Statistical Analysis Plan Amendment 1

Study ID: 220723

Official Title of Study: A Long-Term Extension Study (AtDvance) to Evaluate the Safety and Efficacy of GSK1070806 in Participants with Moderate to Severe Atopic Dermatitis.

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TITLE PAGE

Protocol Title:	Long-Term Extension Study (AtDvance) to Evaluate the Safety and Efficacy of GSK1070806 in Participants with Moderate to Severe Atopic Dermatitis
Study Number:	220723
Compound Number:	GSK1070806
Abbreviated Title:	Long-Term Study (AtDvance) to Evaluate GSK1070806 in Atopic Dermatitis.
Acronym:	AtDvance

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry ID	**ID**
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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	29 May 2024	V2.0 (28 November 2023)	Not Applicable	Original version
SAP Amendment 1	19 Jun 2025	Protocol Amendment 1 (02 August 2024)	Minor typos corrected and abbreviations aligned	To correct typos and align abbreviations
			NCTI number added for the study	The NCTI number for 220723 is available now
			Updates to study design: • Placebo responders in Ph2 parent studies will continue to receive placebo in LTE. Placebo non-responders in Ph2 parent studies will change to top dose in the LTE. • Participants who lose response across all dose groups can be escalated to top dose earlier (from [redacted]).	To align SAP to Protocol Amendment 1
			Change of the wording for study duration, from "approximately" to "maximum".	To align SAP to Protocol Amendment 1
			For PPNRS assessments, added clarification on when the frequency of administration will be	To align SAP to Protocol Amendment 1

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			reduced from daily assessments to assessments only at scheduled visits (after [redacted]).	
			Added baseline definition for Safety, Efficacy and PROs for participants with dosing errors in the Ph2 study	To provide clarity and detail.
			Added Enrolled population in the Analysis Set Section.	Enrolled population is necessary for some of the population tables (e.g. summaries of screen failures).
			Removed drug use from summaries of Demographic and Baseline characteristics section (Section 6.1.2)	eCRF does not cover recreational drug use
			Clarification added that any use of oral systemic medication will lead to discontinuation of the study drug, except the use of short-term oral corticosteroids.	To align SAP to Protocol Amendment 1
			Added clarification on how to address an urgent clinical need including use of rescue medicines.	To align SAP to Protocol Amendment 1

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Added clarification regarding handling of missing data for secondary binary efficacy endpoints.	To align SAP to Protocol Amendment 1
			Analysis set for summaries of age groups has been updated from Assigned to Enrolled (Demographic and Baseline Characteristics section).	To align with the current clinical thinking.
			Added detail to analysis of participants with dosing errors in the LTE.	Added clarity and additional detail.
			Clarification and additional detail added for the interim analyses planned.	Added clarity and additional detail
			Re-definition and clarification added regarding the maintenance of response endpoint.	To align with the current clinical thinking.
			Added clarity regarding escalation to top dose for efficacy and safety assessments.	Added clarity.
			Added clarification that incidence rates and exposure-adjusted incidence rates will be calculated for AEs, SAEs, and AESIs.	To align SAP to Protocol Amendment 1
			Change in the definition of possible Hy's law cases (the stipulation for >35% direct bilirubin is no	In line with the recommendation from GSK

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			longer part of the definition)	Hepatic Safety Panel
			Added eDISH plot Section 4.5.3.1 (Laboratory data)	To align with the current clinical thinking.
			Added detail on handling laboratory data where non-numeric results are recorded	To add detail and clarification
			Update to grade increase value (new grade value 3, previous grade value 2) in the summary of maximum QTc values post-baseline relative to baseline by grade.	To align with the current clinical thinking.
			Additional detail and clarification added regarding the exploratory flare endpoint.	Added clarity to align with the current clinical thinking.
			Subgroup analysis will be performed on secondary efficacy endpoints	To correct the wording as there are no primary efficacy endpoints in the study
			Specification that only analyses related to primary and secondary endpoints (as defined in Section 1.1.1) will be provided due to the study termination.	To specify which analyses will be provided following the early study termination

1. INTRODUCTION

The SAP has been amended after the decision to terminate the 220723 Study. Following the early study termination, the statistical analysis will be performed only on primary and secondary endpoints as well as a subset of exploratory endpoints (as defined in Section 4.6). The statistical analysis for the primary endpoints will be performed only on primary endpoints as defined in Section 1.1.1 as well as endpoints necessary to meet regulatory requirements. The statistical analysis for the secondary endpoints will be performed on secondary endpoints as defined in Section 1.1.1.

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 220723. 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.

At the time of the finalization of this document, the GSK1070806 AtD program had been terminated. The only ongoing parent study at that time was the Ph2b dose-ranging study 219538, therefore, the terminology "parent study" refers only to study 219538.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To describe long term safety of a range of doses and dosing regimens of GSK1070806 in participants with moderate to severe AtD	Incidence of: • Adverse events (AEs) and discontinuation from study treatment due to AEs. • Serious adverse events (SAEs) and adverse events of special interest (AESI).
Secondary	
To evaluate the long-term efficacy of a range of doses and dosing regimens of GSK1070806 in participants with moderate to severe AtD	Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* • PP-NRS Reduction of ≥4 points Achieving a maintained response (for binary endpoints) for at least 16/32/48 and every 48 weeks thereafter after first response in: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline*

Objective(s)	Endpoint(s)
	PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.
Exploratory	
CCI [redacted]	
To evaluate the efficacy of a range of doses and dosing regimens of GSK1070806 on Health Related-Quality of Life (HR-QoL) as assessed by a range of PROs in adults with moderate to severe AtD.	CFB to Weeks 16, 32, 48 and every 48 weeks thereafter in: • DLQI • POEM • WPAI-AD • HADS • PROMIS-Sleep Disturbance 8b • PP-NRS CFB to Week 16 in: • SP-NRS At Week 16,32, 48 and every 48 weeks thereafter achieving: • PP-NRS Reduction of ≥3 points • PP-NRS score of 0
CCI [redacted]	

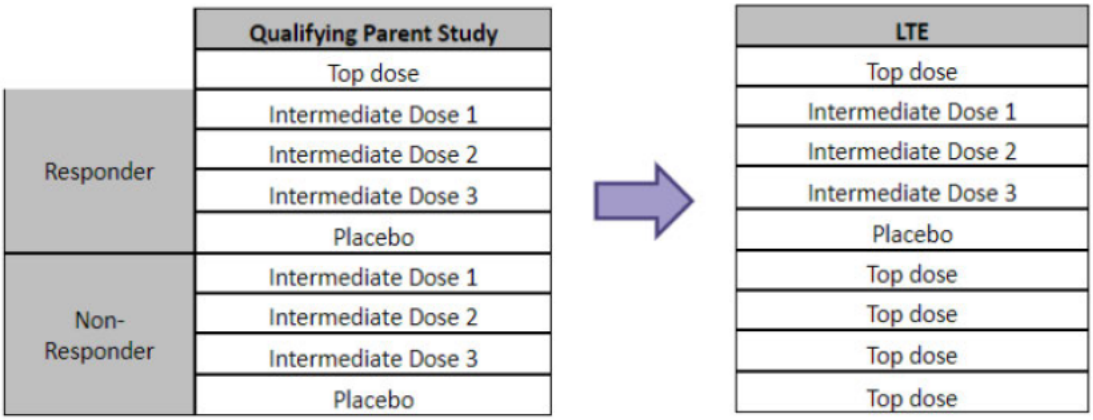
*Please refer to Section 4.1.2 for baseline definitions.

1.1.2. Estimands

Following the early study termination, only the primary estimand will be considered for analysing safety (Estimand 1) and efficacy (Estimand 2) endpoints. No summaries will be provided for the additional estimand for safety (Estimand 1a).

This section describes the estimand strategy for the safety and efficacy objectives.

Both safety/efficacy estimands and their strategy will be applied to the safety/efficacy objectives which will be analyzed by treatment arms defined by the treatment received in the parent study (219538) and the treatment received in the LTE. More information on the treatment arms is provided in Section 4.1.1.



1.1.3. Estimand Strategy for the Primary Objective (Safety)

Table 1 Estimand 1

Estimand 1 – Primary estimand for the primary objective (safety)	
Clinical question of interest	What is the long-term safety of a range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments in participants with moderate to severe AtD as measured by occurrence of AEs, SAEs, AESI, discontinuation from study treatment due to AEs that happen to participants while on treatment (i.e., within the 5 half-lives CCI post last dose)? Rationale: The study is designed to evaluate the long-term safety of a range of doses and regimens of GSK1070806 with or without use of non-medicated background treatments. It is important to evaluate the risk-benefit of GSK1070806 while participants are on treatment so this estimand addresses the scenario in which only safety events attributable to treatment are included. All ICEs will be handled using the While on Treatment strategy defined as 5 half-lives CCI post last dose. The safety estimand applies only for data

Estimand 1 – Primary estimand for the primary objective (safety)	
	collected in the LTE (i.e., does not include the time in the parent study (219538).
Treatment Condition	A range of doses and regimens of SC GSK1070806 with or without use of non-medicated background treatments.
Endpoint	Incidence of: • AEs • SAEs. • AESI. • Discontinuation from study treatment due to AE.
Population	Participants with moderate to severe AtD who have previously been treated with medicated topical treatments only or 1 biologic therapy (in addition to GSK1070806 if the participant received active treatment in their parent study (219538).
Strategy for ICEs	ICEs: • Permanent treatment discontinuation for any reason **Strategy: While on treatment;** any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives CCI [redacted] timeframe) will be excluded • Use of rescue therapy for AtD **Strategy: While on treatment;** any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives CCI [redacted] timeframe) will be excluded • 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 study medication) **Strategy: While on treatment;** any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives CCI [redacted] timeframe) will be excluded
Population-level summary	Number and percentage of participants in each treatment condition.

An additional estimand (estimand 1a) for the safety objectives is defined below. The key difference to the primary safety estimand (estimand 1) is in the strategy for handling all the ICEs. Following the additional estimand 1a, all the ICEs will be handled using the treatment policy. Summaries will include all safety events regardless of whether the ICE happened within the 5 half-lives (CCI [redacted]) post last dose or outside of the 5 half-lives

timeframe and all the safety events will be attributable to treatment (as opposed to the primary estimand (estimand 1) where only events that happen within the 5 half-lives CCI CCI post last dose will be attributable to treatment due to while on treatment strategy).

Table 2 Estimand 1a

Estimand 1a - Additional estimand for the primary objective (safety)	
Clinical question of interest	What is the long-term safety of a range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments in participants with moderate to severe AtD as measured by occurrence of AEs, SAEs, AESI, discontinuation from study treatment due to AEs; regardless of discontinuation of investigational treatment or use of rescue therapy? Rationale: The study is designed to evaluate the long-term safety of a range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments. It is important to evaluate the risk-benefit of GSK1070806 irrespective of permanent treatment discontinuation or use of rescue therapy. 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	A range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments.
Endpoint	Incidence of: • AEs • SAEs. • AESI. • Discontinuation from study treatment due to AE.
Population	Participants with moderate to severe AtD who have previously been treated with medicated topical treatments only or 1 biologic therapy (in addition to GSK1070806 if the participant received active treatment in their qualifying phase 2 parent study (219538)).
Strategy for ICEs	ICEs: • Permanent treatment discontinuation **Strategy: Treatment policy;** all data collected after the ICE (i.e., any safety events which occur post ICE) will be included in summaries • Use of rescue therapy for AtD **Strategy: Treatment policy;** all data collected after the ICE (i.e., any safety events which occur post ICE) will be included in summaries

Estimand 1a - Additional estimand for the primary objective (safety)	
	• 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 study medication) **Strategy: Treatment policy (in line with the strategy for the ICE of treatment discontinuation);** all data collected after the ICE (i.e., any safety events which occur post ICE) will be included in summaries. Summaries will include all safety events regardless of whether the ICE happened within the 5 half-lives (16 weeks) post last dose or outside of the 5 half-lives timeframe.
Population-level summary	Number and percentage of participants in each treatment condition.

1.1.4. Estimand Strategy for the Secondary Objectives (Efficacy)

Table 3 Estimand 2

Primary estimand for the binary and continuous secondary efficacy objectives	
Clinical question of interest	What is the long-term efficacy of range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments in participants with moderate to severe AtD, irrespective of permanent treatment discontinuation or use of rescue therapy for AtD? Rationale: The study is designed to evaluate the long-term efficacy of range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments. This estimand provides evidence of efficacy regardless of whether the participants took the drug as per the protocol and is most closely reflective of usual clinical practice.
Treatment Condition	A range of doses and regimens of SC GSK1070806 with or without use of non-medicated background treatments regardless of permanent treatment discontinuation or use of rescue therapy for AtD (treatment policy strategy).
Endpoints	Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* • PP-NRS Reduction of ≥4 points Achieving a maintained response (for binary endpoints) for at least 16/32/48 and every 48 weeks thereafter after first response in: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline*

Primary estimand for the binary and continuous secondary efficacy objectives	
	PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.
Population	Participants with moderate to severe AtD who have previously been treated with medicated topical treatments only or 1 biologic therapy (in addition to GSK1070806 if the participant received active treatment in their qualifying Ph2 parent study (219538)).
Strategy for ICEs	ICEs: • Permanent treatment discontinuation for any reason **Strategy: Treatment policy (for both continuous and categorical endpoints)**; all data collected after the ICE will be included in summaries. • Use of rescue therapy for AtD **Strategy: Treatment policy (for both continuous and categorical endpoints)**; all data collected after the ICE will be included in summaries. • 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 study medication) **Strategy: Hypothetical (for both continuous and categorical endpoints)**; data collected after the ICE will not be included in summaries, and outcomes will be assumed to be similar to participants who did not experience the ICE.
Population-level summary	• Number and percentage of participants in each treatment condition achieving an endpoint (for binary endpoints: IGA score of 0 or 1, EASI Reduction of ≥75% from Baseline, PP-NRS Reduction of ≥4 points) • Mean and 95% CIs (for continuous endpoints: PCFB EASI).

*Please refer to Section 4.1.2 for baseline definitions.

1.1.5. Estimand Strategy for the Exploratory Objectives (Efficacy)

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

1.2. Study Design

At the time of the finalization of this document, the GSK1070806 AtD program had been terminated. The only ongoing parent study at that time was the Ph2b dose-ranging study 219538, therefore, the terminology "parent study" refers only to study 219538.

[redacted]

Design Features	• A long-term extension (LTE) study to evaluate the safety and efficacy of a range of doses of GSK1070806 (CCI [redacted]) in eligible participants, with moderate to severe AtD who have completed qualifying Ph2 parent GSK AtD clinical studies, that in the opinion of the investigator may benefit from treatment, and have provided consent to the LTE. • The study will have a maximum 5 years of treatment period and a CCI [redacted] safety follow up period. • Participants from one or more parent studies could roll over to the LTE. • Blinding to dose and frequency will be maintained to avoid unblinding bias until respective Ph2 parent study is analyzed or reported (i.e. (double blinded study until Ph2 parent study has reported out and open-label afterwards), except for non-responders at [redacted] of the qualifying

Overview of Study Design and Key Features	
	parent study (219538) who will be placed on the top dose upon entering the LTE. • Treatment allocation in the LTE is based on responder/non-responder study at primary analysis timepoint in the parent study (e.g. achieving EASI75 or IGA0/1 at W16 in Ph2b dose ranging study 219538).
Study intervention	• The below study interventions can be administered in the LTE, depending on the study interventions applicable in the parent study: • CCI [redacted] • Placebo • For the CCI [redacted] regimen treatments (*), placebo injection will be CCI [redacted] of parent study (219538) until the parent study has reported out. • Medicated topical treatments (such as low and moderate TCS) will be permitted as concomitant treatment for AtD symptoms during this study.
Study intervention Assignment	• There is no randomisation in the LTE study but rather treatment allocation. • Responders on active treatment from the qualifying Ph2 parent studies, defined as participants achieving IGA 0/1 or EASI 75 response at primary analysis time-point, will maintain the same dose during the LTE, to better understand long-term maintenance of response. • Non-responders in the qualifying Ph2 parent studies, will be allocated to the top dose to increase the probability of achieving responder status. • From [redacted] of the LTE, participants on rescue therapy that start losing response (i.e. participants unable to maintain the IGA 0/1 or EASI 75 response after having at least 2 weeks of TCS high potency treatment) will have the opportunity to receive the top dose.
Interim Analysis	• Unblinded analyses may be conducted throughout the LTE to support regulatory interactions, internal decision making and discussion about the development plans. • Unblinded interim data from the LTE study is planned to be reviewed at the key milestones from the parent study (219538).Further details are provided in the Section 4.7 (Interim Analyses).
Analyses	• Final analysis: when the last participant completes their Week 280 visit or withdraws from the study prior to Week 280. • All analyses are descriptive in nature.

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested as this study is designed to describe the long-term safety and efficacy of GSK1070806.

2.1. Multiplicity Adjustment

Multiplicity adjustment is not applicable.

3. ANALYSIS SETS

Table 4 Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility when rolling over from the parent study to the LTE.	Study Population
Enrolled	All participants who signed the ICF and entered the LTE 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
Assigned	All participants who were assigned to study intervention in the LTE study.	Study Population
Safety	All assigned participants who receive at least 1 dose of study intervention in this LTE study. Participants will be analyzed according to the intervention they actually received.	Safety Efficacy PROs Study Population
PD	All participants in the Safety analysis set who had at least 1 non-missing PD assessment. Data will be reported according to the actual study intervention.	PD
PK	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values). Data will be reported according to the actual study intervention.	PK

Analysis Set	Definition / Criteria	Analyses Evaluated
Immunogenicity	All participants in the Safety analysis set who had at least 1 Immunogenicity sample collected with analysis result. Participants will be analyzed according to the intervention they actually received.	Immunogenicity

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

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Due to the 220723 study being terminated, the statistical analysis will be performed only on primary and secondary endpoints (as defined in Section 1.1.1) as well as a subset of exploratory endpoints (as defined in Section 4.6). Following the study termination, only the primary estimand will be considered for analysing safety (Estimand 1) and efficacy (Estimand 2) endpoints. No summaries will be provided for the additional estimand for safety (Estimand 1a).

All analyses will be descriptive in nature and will be summarized using appropriate summary statistics and listings. Further details will be given in the OPS.

All the endpoints will be summarised and presented for the following treatment arms, defined as the treatment arms in the qualifying parent study (219538) and the LTE:

- Top dose (parent study) – Top dose (LTE)
- Intermediate dose 1 (parent study) – Intermediate dose 1 (LTE)
- Intermediate dose 2 (parent study) – Intermediate dose 2 (LTE)
- Intermediate dose 3 (parent study) – Intermediate dose 3 (LTE)
- Intermediate dose 1 (parent study) – Top dose (LTE)
- Intermediate dose 2 (parent study) – Top dose (LTE)
- Intermediate dose 3 (parent study) – Top dose (LTE)
- Placebo (parent study) – Placebo (LTE)
- Placebo (parent study) – Top dose (LTE)

The above treatment arms may be pooled together for the purpose of reporting the study if appropriate, e.g. if the number of participants in some of the treatment arms is low. For participants with dosing errors in the parent (219538) study, the treatment allocation

when rolling over to the LTE will be based on the actual treatment received in the parent study rather than randomised treatment (more detail in Appendix 1, Section 6.1.5).

The statistical analysis will be performed according to the Analysis Sets Table 4 in Section 3.

Participants with dose escalation in the LTE

For safety summaries, participants who change doses during the LTE will be included in the treatment arm of the highest dose they received (top dose):

- For instance, if a participant was on a CCI in the parent study, was a responder at W16 in the parent study, and therefore assigned to CCI dose in the LTE and got escalated to the top dose, they would be counted in the CCI (parent) – CCI (LTE) treatment arm.

Sensitivity analysis of safety (i.e. including these participants in the original treatment arm of the LTE) may be provided if deemed necessary.

For the statistical analysis to assess efficacy, participants in the LTE who change doses will be included in the treatment arm of the highest dose they received (top dose) once the escalation to top dose occurred and in the original treatment arm prior to that. For instance, if dose escalation occurred at Week 48, the participant will be included in the original treatment arm prior to Week 48 and in the top dose on and after W48:

- For example, if a participant was on a CCI in the parent study, was a responder at W16 in the parent study and therefore assigned to CCI dose in the LTE, they would be counted in the CCI (parent) – CCI (LTE) treatment arm prior to escalation to the top dose and in CCI (parent) - CCI (LTE) treatment arm on and after escalation to the top dose occurred.

Participants with incorrect dosing in the LTE

For safety summaries, participants who were dosed incorrectly will be included in the treatment arm of the highest dose they received (regardless of whether a correct dose has been administered after the incorrect dose). As the treatment arms represent the participant journey and consist of the treatment received in the parent and in the LTE, in the highly unlikely scenario where the participant journey is not reflective of any of the treatment arms specified, the participant treatment arm would be based only on the treatment they received in the LTE (and the parent treatment arm would be set to be the same as the treatment arm in the LTE).

- For instance, if a participant was on a CCI in the parent study, was a responder at W16 in the parent study, assigned to CCI dose in the LTE and got CCI by error, the participant would be counted in the CCI (parent) – CCI (LTE) treatment arm (as this patient journey matches the existing treatment arm).
- For instance, if a participant was on a CCI in the parent study, was a responder at W16 in the parent study, assigned to CCI dose in the LTE and got CCI by error , the participant would be counted in the CCI (parent) – CCI (LTE) treatment arm (as there is no treatment arm and patient journey corresponding to CCI (parent)

– CCI (LTE), the participant would be counted towards the treatment arm they receive in the LTE and the treatment arm in the parent would be set to match the one in the LTE).

For statistical analyses to assess efficacy, participants who were dosed incorrectly in the LTE will be included in the original treatment arm prior to receiving an incorrect dose and in the treatment arm as the highest dose they received on and after the timepoint when the incorrect dosing has occurred (regardless of whether a correct dose has been administered after the error dose).

For instance, if an incorrect dosing occurred at Week 48, the participant will be included in the original treatment arm in the LTE prior to Week 48 and in the highest dose they received on and after W48. As the treatment arms represent the participant journey and consist of the treatment received in the parent and in the LTE, in the highly unlikely scenario where the participant journey is not reflective of any of the treatment arms specified, the participant treatment arm would be based only on the treatment they received in the LTE (and the parent treatment arm would be set to be the same as the treatment arm in the LTE).

- In a scenario where a participant was on a CCI dose in the LTE prior to an incorrect administration of CCI dose at W48, the participant would be summarized in the CCI (parent) - CCI (LTE) treatment arm prior to W48 and in the CCI (parent) - CCI (LTE) treatment arm on and after Week 48 (as this matches one of the existing treatment arms).
- In a scenario where a participant was on a CCI dose in the LTE prior to an incorrect administration of CCI dose at W48, the participant would be summarized in the CCI (parent) - CCI (LTE) treatment arm prior to W48 and in the CCI (parent) - CCI (LTE) treatment arm on and after Week 48 arm (as there is no treatment arm and patient journey corresponding to CCI (parent) – CCI (LTE), the participant would be counted towards the treatment arm they receive in the LTE and the treatment arm in the parent would be set to match the one in the LTE).
- In a scenario where a participant was on CCI dose prior to an incorrect administration of CCI dose at W48, the participant would be summarized in the CCI (parent) - CCI (LTE) treatment arm prior to W48 and in the CCI (parent) - CCI (LTE) treatment arm on and after Week 48 (i.e same treatment arm both before and after the incorrect administration).

If a participant received an incorrect dose on Day 1 of the LTE (initial dose) and then received planned treatment at the next visits, the approach for safety and efficacy to be followed is the same as outlined above (i.e the treatment arm will be assigned as the highest dose they received):

- In a scenario where Day 1 incorrect dosing was CCI and then the participant received the planned dosing of CCI, the participant will be included in the CCI (parent) - CCI (LTE) treatment arm on Day 1 and all the subsequent visits.
- In a scenario where Day 1 incorrect dosing was CCI and then the participant received the planned dosing of CCI, the participant will be included in the CCI (parent) - CCI (LTE) treatment arm on Day 1 and all the subsequent visits.

- In a scenario where Day 1 incorrect dosing was CCI g and then the participant returned to their original dose of CCI, the participant will be counted towards the CCI (parent) - CCI (LTE) treatment arm on Day 1 and all the subsequent visits).

Participants who prematurely withdrew from study will not be replaced as this is an LTE study. No stratification will be done in the LTE as the patients have been stratified in the qualifying parent study.

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 statistical analyses will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC), R or other widely accepted statistical or graphical software as required. Data will be presented in listings, tables, and figures. Binary and categorical variables will be expressed as frequency counts and proportions, and continuous variables will be presented as mean with standard deviation or as median with interquartile range, depending on distribution.

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.

Participant-level data will be available interactively via RAPIDO Data Viewer at SAC.

4.1.2. Baseline Definition

4.1.2.1. Baseline definition for Safety

For safety analyses, parent study (219538) baseline will be used for all the treatment arms in the LTE. Please refer to Section 4.1.1. for the definition of treatment arms.

4.1.2.2. Baseline definition for Efficacy Endpoints and Patient Reported Outcomes (PROs)

For efficacy analyses, parent study baseline will be used for all the treatment arms in the LTE (i.e. same treatment arms as described in Section 4.1.1) to assess efficacy of endpoints that reflect change or percent change from baseline. Therefore, the baseline definition follows the same definition as the baseline definition in the parent study (219538) for all the treatment arms.

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day 1 pre-dose) in the parent study (219538). If there are multiple assessments of the same type collected at the same scheduled time, the average of these assessments will be used as the baseline.

If baseline data is missing, no derivation will be performed, and baseline will be set to missing.

For PP-NRS and SP-NRS baseline, the baseline score will be averaged from daily values from Day -7 to Day -1 of the parent study (219538) if ≥ 4 (out of 7) days are not missing. If only ≤ 3 days (out of 7) are available, baseline is set to missing.

4.1.3. Treatment Discontinuation Definition

The date of treatment discontinuation will be defined as the CCI after the date of the last dose of study intervention (i.e., date of last dose of study intervention + CCI). 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 their withdrawal from the study.

4.1.4. Intercurrent Events

4.1.4.1. Treatment Discontinuation

Table 5 ICE: Permanent Treatment Discontinuation Handling Strategies

Objective	Estimand	Estimand number	Strategy
Safety	Primary Estimand	Estimand 1	While on treatment
	Additional Estimand	Estimand 1a	Treatment policy
Efficacy	Primary Estimand	Estimand 2	Treatment policy (for both continuous and categorical endpoints)

Following this ICE under the while on treatment approach, any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives (CCI) timeframe) will be excluded. Any missing safety outcomes will not be imputed.

Following this ICE under the treatment policy strategy, for both safety and efficacy, all data collected after the ICE will be included in summaries and will be used. Any missing safety outcomes will not be imputed. Missing data in binary efficacy endpoints will be imputed as non-response prior to subject withdrawal due to the early study termination. Any missing binary data after the subject withdrawal due to the early termination will not be imputed.

4.1.4.2. Treatment discontinuation due to extreme administrative and operational disruptions

Table 6 ICE: Treatment Discontinuation Due to Extreme Administrative and Operational Disruptions Handling Strategies

Objective	Estimand	Estimand number	Strategy
Safety	Primary Estimand	Estimand 1	While on treatment
	Additional Estimand	Estimand 1a	Treatment policy
Efficacy	Primary Estimand	Estimand 2	Hypothetical (for both continuous and categorical endpoints)

The same approach as the one outlined in Section 4.1.4.1 will be followed for while on treatment and treatment policy strategies.

4.1.4.3. Use of rescue therapy for AtD

Table 7 ICE: Use of Rescue Therapy for AtD

Objective	Estimand	Estimand number	Strategy
Safety	Primary Estimand	Estimand 1	While on treatment
	Additional Estimand	Estimand 1a	Treatment policy
Efficacy	Primary Estimand	Estimand 2	Treatment policy (for both continuous and categorical endpoints)

The same approach as the one outlined in Section 4.1.4.1 will be followed for while on treatment and treatment policy strategies.

Allowed rescue medication

During this study, rescue therapy may be needed if the participant experiences clinical worsening of symptoms that are intolerable. At any point in the study, rescue treatment for AtD (high potency topical therapies) may be provided to participants during the study. Investigators will be required to perform an IGA assessment prior to starting rescue

treatment and initiate rescue treatment only in participants who either have an IGA score = 4 or have intolerable symptoms.

In participants who do not improve sufficiently, with the medicated topical treatments (such as low and moderate TCS) after at least 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, this will lead to discontinuation of study drug, except for a short-term use of oral corticosteroids (≤10 days). If a participant requires any of the prohibited medications to address an urgent clinical need, these should be discussed with Medical Monitor if this is possible without delaying the adequate treatment of the participant. Section 6.9.2 of the Protocol Amendment 1 outlines the list of prohibited medications. From [redacted] of the LTE, the participants on rescue therapy that start losing response will have the opportunity to receive the top dose. Loss of response is defined as participants unable to maintain the IGA 0/1 or EASI 75 response after having at least 2 weeks of TCS high potency treatment.

As Protocol Amendment 1 is not approved at the same time in all the countries, there will be a period of time when the study operates under 2 protocol versions (the initial protocol version V2.0 (28 November 2023) and Protocol Amendment 1) with all the countries eventually approving and moving onto Protocol Amendment 1. Under Protocol V2.0 (28 November 2023), participants on rescue therapy that started losing response had the opportunity to receive top dose after [redacted] of the LTE. Therefore, there will be situations for some participants in the study who's first opportunity to be escalated to the top dose was [redacted], whereas for other participants it would be earlier at [redacted] Such participants will be treated in the same way in the statistical analysis.

4.2. Primary Endpoint(s) Analyses

Due to the 220723 study being terminated, the statistical analysis for primary endpoints will be performed only on primary endpoints as defined in Section 1.1.1 as well as endpoints necessary to meet regulatory requirements. Following the study termination, only the primary estimand (Estimand 1) will be considered for analysing the safety endpoints. No summaries will be provided following the additional estimand (Estimand 1a).

The primary objective of this study is to assess long-term safety, which will be evaluated by the incidence of:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Adverse events of special interest (AESI)
- Discontinuation from study treatment due to AEs.

Planned analyses of these endpoints are described in Section 4.5 (Safety Analyses). Data will be summarized using frequency counts, proportions and summary statistics. Incidence rates and exposure-adjusted incidence rates will be calculated for AEs, SAEs,

and AESIs as the study is terminated. Laboratory data, immunogenicity data, ECG data, and vital signs will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards.

Please refer to Section 1.1.1 for primary endpoints, Section 1.1.3 for estimands and Section 4.1.1 for definition of treatment arms used for describing the data.

Please refer to Section 4.1.1 for more detail on describing the data for participants who change dose during the LTE as well as for participants with dosing errors.

4.3. Secondary Endpoint(s) Analyses

Due to the 220723 study being terminated, the statistical analysis will be performed only on secondary endpoints (as defined in Section 1.1.1). No graphs will be produced.

The secondary objective of this study is to evaluate long-term efficacy of GSK1070806 in participants with moderate to severe atopic dermatitis.

The secondary endpoint analyses will be based on the Safety Analysis Set, unless otherwise specified. Data for each secondary endpoint will be summarised using summary statistics, for each scheduled time-point.

The following summaries will be provided in treatment arms defined by the treatment received in the qualifying Ph2 parent study (219538) and the treatment received in the LTE (Section 4.1.1):

- Binary endpoints will be summarised as frequency counts and proportions;
- Continuous endpoints will be summarised as mean with standard deviation or as median with interquartile range, depending on distribution.

Please refer to Section 4.1.1 for more detail on describing the data for participants who change dose during the LTE as well as for participants with dosing errors.

4.3.1. Secondary endpoint(s)

Table 8 Secondary Clinical Efficacy and Patient Reported Outcome (PRO) Endpoints

Clinical Efficacy Endpoints
Continuous
PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.
Binary
Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* Achieving a maintained response (for binary endpoints) for at least 16/32/48 and every 48 weeks thereafter after first response in: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline*
Patient Reported Outcomes (PRO) Endpoints
Binary
Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: PP-NRS Reduction of ≥4 points

*Please refer to Section 4.1.2 for baseline definitions.

4.3.1.1. Definition of Secondary Endpoints

4.3.1.1.1. Definition of IGA

IGA (Investigators' Global Assessment) for AtD is a measure of overall disease severity at the time of assessment and is the established FDA regulatory endpoint.

IGA (continuous score) ranges 0-4, where 0 = clear skin, 1 = almost clear, 2 = mild, 3 = moderate, 4=severe).

IGA can be presented as binary score (e.g. IGA0/1) with the interpretation being the percentage of patients that achieved IGA score of 0 or 1.

The IGA must be conducted prior to conducting the EASI assessment.

Assessors must be trained and certified by an approved vendor at the Sponsor's direction prior to conducting this assessment. A single assessor (if possible) should be assigned for each participant throughout the study for as many visits as possible, to avoid inter-assessor variability in scoring.

4.3.1.1.2. 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.

EASI can be presented as binary score (e.g. EASI75) with the interpretation being the percentage of patients that achieved reduction of ≥75% relative to their baseline score.

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

4.3.1.1.3. Peak Pruritus Numerical Rating Scale (PP-NRS)

PP-NRS is a patient reported measure (PRO) 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].

Participants need to complete the assessment once daily in their e-Diary at approximately the same time each day up to Week 16. The weekly score is based on the average of daily PP-NRS scores for maximum itch intensity reported during the 7 days prior. The weekly

score will be set to missing if there are fewer than 4 daily scores recorded in the 7 days prior.

After Week 16, the frequency of administration will be reduced from daily assessments to assessments only at scheduled visits.

4.3.1.2. Main analytical approach

All the analyses will be descriptive in nature and will be summarized using appropriate summary statistics, graphs, and listings. The summaries will be provided in treatment arms defined by the treatment received in the parent study (219538) vs the treatment received in the LTE (Section 4.1.1). The treatment arms may be pooled together for the purpose of reporting the study if appropriate, e.g. if the number of participants in some of the treatment arms is low.

4.3.1.2.1. Binary Endpoints

The following secondary endpoints will be analysed as binary endpoints:

Clinical Efficacy Endpoints (binary)
Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* Achieving a maintained response (for binary endpoints) for at least 16/32/48 and every 48 weeks thereafter after first response in: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline*

*Please refer to Section 4.1.2 for baseline definitions.

Patient Reported Outcomes (PRO) Endpoints
Binary
Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • PP-NRS Reduction of ≥4 points

*Please refer to Section 4.1.2 for baseline definitions.

Binary endpoints will be summarised using counts, proportions, and percentage of the number of participants in each treatment condition meeting the specified criteria.

Achieving a response (for binary endpoints)

Achieving a response will be assessed for each of the following endpoints:

- IGA score of 0 or 1
- EASI Reduction of ≥75% from Baseline
- PP-NRS Reduction of ≥4 points

To summarise achieving a response:

- The proportion of responders will be presented at each specified timepoint for each of the treatment arms.
    - Treatment arms will be presented as defined in the parent study and the LTE (Section 4.1.1).
    - The denominator is defined as the number of participants (in each treatment arm) with available data at the specified visit.
    - Please refer to Section 4.1.1 for more detail on describing the data for participants who change dose during the LTE as well as for participants with dosing errors.
    - A participant will be regarded as a responder based on the specified timepoint only, regardless of whether they were a responder in the parent study at the primary timepoint (Week 16 in the 219538) or any timepoints in the LTE prior to the specified timepoint.

Achieving a maintained response (for binary endpoints)

Maintenance of response will be assessed for each of the following endpoints:

- IGA score of 0 or 1
- EASI Reduction of ≥75% from Baseline

A participant is defined as having achieved a "maintained response" at a visit of interest if both of the following criteria are met:

- A participant was a responder at Week 16 in the LTE
- The participant remained a responder on all the subsequent visits between Week 16 and a visit of interest.

Given this definition, the earliest timepoint maintenance of response will be assessed at is CCI

To characterize achieving a maintained response (for each of IGA0/1 and EASI75), a summary table of frequency counts (and proportions) will be provided for each of the specified timepoints and treatment arms to describe how many participants keep maintaining the response. For assessment of proportions, the denominator is defined as the number of participants with available data in the corresponding treatment arm at the specified visit.

Treatment arms will be presented as defined in the parent study and the LTE (Section 4.1.1). Escalation to the top dose will be considered as a loss of response (i.e., participants who were maintaining the response and then got escalated to the top dose will not be counted towards the maintenance of response once the escalation to the top dose occurred).

Participants with dosing errors who incorrectly received 200mg dose (top dose) and received the planned dose at the next visit will be treated using the same approach as escalation to top dose.

4.3.1.2.2. Continuous Endpoints

The following secondary endpoints in will be analysed as continuous endpoints:

Clinical Efficacy Endpoints (continuous)
PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.

Continuous endpoints will be summarised using mean and 95% CIs. The analysis will be performed at each timepoint of interest (Weeks 16, 32, 48 and every 48 weeks thereafter).

Line graph based on the combined data from the parent study and the LTE will be produced to illustrate PCFB in EASI at the key timepoints in the parent study and the specified timepoints in the LTE. Treatment arms will be presented as defined in the parent study and the LTE. For generation of the line graph only, cases where a participant switched arm to receive the top dose throughout the LTE will be counted towards the denominator in the initially allocated arm in the LTE (a footnote will be provided).

4.3.1.3. Sensitivity analyses

There are no planned sensitivity analyses for the secondary endpoint.

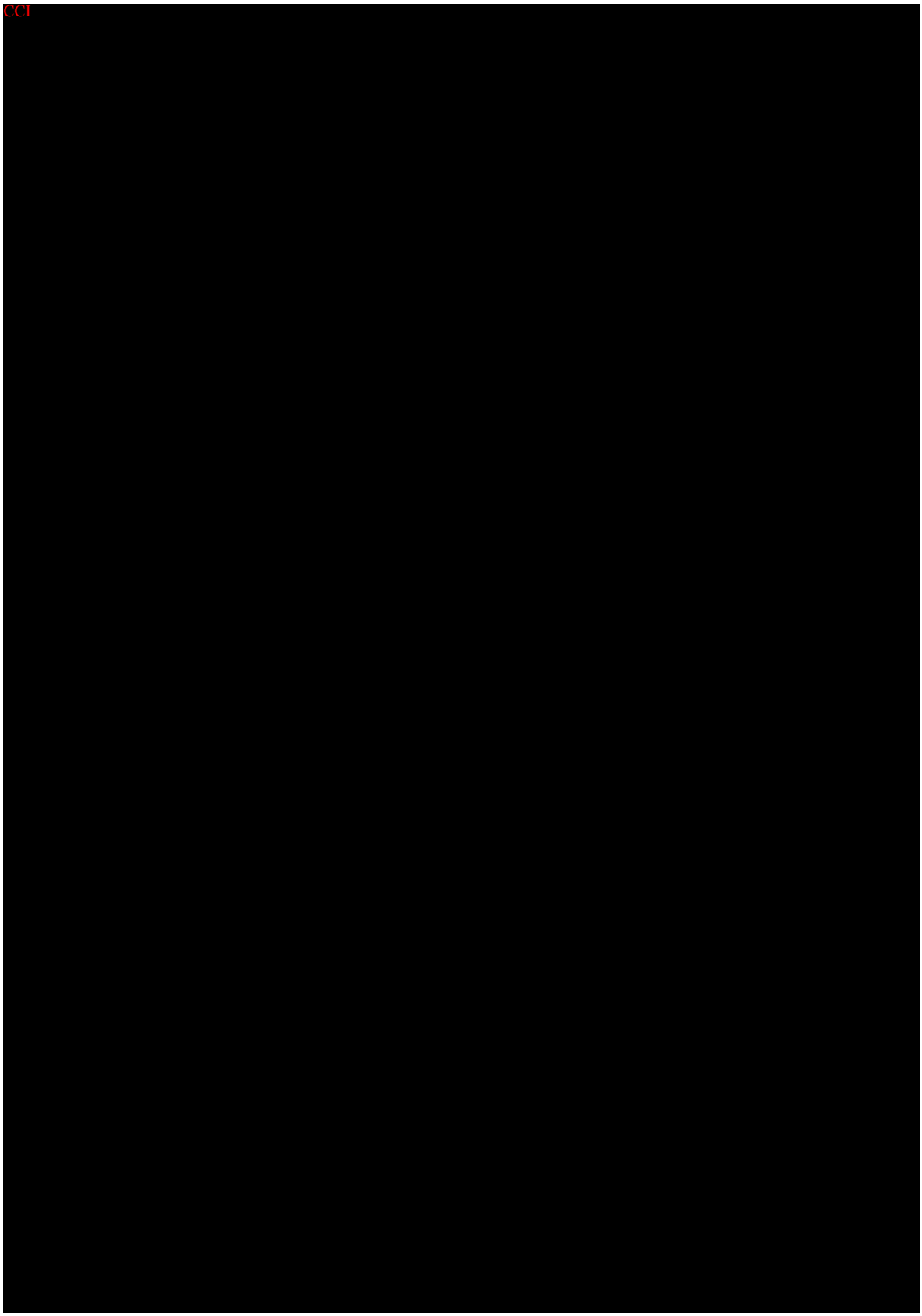
4.3.1.4. Additional estimands

No additional estimands are considered for the secondary objective.

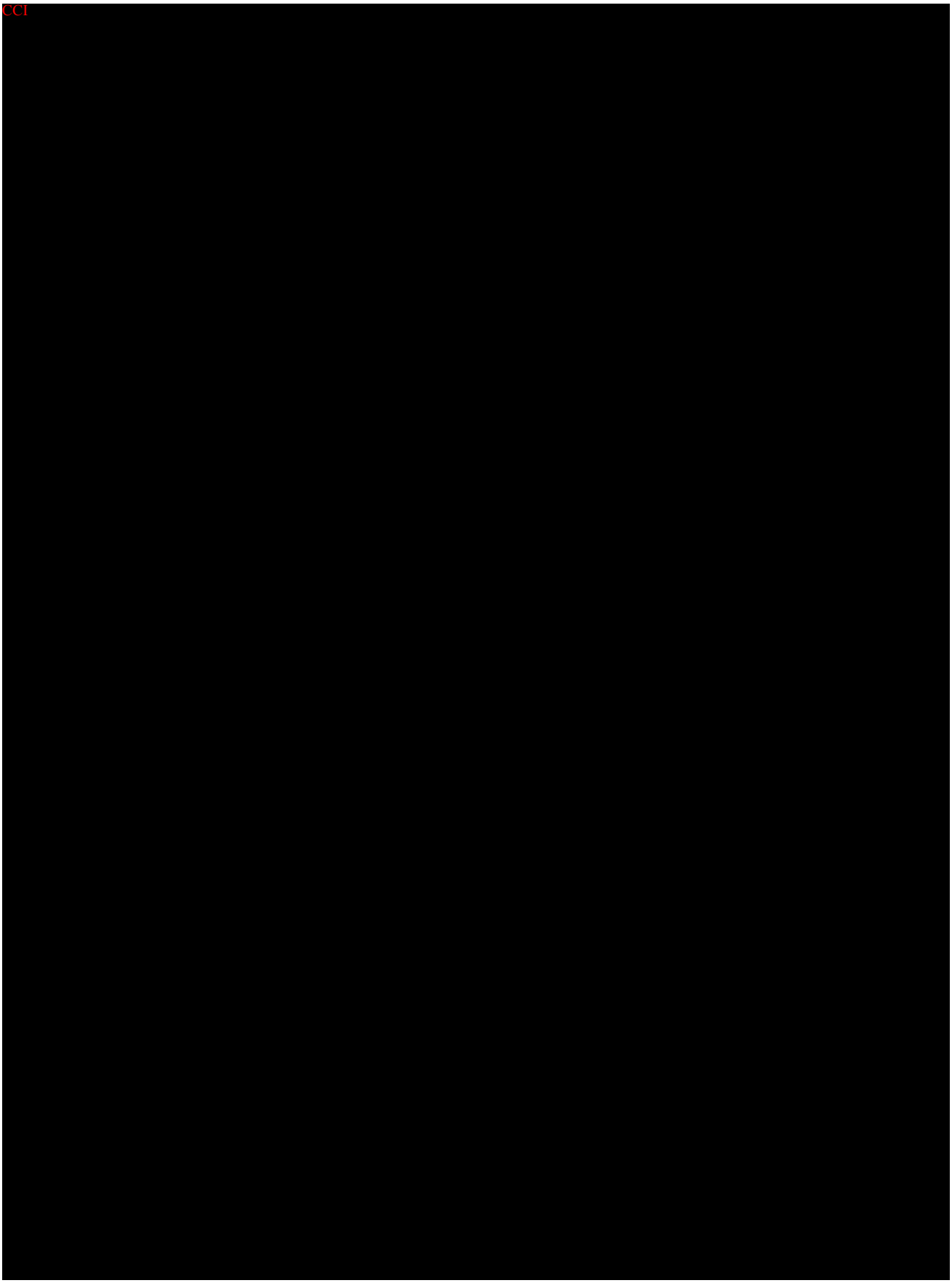
4.4. Exploratory Endpoint Analyses

CCI [redacted]

CCI



CCI



CCI

4.4.2. Patient Reported Outcomes (PROs) Endpoints

Patient Reported Outcomes (PROs) Endpoints
Continuous
CFB to Weeks 16, 32, 48 and every 48 weeks thereafter in: • DLQI • POEM • WPAI-AD • HADS • PROMIS-Sleep Disturbance 8b CFB to Week 16 in: • SP-NRS
Binary
At Week 16,32, 48 and every 48 weeks thereafter achieving: • PP-NRS Reduction of ≥3 points • PP-NRS score of 0

4.4.2.1. Definition of Endpoints

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
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, 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.

Planned timepoints for all the PRO assessments are provided in the SoA Section 1.3 in the Protocol.

For PP-NRS, participants need to complete the assessment once daily in their e-Diary at approximately the same time each day up to Week 16. The weekly score is based on the average of daily PP-NRS scores for maximum itch intensity reported during the 7 days prior. The weekly score will be set to missing if there are fewer than 4 daily scores recorded in the 7 days prior. After Week 16, PP-NRS will only be assessed during the on-site visit according to SoA Section 1.3 in the Protocol.

For SP-NRS, participants need to complete the assessment once daily in their e-Diary at approximately the same time each day up to Week 16 and are asked the following question in their local language: "Please rate your skin pain severity by circling the

number that best describes your worst level of skin pain (for example, discomfort or soreness) in the past 24 hours."

4.4.2.2. Main Analysis

Summary statistics per treatment arm in the LTE vs treatment arm in the parent study will be provided for all the exploratory PRO endpoints as outlined in Section 4.3.1.2 (section 4.3.1.2.2 for continuous endpoints and section 4.3.1.2.1 for binary endpoints).

4.4.3. PK, PD concentration-time profile and ADA formation

4.4.3.1. Pharmacokinetic Analyses (PK)

CCI [redacted]

4.4.3.2. Pharmacodynamic Analyses (PD)

CCI [redacted]

4.5. Safety Analyses

Due to the 220723 study being terminated, the statistical analysis for primary endpoints will be performed only on primary endpoints as defined in Section 1.1.1 as well as endpoints necessary to meet regulatory requirements. Following the study termination, only the primary estimand (Estimand 1) will be considered for analysing the safety endpoints. No summaries will be provided following the additional estimand (Estimand 1a).

Planned timepoints for all safety assessments are provided in the SoA Section 1.3 of the Protocol. The participant will be encouraged to always contact the site in case of any AE.

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified. 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. Data will be summarized using frequency counts, proportions and summary statistics. Incidence rates and exposure-adjusted incidence rates will be calculated for AEs, SAEs, and AESIs. Laboratory data, immunogenicity data, ECG data, and vital signs will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards.

As per the estimands for the safety objectives detailed in Section 1.1.3, all primary safety analyses will use the “while on treatment” approach, i.e. only safety data (events, ECG, lab data) reported within 5 half-lives (CCI [redacted]) post last dose will be included (any safety events that happen after CCI [redacted] after the last dose will be excluded). Missing safety data will not be imputed.

AEs in the LTE will be summarised and presented as AEs that occurred in the LTE with the start date in the LTE. AEs which started during the parent Ph2 (219538) study and are still ongoing at the start of the LTE will be recorded in the LTE eCRF and presented separately as a listing by treatment received in the parent study and treatment received in the LTE. AEs and SAEs that occurred and resolved in the parent Ph2 study will be considered medical history in the LTE on a case by case basis. All the safety summaries will be provided in the treatment arms defined by the treatment received in the parent study (219538) vs the treatment received in the LTE as described in Section 4.1.1. Participants in the LTE who change doses during the LTE due to rescue will be included in the treatment arm as the highest dose they received (top dose), please refer to Section 4.1.1 for more detail.

A supplementary analysis will be performed on key safety outputs (AEs and SAEs by SOC and PT) using the "treatment policy" approach, i.e. all safety events reported in the study will be included. Missing safety data will not be imputed. In the event of database lock occurring whilst there are any ongoing SAEs throughout the LTE, 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

The duration of exposure to study treatment in days, defined as ([treatment stop date – treatment start date] + CCI [redacted]) will be summarized. Last dosing date will be used as treatment stop date. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated.

Participants who received treatment allocation but do not have a treatment start date will be categorized as having zero days of exposure.

For participants with treatment stop date missing, the stop date will be imputed as Week 264 visit date or early discontinuation/withdrawal (EW) date, whichever is earlier.

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.

All AEs and SAEs will be collected from the start of study intervention until the follow-up visit at the time points specified in the SoA in the protocol. All AE and SAE summaries will be based on study intervention (i.e. treatment) emergent events unless otherwise specified. AEs which started during the parent Ph2 (219538) study and are still ongoing at the start of the LTE will be recorded in the LTE eCRF and presented

separately as a listing by treatment received in the parent study and treatment received in the LTE (as described in the section above).

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., AEs with missing relatedness will be considered related to study intervention and included in the table summarising drug-related AEs. 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, and AEs leading to permanent discontinuation of study treatment will be produced.

Separate summaries of the number and percentage of participants 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 Estimand 1 and 1a. 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 ≥ 5% of the participants or above in any treatment group (as defined by the treatment arms in the parent study and treatment arms in the LTE) 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. A summary of serious fatal and non-fatal drug-related AEs by PT and ordered by overall incidence will be produced.

The following summaries will be provided for the SAEs:

- Summary of SAEs by system organ class (SOC) and preferred term (PT) and maximum intensity
- Summary of SAEs by System Organ Class and Preferred Term (Number of Participants and Occurrences)
- Summary of Serious Fatal and Non-Fatal Drug-Related Adverse Events by Overall Incidence

The summaries relating to any SAEs will be repeated for Estimand 1 and 1a.

A summary of AEs by ADA status (Positive [Treatment-induced or boosted participants] and Negative [Treatment-induced negative or treatment-unaffected participants]) may be

produced. If the ADAs have an impact on PK, efficacy, or safety, corresponding figures to these summaries will be produced.

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 within 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 adverse events. 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 participants with the event, number of events, event characteristics (% based on all participants), event characteristics (% based on participants with the event), number of occurrences (% based on all participants), number of occurrences (% based on all participants with the Event), outcome (% based on all participants), outcome (% based on participants with the Event), maximum intensity (% based on all participants), maximum intensity (% based on all participants with the event), action taken (% based on all participants), and action taken (% based on all participants 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 AESI 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.

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. A footnote will be included to highlight that small variations may be observed due to the change in the central lab between the parent study (219538) and the LTE. A listing including normal ranges from the parent study (baseline) and LTE study (post-baseline) will be provided for the laboratory parameters.

Grade shift tables will be presented for all the variables where the grades are available. Urinalysis 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 CTCAE 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 liver events. Possible Hy's law cases are defined as any elevated alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN or ALT ≥3 × ULN and international normalized ratio (INR) >1.5. Total bilirubin ≥2×ULN can be within 28 days following the ALT elevation. All liver events will be summarised together.

eDISH plot of liver parameters (Max ALT (/ULN) plotted against Max Total Bilirubin (/ULN)) might be provided and generated as following:

- Based on each treatment arm separately (i.e. each treatment arm presented in an individual plot)
- Based on all treatment arms (i.e. all treatment arms presented on the same plot with each treatment arm presented with a designated colour/symbol).

The total bilirubin measurement must be within 28 days following the ALT elevation.

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

- Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
- Example 2: 1 Significant Digit = '> x' becomes x + 0.1
- Example 3: 0 Significant Digits = '< x' becomes x – 1 Vital Signs

Vital signs data will be presented in tabular format and summarized descriptively according to GSK standards.

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 10.

Table 10 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

4.5.3.2. ECG

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 in the parent study (219538).

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 11 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 3 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

Following 220723 early study termination, analyses outlined in this section will not be provided.

The subgroups defined in Table 12 are of interest in this study. A separate exploratory analysis using descriptive statistics of secondary efficacy endpoints (IGA0/1, EASI75, PP-NRS4) within each subgroup will be carried out.

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.

Table 12 Definition of Subgroups

Subgroup	Categories	Rationale
Region	• Japan • China • Rest of World	Differential treatment effects by region are not expected. These analyses will inform regulatory submissions in China/Japan for Phase 3.
Previous treatment experience	• Biologic-naïve • Biologic experienced	Interest lies in exploring whether there is a difference in treatment benefit between groups.

In addition to the key efficacy endpoints listed above, the following summaries may be repeated:

- Frequency counts of EASI50/75/90 response
- Frequency counts of IGA scores and IGA0/1 response
- Frequency counts of PP-NRS4 response

4.6.2. Analyses to Support Regional Submission

Following 220723 early study termination, analyses outlined in this section will not be provided.

Since the study will be used to support China/Japan regulatory submission, descriptive analysis will be repeated for population, efficacy and safety analyses 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.

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

4.6.3. Pharmacokinetic and ADA analyses

Following 220723 early study termination, analyses outlined in this section will not be provided, except for the summary of ADA by planned time and treatment as well as immunogenicity incidence summary table. Following DIL 2.0 ADA samples are no longer collected. Therefore, any summaries will not include any data following DIL 2.0 (unless collected in error).

Serum GSK1070806 concentrations may be CCI [redacted] ***. Observed or predicted concentrations may be combined with efficacy, safety, and pharmacodynamic measures of interest to examine potential exposure response relationships. Details of this analysis will be described in a separate SAP and may be reported separately.***

The serum pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified. Missing serum 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 GSK1070806 pre-dose concentrations (Ctau) will be summarized (Geometric Mean, 95% CI, SD, Min, Max, Median) by treatment group and visit. Individual and mean/median pre-dose concentrations of GSK1070806 (stratified by treatment group)

will be plotted. Summary statistics/plots by regional subgroup (Section 4.6.1) may also be presented.

For PK samples taken at the time of confirmed positive ADA result, a summary of the individual neutralizing body titer, individual PK concentration as well as overall treatment group median and range for that time point will also be presented. The outputs and programming details of the analyses will be provided in the OPS.

4.6.4. Pharmacodynamic analyses

Following 220723 Study termination, analyses outlined in this section will not be provided.

Total IL-18 concentrations may be [redacted] ***Observed or predicted concentrations may be combined with pharmacokinetics, efficacy, and safety measures of interest to examine potential exposure response relationships. Details of this analysis will be described in a separate SAP and may be reported separately.***

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 total IL-18 concentration-time data will be summarized using Geometric Mean, 95% CI, SD, Min, Max, Median by treatment group and visit. Individual and mean/median profiles in serum over time (stratified by treatment group) will be plotted. Summary statistics/plots by regional subgroup (Section 4.6.1) may also be presented.

A Target Mediated Drug Disposition (TMDD) model developed using PKPD data from the parent study 219538 may be used to predict % reduction in free IL-18 from baseline [Target Engagement (TE)] over time for each participant. The baseline free IL-18 definition follows the same definition as the baseline definition in the parent study (219538). Predicted TE will be summarised by dosing regimen and visit. The logit transformation will be applied to TE prior to computing the summaries (Mean, 95% CI, Min, Max and Median). Summary statistics/plots by regional subgroup (Section 4.6.1) may also be presented.

4.7. Interim Analyses

After the study termination, unblinded interim data from the 220723 study will not be reviewed at any of the milestones from the parent study, and no further interim analyses in the 220723 LTE study will be conducted.

Unblinded interim data from the LTE study is planned to be reviewed at the following key milestones from the parent Phase 2b study 219538:

- When approximately 100 patients complete W4 visit. LTE data in scope: AE/SAEs;

- When approximately 67 biologic-experienced participants complete the primary W16 visit. LTE data in scope: AE/SAEs;
- When all participants complete W16 visit (this would be considered primary completion of Phase 2b study). LTE data in scope:
  - AE/SAEs
  - Achieving response at Weeks 16, 32, 48, and every 48 weeks thereafter in IGA0/1, EASI75, PP-NRS4;
  - PCFB in the EASI at Weeks 16, 32, 48 and every 48 weeks thereafter
  - PK, PD and ADA (GSK1070806 PK concentrations in serum over time, total IL-18 concentrations in serum over time, incidence of pre-existing ADAs, incidence of treatment-emergent ADAs)
- When all participants complete W28 follow-up visit (final Phase 2b study completion). LTE data in scope :
  - AEs, discontinuation from study treatment due to AEs, SAEs and adverse events of special interest (AESI)
  - Achieving response at Weeks 16, 32, 48, and every 48 weeks thereafter in IGA0/1, EASI75, PP-NRS4;
  - PCFB in the EASI at Weeks 16, 32, 48 and every 48 weeks thereafter

Decisions made at the parent study milestones above may impact the conduct of the LTE study. For instance, if the parent study is stopped for futility or the conclusion of the study means the compound does not progress to Phase 3, the LTE study will be stopped.

After the above, interim analyses will be conducted at the following milestones in the LTE study:

- When all participants (from the parent Ph2b 219538 study who rolled over to the LTE) complete W16 visit in the LTE. LTE data in scope:
  - AEs, discontinuation from study treatment due to AEs, SAEs and adverse events of special interest (AESI)
  - Achieving response at Weeks 16, 32, 48, and every 48 weeks thereafter in IGA0/1, EASI75, PP-NRS4;
  - Achieving a maintained response at Weeks 16, 32, 48, and every 48 weeks thereafter in IGA0/1, EASI75
  - PCFB in the EASI at Weeks 16, 32, 48 and every 48 weeks thereafter
- When all participants (from the parent Ph2b 219538 study who rolled over to the LTE) complete W52 visit
- At every 6 months intervals thereafter.

Additional interim analyses may take place to support regulatory interactions or internal decision making.

In addition, SRT will review blinded safety data on an ongoing basis throughout the study. Descriptive analyses will be performed at all the interim analysis milestones. There are no specific futility rules for the LTE study, but the protocol provides recommendations for handling non-response on an individual participant basis.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 28 November 2023).

There were no changes or deviations to the originally planned statistical analysis specified in the Protocol Amendment 1 (Dated: 2 August 2024).

5. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

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

6.1.1. Participant Disposition

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

6.1.2. 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.

A summary of atopic dermatitis history, including duration since diagnosis, and characteristics will be provided. 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.

Past medical conditions and current medical conditions as of Day 1 visit will be summarized separately.

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

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. 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 the 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 categorised in the protocol deviations dataset.

- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. The summary of concomitant medications will be provided by the corresponding level of Anatomical Therapeutic Chemical (ATC) classification and 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 Section 6.9 in the protocol.

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

The incidence of use of prohibited medications and Rescue Therapy will be summarized, overall and by topical and non-topical groups. Cumulative proportion of participants receiving prohibited medications / Rescue Therapy during the treatment period will be plotted.

6.1.5. Treatment arm definition for Safety, Efficacy and PROs for participants with dosing errors in the qualifying Ph2 study (parent)

For participants who were dosed incorrectly in the parent study (219538), the baseline of the parent study will be aligned with the actual treatment participants received in the parent study (rather than randomised treatment). Treatment allocation when rolling over to the LTE will also be based on the actual treatment received in the parent study rather than a randomised treatment. Below are some examples using hypothetical scenarios:

- A participant received a wrong (but protocol defined) dose on both Day 1 in the parent study (e.g. CCI instead of CCI and CCI in the parent study (e.g. CCI instead of CCI If the participant was a responder, he/she would be allocated to the arm in the LTE that corresponds to the actual treatment received in the parent study (CCI In this scenario, if the participant was a responder, he/she would be summarised in the CCI (parent) – CCI (LTE) treatment arm in the LTE. If the participant was not a responder, he/she would be summarized in the CCI (parent) – CCI (top dose) in the LTE.
- A participant received a wrong (but protocol defined) dose on Day 1 in the parent study (e.g. CCI instead of CCI and correct dose as per randomization at CCI in the parent study (e.g. CCI The actual arm for the participant in the parent study would be determined and mapped based on the PK/PD (e.g. CCI). If the participant was a responder, he/she would be allocated to the arm in the LTE that corresponds to the actual treatment received in the parent study (CCI In this scenario, if the participant was a responder, he/she would be summarised in the CCI (parent) – CCI (LTE) treatment arm in the LTE. If the participant was not

a responder, he/she would be summarized in the [redacted] (parent) – [redacted] (top dose) in the LTE.

6.1.6. Difference in the treatment arm allocation when rolling over to the LTE from the qualifying parent study, based on Protocol V2.0 (initial protocol) vs Protocol Amendment 1 (2 Aug 2024)

Prior to Protocol Amendment 1 (2 Aug 2024) implementation, under Protocol V2.0 (28 Nov 2023) participants who were on the placebo arm in the parent study would be allocated to the top dose when rolling over to the LTE, regardless of their responder status in the parent study. Due to Protocol Amendment 1 not being approved at the same time in all the countries, there will be a period of time where the study operates under two versions of the protocol. Therefore, there might be an unlikely scenario considering responders on placebo:

- Some of the placebo responders in the parent study will be allocated to top dose when rolling over to the LTE, i.e. country is still operating under the Protocol V2.0 (28 Nov 2023) version. Such participants will be summarised in the "placebo (parent) – top dose (LTE) treatment arm.
- Some of the placebo responders in the parent study will be allocated to placebo when rolling over to the LTE, i.e. Protocol Amendment has been approved and the country operates under the approved Protocol Amendment 1. Such participants will be summarised in the "placebo (parent) – placebo (LTE) treatment arm.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

Due to the 220723 study being terminated, eCOA compliance will only be assessed on a Study level (Section 6.2.1) up to 8th April 2025 (the date of the 220723 study termination). The Study level eCOA compliance will be reported for the study overall (i.e., pooling all treatment arms together). No endpoint level compliance will be assessed.

eCOA data (i.e. assessments collected via tablet or phone) is collected within this study. Details for calculating compliance, at the study level, and for individual endpoints derived from it, 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.

The following data is classified as eCOA:

Measurement	eCOA category	Device
Secondary Endpoints Measures		
EASI (Eczema Area and Severity Index)	eClinRo	Tablet
5-point Investigator's Global Assessment (IGA)	eClinRo	Tablet
PP-NRS	ePRO	CCI [redacted]
Exploratory Endpoint Measures		
CCI [redacted]		

Compliance will be assessed for the secondary eCOA endpoints only at the timepoints of interest specified, i.e:

Secondary eCOA endpoints
Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* • PP-NRS Reduction of ≥4 points
Achieving a maintained response (for binary endpoints) for at least CCI [redacted]: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline*
PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.

*Please refer to Section 4.1.2 for baseline definitions.

6.2.1. Study Level compliance

Compliance will be assessed for the **secondary eCOA endpoints only** (as listed above). Overall eCOA compliance (across the eCOAs listed and all participants) for the study is calculated as:

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

Total number of complete eCOAs is a sum of completed eCOA scores for each specified endpoint across the study (i.e, calculated across all patients and timepoints). An eCOA is considered complete if there is no missing data within the assessment.

Example below demonstrates a potential scenario on how study compliance would be calculate assuming:

- 100 participants and 2 eCOA endpoints (IGA and EASI), measured at 3 timepoints
- Overall compliance for IGA across all participants across all timepoints specified = 80% (i.e. in this example, 240 eCOA scores were completed out of 100 x 3 total number of scores)
- Overall compliance for EASI across all participants across all timepoints specified = 90% (i.e. 270 eCOA scores were completed out of 100 x 3 total number of scores)

Study level compliance = 85% as per calculation below:

$$\frac{240 + 270}{(3\ IGA\ measurements + 3\ EASI\ measurements)\ \times 100}$$

For assessment of the overall eCOA compliance, PP-NRS will be included in the formula as a weekly (rather than daily) score up to [redacted] and as a score collected at visits as per SoA after [redacted]

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

6.2.2. Endpoint Level Compliance

Following 220723 Study termination, analyses outlined in this section will not be provided.

PP-NRS

PP-NRS is assessed daily via eDiary up to [redacted] in the LTE and at least 4 daily scores are required to compute a weekly PP-NRS score for a participant. The weekly score is based on the average of daily PP-NRS scores for maximum itch intensity reported during the 7 days prior. The weekly score will be set to missing if there are fewer than 4 daily scores recorded in the 7 days prior. After [redacted] PP-NRS score is assessed only at scheduled visits and recorded by the participant.

To assess compliance up to [redacted]

The number/percentage of participants with weekly PP-NRS scores available will be summarized by the treatment arms in the parent study and the LTE, using a frequency table and presented by week. In this summary the denominator will be the number of expected PP-NRS data entries (i.e., the number of participants who rolled over to the LTE and have not withdrawn from the study at the timepoint specified) and the numerator will be the number of participants with the PP-NRS data present at the specified timepoint among the participants contributing to the denominator. The overall compliance of up to [redacted] will be calculated as the average of all weeks' compliance.

Target compliance level for this endpoint is defined as 85% (for each week and overall) and is in line with the QTL (defined as "Percentage of participants with weekly PP-NRS score missing up to [redacted]"; QTL threshold will be breached if >15% of participants will have weekly PP-NRS score [redacted]).

To assess compliance after [redacted]

The number/percentage of recorded PP-NRS values by the participant at Weeks 32, 48 and every 48 weeks thereafter will be summarized by the treatment arms in the parent study and the LTE, using a frequency table. In this summary the denominator will be the number of expected PP-NRS data entries (i.e., the number of participants who attended the scheduled visit at the specified timepoint and have not withdrawn from the study) and the numerator will be the number of participants with the PP-NRS data present at the specified timepoint among the participants contributing to the denominator. The overall compliance will be calculated as the average of all weeks' compliance.

Target compliance level for PP-NRS across all the patients at each of the specified Weeks (as well as overall) is defined as 80%.

IGA

The number/percentage of recorded IGA values by qualified investigator/study staff at Weeks 16, 32, 48 and every 48 weeks thereafter will be summarized by the treatment arms in the parent study and the LTE, using a frequency table. In this summary the denominator will be the number of expected IGA data entries (i.e., the number of participants who attended the scheduled visit at the specified timepoint and have not withdrawn from the study) and the numerator will be the number of participants with the IGA data present at the specified timepoint among the participants contributing to the denominator. The overall compliance will be calculated as the average of all weeks' compliance.

Target compliance level for IGA across all the patients at each of the specified Weeks (as well as overall) is defined as 80%.

EASI

The number/percentage of recorded EASI values by qualified investigator/study staff at Weeks 16, 32, 48 and every 48 weeks thereafter will be summarized by the treatment arms in the parent study and the LTE, using a frequency table. In this summary the denominator will be the number of expected EASI data entries (i.e., the number of participants who attended the scheduled visit at the specified timepoint and have not withdrawn from the study) and the numerator will be the number of participants with the EASI data present at the specified timepoint among the participants contributing to the denominator. The overall compliance will be calculated as the average of all weeks' compliance.

Target compliance level for EASI across all the patients at each of the specified Weeks (as well as overall) is defined as 80%.

6.3. Appendix 2 Data Derivations Rule

6.3.1. 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 within the LTE study.

Treatment period is defined as time from first dose in the LTE up to and including the Week 264 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 Week 264 visit + 12 weeks.

6.3.2. Study Day and Reference Dates

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

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

6.3.3. Assessment Window

For data summaries by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a target visit based on the visit windows defined in the table below.

If there are multiple assessments within the same window, a scheduled visit will be prioritised over un-scheduled 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. In case of laboratory data, central laboratory assessments will be prioritised over local laboratory assessments.

220723	Analysis window			
Visit	Window start (study day)	Target study day in the window	Window end (study day)	Target visit to be slotted to
1		-28		Day -28
2		1		Day 1
3	2	15	21	Week 2 (Day 15)
4	22	29	42	Week 4 (Day 29)
5	43	57	70	Week 8 (Day 57)
6	71	85	98	Week 12 (Day 85)
7	99	113	126	Week 16 (Day 113)
8	127	141	154	Week 20 (Day 141)
9	155	169	182	Week 24 (Day 169)
10	183	197	210	Week 28 (Day 197)
11	211	225	238	Week 32 (Day 225)
12	239	253	266	Week 36 (Day 253)
13	267	281	294	Week 40 (Day 281)
14	295	309	322	Week 44 (Day 309)
15	323	337	350	Week 48 (Day 337)
16	351	365	378	Week 52 (Day 365)
17	379	393	406	Week 56 (Day 393)
18	407	421	434	Week 60 (Day 421)
19	435	449	462	Week 64 (Day 449)
20	463	477	490	Week 68 (Day 477)
21	491	505	518	Week 72 (Day 505)
22	519	533	546	Week 76 (Day 533)
23	547	561	574	Week 80 (Day 561)
24	575	589	602	Week 84 (Day 589)
25	603	617	630	Week 88 (Day 617)
26	631	645	658	Week 92 (Day 645)
27	659	673	686	Week 96 (Day 673)
28	687	701	714	Week 100 (Day 701)
29	715	729	742	Week 104 (Day 729)
30	743	757	770	Week 108 (Day 757)
31	771	785	798	Week 112 (Day 785)
32	799	813	826	Week 116 (Day 813)
33	827	841	854	Week 120 (Day 841)
34	855	869	882	Week 124 (Day 869)

220723	Analysis window			
Visit	Window start (study day)	Target study day in the window	Window end (study day)	Target visit to be slotted to
35	883	897	910	Week 128 (Day 897)
36	911	925	938	Week 132 (Day 925)
37	939	953	966	Week 136 (Day 953)
38	967	981	994	Week 140 (Day 981)
39	995	1009	1022	Week 144 (Day 1009)
40	1023	1037	1050	Week 148 (Day 1037)
41	1051	1065	1078	Week 152 (Day 1065)
42	1079	1093	1106	Week 156 (Day 1093)
43	1107	1121	1134	Week 160 (Day 1121)
44	1135	1149	1162	Week 164 (Day 1149)
45	1163	1177	1190	Week 168 (Day 1177)
46	1191	1205	1218	Week 172 (Day 1205)
47	1219	1233	1246	Week 176 (Day 1233)
48	1247	1261	1274	Week 180 (Day 1261)
49	1275	1289	1302	Week 184 (Day 1289)
50	1303	1317	1330	Week 188 (Day 1317)
51	1331	1345	1358	Week 192 (Day 1345)
52	1359	1373	1386	Week 196 (Day 1373)
53	1387	1401	1414	Week 200 (Day 1401)
54	1415	1429	1442	Week 204 (Day 1429)
55	1443	1457	1470	Week 208 (Day 1457)
56	1471	1485	1498	Week 212 (Day 1485)
57	1499	1513	1526	Week 216 (Day 1513)
58	1527	1541	1554	Week 220 (Day 1541)
59	1555	1569	1582	Week 224 (Day 1569)
60	1583	1597	1610	Week 228 (Day 1597)
61	1611	1625	1638	Week 232 (Day 1625)
62	1639	1653	1666	Week 236 (Day 1653)
63	1667	1681	1694	Week 240 (Day 1681)
64	1695	1709	1722	Week 244 (Day 1709)
65	1723	1737	1750	Week 248 (Day 1737)
66	1751	1765	1778	Week 252 (Day 1765)
67	1779	1793	1806	Week 256 (Day 1793)
68	1807	1821	1834	Week 260 (Day 1821)

220723	Analysis window			
Visit	Window start (study day)	Target study day in the window	Window end (study day)	Target visit to be slotted to
69	1835	1849	1862	Week 264 (Day 1849)
70	1863	1877	1890	Week 268 (Day 1877)
71	1891	1905	1918	Week 272 (Day 1905)
72	1919	1933	1946	Week 276 (Day 1933)
73	1947	1961		Week 280 (Day 1961)

As mentioned in the protocol Section 1.3 (Schedule of Activities, Table 1, footnotes "c" and "d"), some of the assessments may need to be repeated in the LTE depending on whether Day 1 (Visit 2) of the LTE is on the same day as EoS visit (or within 3 days) from the qualifying Ph2 parent study.

Demographic, dosing, inclusion/exclusion criteria, medical history, disease history, AE/SAE, concomitant medication and dispensing diary will be entered by the site into the eCRF of the LTE, regardless whether Day 1 (Visit 2) of the LTE is on the same day, within 3 days or outside of the 3-day window as EoS visit of the qualifying parent study.

If Visit 2 is not on the same day as EoS visit from the qualifying Ph2 parent study (or not within 3 days)

In case TCS wash-out is to be initiated at EoS visit in qualifying Ph2 parent study, Day 1 visit (Visit 2) is to be performed at the latest 9 days after EoS visit of qualifying Ph2 parent study.

Data for the following assessments will not be copied from EoS visit and assessments will need **to be conducted again** at Day 1 of the LTE (Visit 2):

Clinical Efficacy Assessments
• IGA • EASI
Patient Reported Outcomes (PRO) Measures
• PP-NRS • SP-NRS • DLQI • POEM • WPAI-AD • HADS • PROMIS-Sleep Disturbance 8b

For clinical efficacy and PRO assessments, the new data collected is entered as Day 1 (Visit 2) of the LTE. For PROs that are measured using daily eDiary (PPNRS and SPNRS), the eDiary entry is started with Day 1 (Visit 2) measurement.

Laboratory samples and safety assessments do not need to be repeated. The data from the qualifying Ph2 parent study will be combined with the LTE data at the ADaM programming level.

If Visit 2 is on the same day as EoS visit from the qualifying Ph2 parent study (or within 3 days)

If no TCS wash-out is needed or if the TCS wash-out is completed at EoS visit of qualifying Ph2 parent study, the EoS visit will be Day 1 (Visit 2) of the LTE. EoS visit will be the same as Day 1 (Visit 2) of the LTE if it is within 3 days of the EoS visit of qualifying Ph2 parent study.

All Day 1 (Visit 2) assessments and samplings will be from the EoS visit from qualifying Ph2 parent study. **No** clinical efficacy or PRO endpoints **need to be repeated**. Clinical efficacy and PROs assessment data from the EoS visit will be combined with the LTE data at the ADaM programming level.

For PROs that are measured using the daily eDiary (PPNRS and SPNRS), the last daily value from the parent study will be entered as Day 1 (Visit 2) value in the LTE. The eDiary entry in the LTE will be started with Day 2 with new values from the assessments from the LTE.

Laboratory samples and safety assessments do not need to be repeated. The data from the qualifying Ph2 parent study will be combined with the LTE data at the ADaM programming level.

6.3.4. 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.

6.3.5. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• 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>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>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>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
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.</td></tr>
</table>
</td></tr>
</table>

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

6.3.6. Early PK Access Key Activities

Designated independent representative(s) may be given controlled early access to unblinded data for performing population PK and PKPD (which includes efficacy data) dataset preparation and draft PK and PKPD model development using PK and PKPD unblinded datasets, including baseline demographic characteristics.

6.3.7. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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7. REFERENCES

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