sites in China mainland, Japan, South Korea.

For the primary study analysis, analyses will be performed on the total number of participants who have completed their [redacted] (or Early Withdrawal) study visit.

For analyses involving a statistical model, if data permit, the same analytic approach will be applied to the subpopulation. The statistical model may be adapted in case of convergence issues.

For the Japan subpopulation, analyses will be repeated on the additional estimand to the primary for PCFB EASI and on the additional estimands (binary) for the secondary efficacy objectives for IGA0/1, EASI75, and PP-NRS4, in which the use of rescue ICE is handled with a treatment policy strategy.

Full details of the planned analyses will be documented in the OPS.

4.6.3. Pharmacokinetic analysis

Given the study has been terminated, analyses in this section will be detailed in a separate SAP, and may be reported separately except for the listing of pharmacokinetics concentration-time data which will still be produced as part of the S&P SAC package.

4.6.4. Pharmacodynamic analysis

Given the study has been terminated, analyses in this section will be detailed in a separate SAP and may be reported separately.

Pharmacodynamic data will be used to develop the D-E-R model and may be reported in a separate document.

Missing concentration data will be considered as Missing at Random and no imputations for missing data will be carried out. All calculations will be based on actual sampling times.

Observed concentration-time data CCI) will be summarized (Geometric Mean, 95% CI, SD, Min, Max, Median) by treatment group. Individual and mean/median profiles in serum over time (stratified by treatment group) will be plotted. Summary statistics/plots by subgroups (Section 4.6.1) may also be presented.

Dependent upon the final dose-exposure-response model structure (Section 4.3.1.2) model predicted maximum (Cmax), minimum (Ctau) and/or average (Cavg) reductions in CCI may be summarized by treatment group. Summary statistics/plots by subgroups (Section 4.6.1) may also be presented.Definition of endpoints

- Total CCI concentrations over time
- Free CCI concentrations in serum at baseline
- CCI in serum at baseline

4.6.4.1. Main analytical approach

Total CCI concentrations will be summarized over time using descriptive statistics. CCI CCI and CCI in serum at baseline will be summarized using descriptive statistics.

4.6.5. Immunogenicity

The number and percentage of participants who become positive for ADAs will be summarized by visit and the overall study.

Overall summary of immunogenicity incidence and titers will be reported.

The outputs and programming details of the analyses will be provided in the OPS and Immunogenicity Display Standard.

The effects of immunogenicity against GSK1070806 on PK, safety, and efficacy may also be explored and reported separately.

4.7. Interim Analyses

An interim analysis for overall study futility will be performed when approximately 100 participants have completed their Week 4 (or Early Withdrawal) study visit. IGA scores

will be used to build a predictive distribution for achieving IGA score of 0 or 1 at [redacted] to enable decisions on study futility.

The objective of the interim analysis is to assess futility based on the difference from placebo in efficacy endpoints at [redacted], resulting in either continuing the study with no change to the planned randomization or study arms, or stopping the study for futility.

As defined in the iDRC charter version 4, an additional aspect to the second interim analysis was added prospectively to assess futility in the bio-IR population. For further details, see the iDRC charter.

Additional administrative interim analyses may occur in order to inform internal decision making and/or to inform regulatory interactions. These additional analyses may also be for subpopulations only for regulatory purposes. Full details of all interim analyses will be prospectively outlined in the iDRC charter.

Specific details regarding all interim analyses will be outlined in the iDRC charter. This will include an outline of how the internal data review committee will ensure data integrity and appropriate quality control of data prior to making decisions and an outline of the committee membership.

4.8. Changes to Protocol Defined Analyses

A deviation to the planned statistical analysis specified in the protocol (Dated: 7 June 2024) for Bayesian statistical analysis of continuous endpoints: no longer explicitly pre-programming to impute a participant's own worst observation after the ICE of use of rescue. The updated methodology implicitly uses worst observed values to estimate the marginal treatment effects. The treatment difference from this model will be summarized as median and 95% credible interval (CrI) of the posterior distribution, no longer including mean and SD as per protocol.

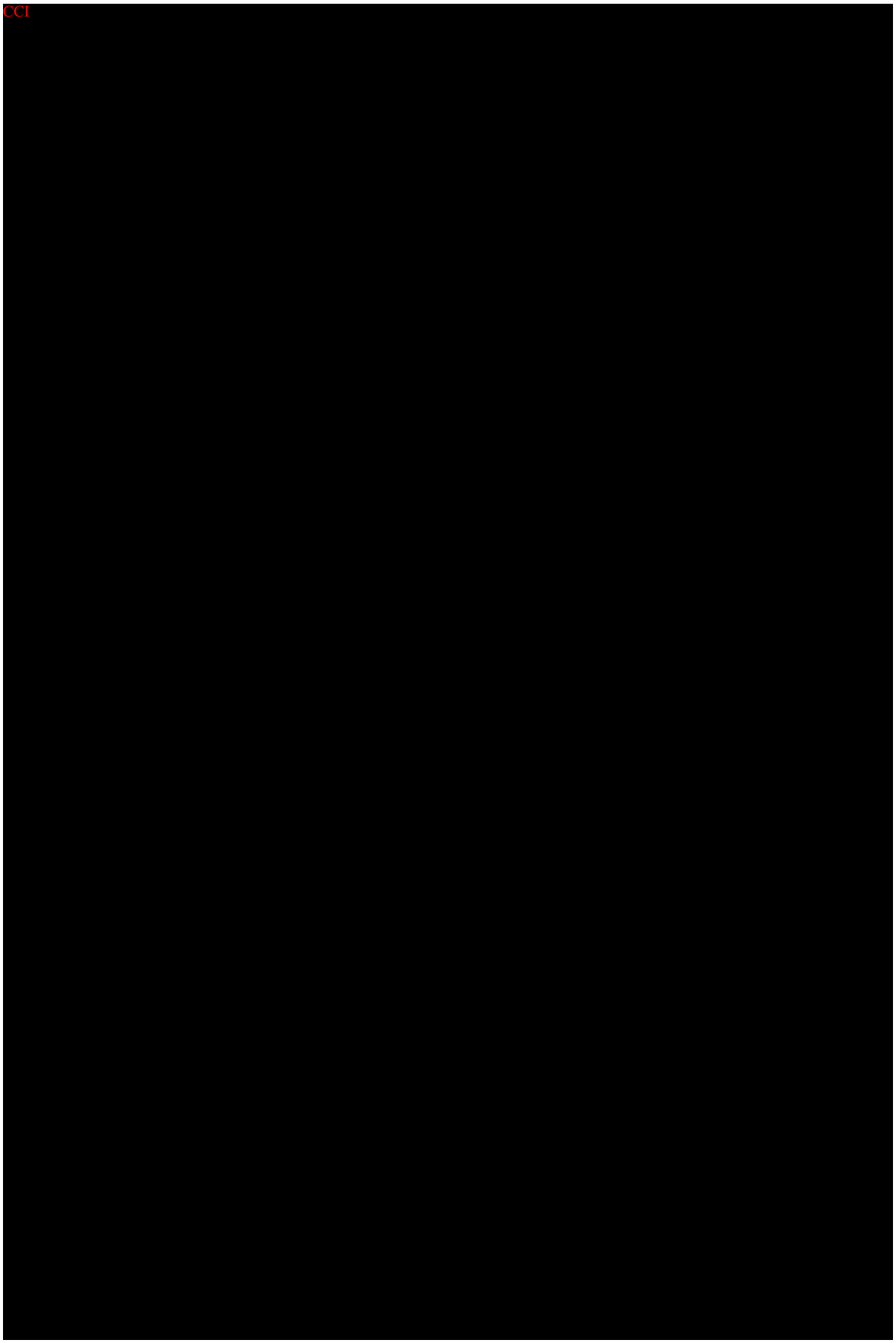
Given the study has been terminated, there will only be one final analysis instead of a primary and end of study analysis. All efficacy analyses will use the modified full analysis set instead of the full analysis set given data after study termination may be subject to bias or may not be collected. The summary of intercurrent events will also use the modified full analysis set. Statistical analysis of secondary endpoints except IGA0/1, EASI75, and PP-NRS4 will no longer be performed; descriptive statistics will be produced instead. This has been deemed appropriate for disclosure purposes given the study has been terminated.

Key laboratory parameters have now been defined in the SAP and will be disclosed.

5. SAMPLE SIZE DETERMINATION

CCI [redacted]

CCI



CCI

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Primary Analysis Approach

Refer to Table 1 for details on Estimand 1 for which this technical appendix applies.

6.1.1. Description

The target is the difference in mean percentage change from baseline EASI at [redacted] for participants with moderate to severe AtD (either biologic naïve or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy when they are treated with SC GSK1070806 CCI [redacted] or placebo every [redacted] for [redacted]. This includes any subsequent effects that occur if participants discontinue treatment before [redacted] The use of rescue therapy for AtD before [redacted] is considered a negative outcome reflected by using the patients' worst observed pre-rescue values. It is also assuming there were no administrative or operational disruptions.

6.1.2. Potential Outcome Notation

The effect targeted in this estimation can be represented mathematically as a functional of potential outcomes defined below. The following definitions apply to each individual participant i. Specifically, we define:

- Y_{ij} as the outcome (PCFB EASI score) at week $j = 0, \ldots, J$.
- $Z_i \in (A, C)$ as the treatment assignment to active (GSK1070806 CCI) and control (Placebo) respectively.
- $R_i = 1, \ldots, J$ as the week that rescue medication was taken ($R_i > j$ indicates no IE has occurred by week j).
- $D_i = 1, \ldots, J$ as the week that permanent treatment discontinuation occurs ($D_i > j$ indicates no IE has occurred by week j).
- $S_i = 1, \ldots, J$ as the week that site closure treatment discontinuation occurs ($S_i > j$ indicates no IE has occurred by week j).
- W_i as the worst observed outcome prior to use of rescue.

This notation allows us to define the potential outcomes for a participant conditional their treatment assignment, permanent discontinuation, use of rescue and site closure discontinuation as $Y_{ij}^{(Z_i, D_i, R_i, S_i)}$. It also allows us to define the occurrence of the different potential outcomes as the indicator $I_{ij}^{(Z_i, D_i, R_i, S_i)}$ and similarly the worst observed potential outcome $W_i^{(Z_i, D_i, R_i, S_i)}$. Using these potential quantities, we can represent the expected value at each visit under each treatment as:

$$\psi_{jC} = \mathbb{E}\left[I_{ij}^{(Z_i=C,\ D_i,\ R_i>j,\ S_i>j)} \cdot Y_{ij}^{(Z_i=C,\ D_i,\ R_i>j,\ S_i>j)} + I_{ij}^{(Z_i=C,\ D_i,\ R_i\leq j,\ S_i>j)} \cdot W_i^{(Z_i=C,\ D_i,\ R_i\leq j,\ S_i>j)}\right]$$

$$\psi_{jA} = \mathbb{E}\left[I_{ij}^{(Z_i=A,\ D_i,\ R_i>j,\ S_i>j)} \cdot Y_{ij}^{(Z_i=A,\ D_i,\ R_i>j,\ S_i>j)} + I_{ij}^{(Z_i=A,\ D_i,\ R_i\leq j,\ S_i>j)} \cdot W_i^{(Z_i=A,\ D_i,\ R_i\leq j,\ S_i>j)}\right]$$

In words, ψ_{jA} and ψ_{jC} are the expected values for the mixture of values for patient outcomes when no rescue is taken (and no site closure discontinuation occurs) and the worst pre-rescue patient outcomes when rescue is taken (and no site closure discontinuations occurs). The mixing for these values is provided by the occurrence of using rescue (when no site closure discontinuation occurs). These quantities include any effects of permanent discontinuation (as there are no conditions imposed on D_i) but are in the absence of any effects from discontinuation for site closures (all sections have the condition $S > j$). The effect of interest (estimand) at each visit is then:

$$\Delta_j = \psi_{jA} - \psi_{jC}.$$

The effect specified above is a population-based quantity and does not depend on a particular estimation method. From studying the algebraic definition, it can be seen there are three possible drivers of the effect: 1. a difference in outcome for treatments when no rescue is used, 2. a difference in using rescue between treatments, and 3. a difference in worse observed value when rescue is used.

6.1.3. Estimation

We estimate the effect of interest using a Bayesian analysis where we model the outcomes and the occurrence of IEs necessary to construct the estimate of the effect above. Because the worst observed pre-rescue value is used to reflect the negative outcome of using of rescue medication, outcomes after the use of rescue will be set to missing and will not contribute to the analysis model. The effect defined above will be constructed using a function of the joint posterior and a raw estimate of the average worst pre-rescue value in each treatment arm for participants that used rescue. Although using this approach is a simplification, it means we do not need to explicitly use or impute the worst observed values for each patient, which creates a complicated mixture likelihood.

To illustrate how an estimate of our target effect can be constructed, we specify ψ_{jZ}, as a series of conditional expectations:

$$\mathbb{E}_{X_i}\left[\mathbb{E}_{D_i,R_i,S_i}\left[\mathbb{E}_{Y_{ij},W_i}\left[I_{ij}^{(Z_i,D_i,R_i>j,S_i>j)}\cdot\left(Y_{ij}|Z_i,D_i,R_i>j,S_i>j,X_i\right)+\left(1-I_{ij}^{(Z_i,D_i,R_i>j,S_i>j)}\right)\right.\right.\right.$$
$$\left.\left.\left.\cdot\left(W_i|Z_i,D_i,R_i\leq j,S_i>j\right)\right]\right]|X_i\right]$$

Taking the inner most expectation of Y_{ij} and W_i gives the conditional mean for each (note $\overline{W_i}$ is not conditional on X_i):

$$\mathbb{E}_{X_i}\left[\mathbb{E}_{D_i,R_i,S_i}\left[I_{ij}^{(Z_i,D_i,R_i>j,S_i>j)}\cdot\left(\mu_{ij}|Z_i,D_i,R_i>j,S_i>j,X_i\right)+\left(1-I_{ij}^{(Z_i,D_i,R_i>j,S_i>j)}\right)\right.\right.$$
$$\left.\left.\cdot\left(\overline{W}_i|Z_i,D_i,R_i\leq j,S_i>j\right)\right]|X_i\right]$$

Taking the expectation over D_i, R_i and S_i leads to D_i dropping out of the expression as there is no conditioning on it and the indicators become individual probabilities:

$$\mathbb{E}_{X_i}\left[P_{ij}(R_i>j,S_i>j|Z_i,X_i)\cdot\left(\mu_{ij}|Z_i,R_i>j,S_i>j,X_i\right)+\left(1-P_{ij}(R_i>j,S_i>j|Z_i,X_i)\right)\right.$$
$$\left.\cdot\left(\overline{W}_i|Z_i,R_i\leq j,S_i>j\right)|X_i\right]$$

Finally, we take expectations over the individual specific covariates giving the population-based treatment means ψ_{jZ}:

$$\psi_{jZ}=P_{ij}(R_i>j,S_i>j|Z_i)\cdot\left(\mu_{ij}|Z_i,R_i>j,S_i>j\right)+\left(1-P_{ij}(R_i>j,S_i>j|Z_i)\right)$$
$$\cdot\left(\overline{W}_i|Z_i,R_i\leq j,S_i>j\right)$$

This illustrates we can construct an estimate of the target effect by estimating conditional outcome means, probability of IEs and a conditional mean worst observed outcome.

As the effect we target is in the absence of site closures, we can also simplify the estimation by not including any outcomes after this IE and therefore $P_{ij}(R_i>j,S_i>j|Z_i)$ can be estimated as the probability of rescue on participants with no site closure discontinuation.

6.1.4. Outcome model:

A participant's PCFB across visits are assumed to come from a multivariate normal. The model for the mean vector will be specified with no intercept and will include direct interaction terms for treatment group by visit, baseline EASI score by visit and the following baseline covariates: region (China vs Japan vs Rest of World) and prior treatment experience (biologic naïve vs biologic experienced). The model will assume a single unstructured variance covariance matrix across both treatment groups.

Since dosing only occurs twice (at Day 1 and [redacted] and also the long PD effect ([redacted] half-life), this model will not include terms to distinguish between participants who completed their protocol defined dosing (received both doses) and those who discontinued treatment prior to their second dose. Any missing data bias resulting from making this simplification [Drury, 2022; Bell, 2024] is expected to be minimal.

Below is a basic schematic of the main outcome model:

$$\begin{bmatrix} Y_{i1} - Y_{i0} \\ \vdots \\ Y_{iJ} - Y_{i0} \end{bmatrix} \sim MVN\left(\begin{bmatrix} \alpha_{11} \cdot \mathbb{I}_{Z_i=C} + \alpha_{12} \cdot \mathbb{I}_{Z_i=A} + \beta_{10} \cdot Y_{i0} + \theta_1 \cdot \mathbb{I}_{X_{i1}=ROW} + \theta_2 \cdot \mathbb{I}_{X_{i2}=Naive} \\ \vdots \\ \alpha_{J1} \cdot \mathbb{I}_{Z_i=C} + \alpha_{J2} \cdot \mathbb{I}_{Z_i=A} + \beta_{J0} \cdot Y_{i0} + \theta_1 \cdot \mathbb{I}_{X_{i1}=ROW} + \theta_2 \cdot \mathbb{I}_{X_{i2}=Naive} \end{bmatrix}, \begin{bmatrix} \Sigma_{11} & \cdots & \Sigma_{1J} \\ \vdots & \ddots & \vdots \\ \Sigma_{J1} & \cdots & \Sigma_{JJ} \end{bmatrix} \right)$$

Where:

- $\alpha_{11}, \ldots, \alpha_{1J}$ and $\alpha_{12}, \ldots, \alpha_{J2}$ are the treatment by time parameters combined with condition indicators $\mathbb{I}_{Z_i=C}$ and $\mathbb{I}_{Z_i=A}$.
- $\beta_{10}, \ldots, \beta_{J0}$ are the baseline by time parameters.
- θ_1 and θ_2 are parameters for the baseline covariates region and treatment experience respectively, combined with indicators $\mathbb{I}_{X_{i1}=ROW}$ and $\mathbb{I}_{X_{i2}=Naive}$.

6.1.5. ICE models:

A subject who has withdrawn from the study without any use of rescue medication prior to their withdrawal would still have been at risk of experiencing the IE had they remained in the study. To correctly reflect this in the estimation, the IE use of rescue medication will be modelled. The visit of IE occurrence is assumed to come from a geometric distribution. The model for the probability of using rescue medication will have no intercept and will include main effects for treatment group and baseline EASI and also include the following baseline covariates: region (China vs Japan vs Rest of World) and previous treatment experience (biologic naïve vs biologic experienced). Below is a basic schematic of the IE models:

$$R_i \sim GEO(\pi_R)$$

$$logit(1 - \pi_R) = \gamma_1 \cdot \mathbb{I}_{Z_i=C} + \gamma_2 \cdot \mathbb{I}_{Z_i=A} + \delta_1 \cdot Y_{i0} + \vartheta_1 \cdot \mathbb{I}_{X_{i1}=ROW} + \vartheta_2 \cdot \mathbb{I}_{X_{i2}=Naive}$$

Where:

- $\gamma_1$and γ_2 are the treatment parameters combined with condition indicators $\mathbb{I}_{Z_i=C}$ and $\mathbb{I}_{Z_i=A}$
- δ_1, ϑ_1 and ϑ_2 are the parameters for baseline EASI, region and treatment experience respectively.

6.1.6. Modelling:

The models for the outcome and the ICE will be fitted separately in two Bayesian models in SAS, each with burn in and number of samples determined based on the worm plots and computation time. Priors will be non-informative priors on all parameters, specifically:

- All outcome model mean and ICE model parameters will have a $Normal(0,10^6)$
- All outcome model variance covariance matrix will use an $iwish\left(J+3, I_{J\times J}\cdot (J+3)\right)$ where J is the number of visits and $I_{J\times J}$ is a $J\times J$ identity matrix.

6.1.7. Treatment Effect Construction

The effects of interest will be constructed as functions of the posterior parameters and participant data. A standardization (G-computation) approach will be used to marginalize over the baseline covariates [Van Lancker, 2024]. Specifically, the posterior draws for the parameters will be combined with patient data from each arm and subject specific mean PCFB EASI and probabilities of rescue will be predicted and combined with the raw mean worst PCFB EASI score for that treatment and then averaged. Algebraically ψ_{jA} and ψ_{jC} will be estimated as:

$$\hat{\psi}_{jA}^{[k]} = \frac{1}{N_A}\sum_{i=1}^{N_A} \hat{p}_{ijA}^{[k]}(R_i > j)\cdot \hat{\mu}_{ijA|R_i>j}^{[k]} + \left(1-p_{ijA}^{[k]}(R_i>j)\right)\cdot \overline{w}_{jA|R_i\leq j}$$

$$\hat{\psi}_{jC}^{[k]} = \frac{1}{N_C}\sum_{i=1}^{N_C} \hat{p}_{ijC}^{[k]}(R_i > j)\cdot \hat{\mu}_{ijC|R_i>j}^{[k]} + \left(1-p_{ijC}^{[k]}(R_i>j)\right)\cdot \overline{w}_{jC|R_i\leq j}$$

Where:

- $k = 1,\ldots,5000$ is each draw from the joint posterior.
- $\hat{p}_{ijZ}^{[k]}(R>j)$ is the k^{th} posterior draw for the probability of not using rescue on treatment Z at visit j for patient i.
- $\hat{\mu}_{jZ|R>j}^{[k]}$ is the k^{th} posterior draw for the mean PCFB EASI when not using rescue on treatment Z at visit j for patient i.
- $\overline{w}_{jZ|R\leq 0}$ is the raw sample mean of worst pre-rescue PCFB EASI score for patients using rescue on treatment Z at visit j.

The posterior distribution for the effect of interest will be estimated at each timepoint as:

$$\hat{\Delta}_j^{[k]} = \hat{\psi}_{jA}^{[k]} - \hat{\psi}_{jC}^{[k]}$$

The posterior distribution of effect will be summarized using median and 95% credible intervals.

6.2. Appendix 2 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Full Analysis Set. A summary of the number of participants in each of the participant level analysis sets will be provided. In this multicenter global study, enrolment will be presented by country and site.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications will be based on GSK Core Data Standards. Details of planned displays are presented in the OPS.

6.2.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. A participant is considered to have completed the study if they have completed all planned study assessments including the follow-up visit.

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

The number of participants with each intercurrent event will be summarized by treatment group using the modified FAS. This summary will also be produced by region.

Rescreening of screen failures is allowed once as per protocol. Rescreened participants will be summarized under their latest participant number unless otherwise specified.

6.2.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, race, ethnicity, height, weight and BMI at screening will be summarized with descriptive statistics. In addition, the following age categories will be summarized: 18-64, 65-84 and >=85 based on the Enrolled Analysis Set. If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version should be produced.

A summary of atopic dermatitis history, including duration since diagnosis, and characteristics will be provided, for the overall population, by previous treatment experience, and by reason for stopping previous treatment. Disease treatment failure history will be summarized based on the targeted eCRF, including what atopic dermatitis treatments were previously taken by a participant and the reason for treatment failure.

A summary of efficacy parameters will include baseline EASI score, baseline IGA score, baseline PPNRS, baseline BSA, and baseline SCORAD.

Past medical conditions and current medical conditions as of screening will be summarized separately.

Substance use, including smoking history, tobacco use, alcohol and drug history will be summarized.

6.2.3. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment, prohibited medication) will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. Given the study has been terminated, the protocol deviation management plan (PDMP) was updated post termination decision; changes to the definition of important PDs are detailed in this updated PDMP. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorized in the protocol deviations dataset. This dataset will be the basis for the summaries of important protocol deviations.

6.2.4. Prior and Concomitant Medications

Concomitant medications will be coded and summarized using Anatomical Therapeutic Chemical (ATC) 2 and standardized term (ingredient(s)). The summary will be created using ingredient base names, i.e., ingredients with the same base name but different salt will appear under one base name in the summary.

Concomitant medications include any medication that was taken at some point during the treatment period or follow up period as defined in 6.4.2.

A summary of prohibited medications and Rescue Therapy will be produced by ATC2 term and ingredient.

The incidence of use of prohibited medications and rescue therapy will be summarized, overall and by topical and non-topical groups. All uses of rescue therapy will be included, not only persistent use cases. Cumulative proportions of participants receiving persistent rescue therapy will be summarized overall in a table and by region in a figure.

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

eCOA data (i.e. assessments collected via tablet or phone) are collected within this study. Details for calculating compliance at the study level and individual domain level are presented in this section.

Compliance is the state of being in accordance with the established protocol guidelines or specifications: i.e., the overall number of datapoint collected vs the overall number of datapoint expected. Datapoints after treatment discontinuation remain expected until (if) a participant withdraws from the study. Datapoints are not expected from any participant after study withdrawal. For study withdrawal, datapoints are no longer expected immediately following the date of withdrawal. In the event of triggering primary completion before all participants have reached [redacted], only participants who have reached the visit will have datapoints expected. Datapoints are not expected post study termination communication (8 April 2025) and the overall compliance table will be based on the modified full analysis set.

eCOA compliance will be calculated up to [redacted] at the final analysis. Table 24 details the data that are classified as eCOA:

Table 24 eCOA Data Domains

Measurement	eCOA category	Device
Primary Endpoint Domain		
EASI	eClinRO	Tablet
Secondary Endpoint Domains		
IGA	eClinRO	Tablet
PP-NRS	ePRO	Phone
SCORAD	eClinRO	Tablet
BSA	eClinRO	Tablet
SP-NRS	ePRO	Phone
PROMIS-Sleep disturbance 8b	ePRO	Phone
FACIT-Fatigue	ePRO	Phone
BFI-item 3	ePRO	Phone
POEM	ePRO	Phone
DLQI	ePRO	Phone
HADS	ePRO	Phone
WPAI-AD	ePRO	Phone

The calculation of overall study compliance will use all domains defined in Table 24. Only EASI, IGA, and PP-NRS will have individual domain compliance calculated.

6.3.1. Study Level Compliance

Compliance will be assessed for the primary and secondary eCOA domains only. Overall eCOA compliance (across the eCOA domains specified and all participants) for the study is calculated as:

$$\frac{Total\ number\ of\ complete\ eCOAs}{Expected\ number\ of\ complete\ eCOAs\ per\ participant} \times Total\ number\ of\ participants$$

For the final analysis, the total number of complete eCOAs is a sum of completed eCOAs for each specified domain across the treatment period in the study (i.e calculated across all patients and timepoints up to [redacted]).. An eCOA is considered complete if there are no missing data within the assessment.

For the assessment of the overall eCOA compliance, all daily diary assessments (PP-NRS, SP-NRS, BFI-item 3) will be included in the formula using complete weekly (rather than daily) assessments. A participant is categorized as compliant if the participant has recorded at least four daily scores for the week.

The target study level compliance is 80%.. The study eCOA compliance will be reported for the study overall (i.e pooling all treatment arms together) as well as by treatment arm.

6.3.2. Endpoint Level Compliance

Given the study has been terminated, analyses in this section will no longer be performed.

Overall compliance for each domain in this section is calculated as the average of all weeks' compliance up to [redacted] for the primary analysis and up to Week 28 for the end of study analysis.

PP-NRS

Using the endpoint definition as per Section 4.4.2.1, to assess compliance, the number/percentage of participants with weekly PP-NRS scores available will be summarized by treatment arm and week using a frequency table.

The target compliance level for this domain is 95% (for each week and overall). This is in line with the related QTL although the definition is extended here to encompass all weeks up to [redacted] at the primary analysis and up to Week 28 for the end of study analysis(QTL defined as "Percentage of subjects with more than three PP-NRS daily scores missing at the visits: Week 4 and [redacted]"; QTL sub-threshold will be breached if >5% of participants have weekly PP-NRS missing at Week 4 and [redacted]).

IGA

The number/percentage of participants with an IGA score available will be summarized by treatment arm and week using a frequency table.

The target compliance level for this domain is 85% (for each week and overall). This is in line with the related QTL although the definition is extended here to encompass all weeks up to [redacted] at the primary analysis and up to Week 28 for the end of study analysis (QTL defined as "Percentage of subjects with IGA score missing at [redacted]"; QTL sub-threshold will be breached if >15% of participants have IGA score missing at [redacted]).

EASI

The number/percentage of participants with an EASI score available will be summarized by treatment arm and week using a frequency table.

The target compliance level for this domain is 85% (for each week and overall). This is in line with the related QTL although the definition is extended here to encompass all weeks up to [redacted] at the primary analysis and up to Week 28 for the end of study analysis (QTL defined as "Percentage of subjects with EASI score missing at [redacted] QTL sub-threshold will be breached if >15% of participants have EASI score missing at Week 16).

6.4. Appendix 4 Data Derivation Rules

6.4.1. Patient Reported Outcomes

Table 25 Description of Patient Reported Outcomes

Endpoint	Description and/or derivation of score
PP-NRS	PP-NRS is a patient reported measure of pruritus (itch) intensity assessing worst itch (in the past 24 hours) using an 11-point scale (from 0 to 10), with 0 being no itch and 10 being the worst imaginable itch [Yosipovitch, 2019].
SP-NRS	SP-NRS is a patient reported measure assessing worst level of skin pain (in the past 24 hours) using an 11-point scale (from 0 to 10), with 0 being no pain and 10 being the worst pain imaginable.
PROMIS-Sleep disturbance 8b	The PROMIS Short Form Sleep disturbance 8b is a PRO instrument designed to assess self-reported sleep disturbance for which the recall period is the past 7 days. The items are rated on a 5-point verbal rating scale. Items are summed giving a range in raw score from 8 to 40, with higher scores indicating greater severity of sleep disturbance. Raw scores are converted to T-scores [Lei, 2020]. The T-score rescales the raw score into a standardized score with a mean of 50 and a SD of 10
FACIT-Fatigue	The FACIT-Fatigue scale is a short, 13-item measure that assesses self-reported fatigue and its associated impact for daily activities over the past week. The items are rated on a 5-point Likert-type scale (i.e., 4 = not at all to 0 = very much). The scale range is 0 to 52, with 0 being the worst possible score and 52 being the best possible score (indicating no fatigue) [Montan, 2018].

Endpoint	Description and/or derivation of score
BFI- item 3	The BFI has 9 items. BFI item 3 assesses the worst level of fatigue related concepts (i.e., tiredness, weariness) during the past 24 hours. Participants report their worst level of fatigue daily, for the previous 24 hours, using a numerical rating scale ranging from 0 (no fatigue) to 10 (as bad as you can imagine).
POEM	POEM is a 7-item questionnaire that assesses symptoms of dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping over the last week. The scoring symptom ranges from 0 (absent disease) to 28 (severe disease). Higher score indicates poor QoL.
DLQI	The DLQI is a 10-item questionnaire [Finlay, 1994]. The DLQI is calculated by summing the scores of the 10 questions, ranging from 0 to 30 with higher scores indicating more impaired QoL. A score of 0 or 1 means that the disease has no effect at all.
HADS	The HADS is a self-reported questionnaire which measures depression and generalized anxiety, in the past week. Each item on the questionnaire ranges from 0 (no, not at all) to 3 (yes, definitely). The scale ranges from 0 to 21 for each part, anxiety and depression, with lower score indicating better QoL.
WPAI-AD	The WPAI-AD is a validated, patient-reported, quantitative assessment of absenteeism (work time missed), presentism (reduced on-the-job effectiveness), work productivity loss and activity impairment due to a specific health problem.
ACQ5	ACQ-5 measures adequacy of clinical asthma control. It is a 5-item questionnaire that is scored on a 7-point Likert scale with a recall period of 1 week. The ACQ-5 has been shown to reliably measure asthma control and distinguish participants with well-controlled asthma (score ≤0.75 points) from those with uncontrolled asthma (score ≥1.5 points). The total ACQ-5 score is the mean score of all questions, a lower score indicated better asthma control. The ACQ-5 would be assessed only in participants with known history of asthma.

6.4.2. Study Period

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

Pre-Intervention is defined as time prior to the first dose of study intervention.

Treatment period is defined as time from first dose up to and including the [redacted] visit. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECG, Lab, and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Follow up is defined as any time post the treatment period window, i.e. any time in the period after the [redacted] visit + 12 weeks.

6.4.3. Study Day and Reference Dates

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

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

The study day is calculated as below:

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

6.4.4. Assessment Window

For data summaries by visit, scheduled visits with nominal visit description as well as the worst-case post baseline will be displayed. Clinical efficacy and PRO efficacy, except those measured daily or weekly, from unscheduled and early withdrawal will be slotted into a target visit based on the visit windows defined the following tables in:

- Section 6.4.4.1 for EASI, IGA, and BSA
- Section 6.4.4.2 for SCORAD
- Section 6.4.4.3 for PROMIS-Sleep Disturbance 8b, PGIS-SD, FACIT-Fatigue, PGIS-Fatigue, DLQI, HADS, WPAI-AD
- Section 6.4.4.4 for PGIS-nocturnal scratching (severity)
- Section 6.4.4.5 for PGIS-nocturnal scratching (change)
- Section 6.4.4.6 for ACQ-5
- Section 6.4.4.7 for POEM

Visit number is per the schedule of assessment in the protocol.

Safety data from unscheduled visits will be included in the derivation of worst-case post baseline assessment. All unscheduled visits will be displayed in the listing. PK and PD data will not be subject to visit slotting as actual study day will be used in the analysis.

If there are multiple assessments within the same window, a scheduled visit will be prioritized over unscheduled visits. If all assessments within the same window are from unscheduled visits, the closest one to the target day will be used in the slotting. If multiple assessments are equally close or taken on the same day, the worst case will be used.

6.4.4.1. Analysis Window for EASI, IGA, BSA

	Analysis window			
Visit	**Window start (study day)**	**Target study day in the window**	**Window end (study day)**	**Target visit to be slotted to**
2		1		Week 0 (Day 1)
4	2	8	11	Week 1 (Day 8)
5	12	15	21	Week 2 (Day 15)
7	22	29	35	Week 4 (Day 29)
8	36	43	49	Week 6 (Day 43)
9	50	57	63	Week 8 (Day 57)
10	64	71	77	Week 10 (Day 71)
11	78	85	91	Week 12 (Day 85)
12	92	99	105	Week 14 (Day 99)
13	106	113	126	Week 16 (Day 113)
14	127	141	154	Week 20 (Day 141)
15	155	169	182	Week 24 (Day 169)
16	183	197	210	Week 28 (Day 197)

6.4.4.2. Analysis Window for SCORAD

	Analysis window			
Visit	**Window start (study day)**	**Target study day in the window**	**Window end (study day)**	**Target visit to be slotted to**
2		1		Week 0 (Day 1)
5	2	15	21	Week 2 (Day 15)
7	22	29	42	Week 4 (Day 29)
9	43	57	70	Week 8 (Day 57)
11	71	85	98	Week 12 (Day 85)
13	99	113	126	Week 16 (Day 113)
14	127	141	154	Week 20 (Day 141)
15	155	169	182	Week 24 (Day 169)
16	183	197	210	Week 28 (Day 197)

6.4.4.3. Analysis Window for PROMIS-Sleep Disturbance 8b, PGIS-SD, FACIT-Fatigue, PGIS-Fatigue, DLQI, HADS, WPAI-AD

	Analysis window			
Visit	Window start (study day)	Target study day in the window	Window end (study day)	Target visit to be slotted to
2		1		Week 0 (Day 1)
7	2	29	42	Week 4 (Day 29)
9	43	57	70	Week 8 (Day 57)
11	71	85	98	Week 12 (Day 85)
13	99	113	126	Week 16 (Day 113)
14	127	141	154	Week 20 (Day 141)
15	155	169	182	Week 24 (Day 169)
16	183	197	210	Week 28 (Day 197)

6.4.4.4. Analysis Window for PGIS-nocturnal scratching (severity)

	Analysis window			
Visit	Window start (study day)	Target study day in the window	Window end (study day)	Target visit to be slotted to
2		1		Week 0 (Day 1)
9	29	57	84	Week 8 (Day 57)
13	85	113	141	Week 16 (Day 113)

6.4.4.5. Analysis Window for PGIS-nocturnal scratching (change)

	Analysis window			
Visit	Window start (study day)	Target study day in the window	Window end (study day)	Target visit to be slotted to
9	29	57	84	Week 8 (Day 57)
13	85	113	141	Week 16 (Day 113)

6.4.4.6. Analysis Window for ACQ-5

	Analysis window			
Visit	**Window start (study day)**	**Target study day in the window**	**Window end (study day)**	**Target visit to be slotted to**
2		1		Week 0 (Day 1)
13	85	113	141	Week 16 (Day 113)

6.4.4.7. Analysis Window for POEM

Analysis window			
Window start (study day)	**Target study day in the window**	**Window end (study day)**	**Target visit to be slotted to**
	1		Week 0 (Day 1)
2	8	11	Week 1 (Day 8)
12	15	18	Week 2 (Day 15)
19	22	25	Week 3 (Day 22)
26	29	32	Week 4 (Day 29)
33	36	39	Week 5 (Day 36)
40	43	46	Week 6 (Day 43)
47	50	53	Week 7 (Day 50)
54	57	60	Week 8 (Day 57)
61	64	67	Week 9 (Day 64)
68	71	74	Week 10 (Day 71)
75	78	81	Week 11 (Day 78)
82	85	88	Week 12 (Day 85)
89	92	95	Week 13 (Day 92)
96	99	102	Week 14 (Day 99)
103	106	109	Week 15 (Day 106)
110	113	116	Week 16 (Day 113)
117	120	123	Week 17 (Day 120)
124	127	130	Week 18 (Day 127)
131	134	137	Week 19 (Day 134)
138	141	144	Week 20 (Day 141)
145	148	151	Week 21 (Day 148)
152	155	158	Week 22 (Day 155)
159	162	165	Week 23 (Day 162)
166	169	172	Week 24 (Day 169)
173	176	179	Week 25 (Day 176)
180	183	186	Week 26 (Day 183)
187	190	193	Week 27 (Day 190)
194	197	200	Week 28 (Day 197)

6.4.5. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

Elsewhere, mean of the measurements will be calculated where required and used in any derivation of summary statistics but if listed, all data will be presented.

Participants having both high and low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables.

6.4.6. Handling of Partial Dates

Table 26 Handling of Partial Dates

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td>General</td><td colspan="2">• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td colspan="2">• Partial dates for AE recorded in the CRF will be imputed using the following conventions:</td></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
  • Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
  • Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td></td><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td></td><td>Missing end day and month</td><td>No Imputation</td></tr>
</table>

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

6.4.7. Early PK Access Key Activities

Designated independent representative(s) may be unblinded for preparing population PK and PKPD dataset(s) and for performing PK and PKPD model development/refinement using PK and PKPD unblinded datasets, including but not limited to: concentration-time data, dosing information, baseline demographic characteristics, and vital sign, laboratory, and PD information]. Details of PKPD data access will be specified in a separate analysis plan.

Early access to unblinded PK, treatment assignment, and Immunogenicity data prior to database lock will be granted to a separate and limited analysis team to complete population PK modeling and simulation analyses prior to database lock. GSK plans to put multiple safeguards in place to ensure the integrity of the study data and blinding will be preserved. This will include assigning roles (data management, programming, statistical analysts, external vendors, etc) with no involvement in the current study and who are completely independent of the study team involved in conduct and interpretation of the

study. Similarly, independent clinical PK analysts with no involvement in the study will perform analysis of the PK data and model development. In addition, the computing environments in which the raw data, datasets, model development progress, and modelling results will be stored will have secure directory structures and restrict access only available to those roles not involved with the current study.

6.4.8. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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6.5. Appendix 5 Marginal Treatment Effects

This section details the method to calculate the posterior distribution of the risk difference corresponding to marginal treatment effects for the binary analysis.

Algorithm for All Comer Analysis:

1. Fit Bayesian Logistic Regression Model that regresses the outcome on treatment assignments and prespecified baseline covariates (Treatment Arm, Baseline Covariate, Region, Previous Treatment Experience, etc.). The model should include an intercept term. This will generate many posterior samples (e.g. 20000) of each coefficient.
2. Then for each subject, regardless of treatment group assignment, compute the model-based prediction of the probability of response under Active using the subject's specific baseline covariates, using each of the posterior samples of the coefficients.
3. For every set of posterior samples, estimate the average response under Active by averaging the probabilities estimated in Step 2 across all subjects in the trial.
4. Repeat step 2 & 3 using all the 20000 posterior samples of coefficients and will have 20000 average response rates for Active.
5. For each subject, regardless of treatment group assignment, compute the model-based prediction of the probability of response under Placebo using the subject's specific baseline covariates, using each of the posterior samples of the coefficients.
6. For every set of posterior samples, estimate the average response under Placebo by averaging the probabilities estimated in Step 5 across all subjects in the trial
7. Repeat step 5 and 6 using all the 20000 posterior samples of coefficients and will have 20000 average response rates for Placebo.
8. The estimates of average responses rates in the two treatment groups from Steps 4 and 7 represent the posterior distribution of the proportion of response in each arm and can be used to derive the posterior distribution of the risk difference by

subtracting the 20000 estimated response rates of Placebo from 20000 estimated response rates of Active.

Algorithm for Subgroup Analysis:

1. Fit Bayesian Logistic Regression Model that regresses the outcome on treatment assignments, prespecified baseline covariates and an interaction term between treatment and the subgroup of interest (e.g. previous treatment experience).
2. The model output would have posterior samples for Active and Placebo arm with interaction of each subgroup level. (For example: Active:Bio-Experienced, Placebo:Bio-Experienced, Active:Bio-Naïve, Placebo:Bio-Naïve), along with samples from other coefficients e.g. intercept, baseline etc.
3. Then to calculate the posterior distribution of the responder rates, the subjects' dataset is divided according to the different levels of the subgroup. (For example: Bio-Experienced & Bio-Naïve).
4. Use the samples of the coefficients that are applicable only to the particular subgroup (for example: intercept, baseline, Active:Bio-Experienced and Placebo:Bio-Experienced for the Bio-Experienced subgroup) and repeat steps 2-8 in the algorithm for all comer analysis for each subgroup for calculating the posterior distribution of the responder rates.
5. 20000 response rates would be obtained for Active and Placebo group in each subgroup which can then be used to derive the posterior distribution of the difference between Active and Placebo within each level of the subgroup, in a similar manner to step 8 in the algorithm for all comer analysis.

7. REFERENCES

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