Statistical Analysis Plan

Study ID: 215253

Official Title of Study: A Phase Ib, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study of the Clinical Effect, Safety and Tolerability of a Single Intravenous Infusion of GSK1070806 in Moderate to Severe Atopic Dermatitis Patients

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TITLE PAGE

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Study Number: 215253

Compound Number: GSK1070806

Abbreviated Title: Clinical Effect, Safety and Tolerability of GSK1070806 in Atopic Dermatitis.

Sponsor Name: GlaxoSmithKline Research & Development Limited

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP Original version	15 Mar 2022	Protocol Amendment 1 (25 Feb 2022)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Pharmacology Study Report (CPSR) for Study 215253. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To compare the clinical effect of a single intravenous (IV) infusion of 2 mg/kg of GSK1070806 versus placebo in moderate to severe Atopic Dermatitis in the Biologic Naïve (BN) population (Group 1).	• Percent change from baseline (PCFB) in the Eczema Area and Severity Index (EASI) at Week 12
Secondary	
• To further compare the clinical effect (GSK1070806 versus placebo) in the BN population (Group 1).	• Change from Baseline (CFB) in the EASI at Week 12. • EASI 50/75/90 defined as ≥ 50/75/90% reduction in the EASI from Baseline at Week 12. • Investigator Global Assessment (IGA) score of 0 or 1 at Week 12.
• To estimate the clinical effect of GSK1070806 in the dupilumab inadequate responder (Dupi-IR) population (Group 2).	• PCFB in the EASI at Week 12.

• To assess safety and tolerability (GSK1070806 versus placebo) in the combined AtD population (Groups 1 and 2).	• Incidence of serious adverse events (SAEs) and adverse events (AEs).
	• Incidence of clinically important findings in:
	  • Vital signs
	  • Electrocardiogram
	  • Laboratory: haematology, clinical chemistry and urinalysis.

• To assess anti-drug antibody (ADA) formation in the combined AtD population (Groups 1 and 2).	• Incidence of ADAs

Objectives	Endpoints
CCI	

Primary estimand

The primary clinical question of interest is: What is the treatment effect on Eczema Area and Severity Index (EASI) after 12 weeks of treatment with a single intravenous (IV) infusion of 2 mg/kg GSK1070806 versus placebo in Biologic Naïve participants (Group 1) with moderate to severe Atopic Dermatitis in the absence of use of Rescue Therapy.

The primary estimand is described by the following attributes:

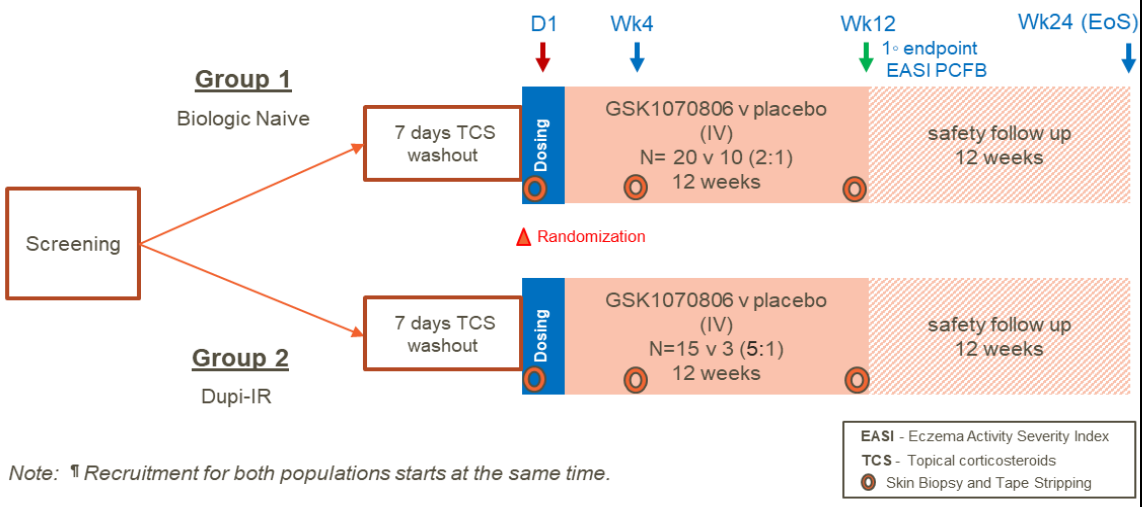
- Population: Biologic Naïve (BN) participants with moderate to severe Atopic Dermatitis.
- Treatment condition: A single 2 mg/kg one-hour IV infusion of either GSK1070806 or placebo at Day 1.
- Variable / endpoint: Percent change from Baseline to Week 12 in the EASI.
- Summary measure: Difference (GSK1070806 - placebo) in mean percent change from baseline in EASI at Week 12.
- Intercurrent events: Use of Rescue Therapy. It will be handled with a hypothetical strategy, i.e. values after use of Rescue Therapy will be set to missing.

Rescue Therapy is defined in this document as the use of any prohibited medication (as defined in the protocol section 6.8.2) that is considered as an important protocol deviation.

Rationale for estimand: The study is designed to evaluate the treatment effect attributable to GSK1070806. It is important that this effect is not confounded by the effect of other treatments. Therefore, for participants who use any Rescue Therapy, a hypothetical strategy will be used in order to estimate the treatment effect in the absence of use of Rescue Therapy.

1.2. Study Design

Overview of Study Design and Key Features



Note: ¶ Recruitment for both populations starts at the same time.

Design Features	• Multi-centre, randomized, double-blind, parallel group, placebo-controlled study of GSK1070806 administered as a single 2 mg/kg IV infusion to investigate the efficacy and safety in moderate-severe AtD participants. The primary efficacy endpoint will be measured at Week 12.

Overview of Study Design and Key Features	

	• The overall study duration for an individual participant is not expected to exceed 28 weeks (Screening is 4 weeks; Treatment Period is 12 weeks; Follow-Up Period is 12 weeks). The End of Study (Week 24, Day 169) would allow for continued safety monitoring beyond the Week 12 primary endpoint.
	
	• The study will assess the impact of GSK1070806 in two groups of patients with moderate-to-severe AtD. Groups 1 and 2 will be conducted in parallel.
	
	  • Group 1: Patients naïve to biologic treatment (and who have failed topical therapies).
	  • Group 2: Patients who have not adequately responded (or have been intolerant) to dupilumab (Dupixent).

Study intervention	• All participants must meet all clinical criteria at the point of randomization (for subsequent dosing on Day 1) and must stop using topical treatments (corticosteroids, calcineurin inhibitors or Phosphodiesterase 4 [PDEIV] inhibitors) for at least 7 days (starting on Day -7) prior to dosing on Day 1. • GSK1070806 and placebo are double blinded. Participants will receive either GSK1070806 or placebo on Day 1.

Study intervention Assignment	• Approximately 64 patients are expected to be screened to achieve approximately 48 randomly assigned participants.
	
	  • Group 1: N = 30. 20 participants will receive GSK1070806, 10 will receive placebo in a 2:1 ratio. Approximately 40 BN patients may need to be consented for screening to provide 30 randomized.
	  • Group 2: N = 18. 15 participants will receive GSK1070806, 3 will receive placebo in a 5:1 ratio. Approximately 24 Dupi-IR patients may need to be consented for screening to provide 18 randomized.

Interim Analysis	The details of the planned analysis and timing will be documented in the Interim Charter. Refer to Section 4.7 for details.
Analyses	• Primary completion analysis: when the last participant in Group 1 completes the Week 12 visit or withdraws from the study prior to Week 12.

Overview of Study Design and Key Features	
	• Final analysis: when the last participant completes the Week 24 visit or withdraws from the study prior to Week 24

2. STATISTICAL HYPOTHESES

There is no formal hypothesis to be tested.

2.1. Multiplicity Adjustment

There will be no adjustment for multiplicity.

3. ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed the ICF and are screened for eligibility.	• Study Population
Enrolled	• All participants in the Screened analysis set who entered the study.	• Study Population
Randomised	• All participants in the Enrolled analysis set who were randomly assigned to study intervention in the study. • Participants will be analysed according to the intervention they were randomized to receive.	• Study Population
Safety	• All participants in the Randomized analysis set who received the study intervention. • Participants will be analysed according to the intervention they actually received.	• Efficacy • Safety • Biomarker • PROs
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Participants will be analysed according to the intervention they actually received.	• PK
COVID-19	• All participants in Safety analysis set who had confirmed COVID-19 diagnosis.	• Safety

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

4. STATISTICAL ANALYSES

4.1. General Considerations

Unless otherwise specified, the Enrolled or Randomized Analysis Sets will be used for all Study Population analyses (detailed in the Output and Programming Specification (OPS)), the Safety Analysis Set will be used for all Efficacy, Safety, Biomarker, and PRO analyses, and PK Analysis Set will be used for PK analyses.

In the case of wrong group (i.e., Group 1 vs Group 2) assignment at the time of randomization, the analyses will be performed based on the actual group per data collected in the CRF.

Unless otherwise specified, summary tables will provide the following descriptive statistics as a minimum:

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

4.1.1. Bayesian inference

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

Prior distributions are given in the analysis sections below and will be reported in the Clinical Pharmacology Study Report (CPSR).

Posterior distributions for each arm and for the treatment difference between arms will be summarized using posterior median, 95% equal-tailed credible intervals (CrI), and posterior probabilities of the true treatment difference being greater than pre-specified thresholds.

The inference will be carried out as follows:

- 2 chains will be run, with different (over-dispersed) initial values in order to assess convergence. Posterior summaries will use only 1 chain.
- A minimum burn-in period of 1,000 MCMC samples (for each chain) will be used.
- A minimum of 10,000 MCMC samples (for each chain) will be run to generate samples of the posterior distribution.
- A thinning sample may be used to improve convergence. If k is the thinning ratio, the number of MCMC samples will be minimum $k \times 10{,}000$.

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

- Ratio of Monte Carlo error /posterior SD should be as small as to ensure that only a fraction of the posterior variability is due to simulation error.
  The final MCMC samples will be such that this ratio for the key parameters in the model is ≤ 0.01.

- Gelman & Rubin diagnostic is based on the ratio of the pooled variance across the chains over the overall within-chain variance. Values close to 1 indicate that each of the subsets of MCMC samples is close to the target posterior distribution.
  A cut-off of 1.1 will be used.

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

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

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits, unless otherwise stated. If time is

not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

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

For skin punch biopsy, there is a Lesional Baseline and a Non-lesional Baseline.

4.2. Primary Endpoint Analyses

4.2.1. Definition of Percent change from baseline in the EASI

The primary endpoint is the Percent change from baseline in the EASI at Week 12 in Group 1, and the estimand is described in Section 1.1.

4.2.2. Main analytical approach

The analysis will be carried out for Group 1 only, using data up to Week 12.

The analysis will be based on the Safety analysis set. Participants will be analysed according to the treatment they received.

EASI scores collected after use of Rescue Therapy will be set to missing.

Missing observations will be assumed to be Missing at Random (MAR), i.e. assume that the missing part, given the history, will be like the data observed in the absence of Rescue Therapy.

Endpoint(s)	
• Percent Change from Baseline in the EASI at Week 12 (Group 1) (Hypothetical Strategy, robust MAP Prior)	
Analysis Method	
Bayesian repeated measures model	
Model Specification	
Outcome	Percent change from baseline in the EASI
Predictors	• Baseline EASI score (continuous) • Treatment (categorical, reference: placebo) • Visit (categorical, weeks 2, 4, 8, 12, reference: Week 12) • Treatment*visit interaction (categorical) • Baseline EASI*visit interaction (continuous)

	Baseline EASI score will be centered around its observed mean prior to inclusion in the model
Prior distributions for parameters associated to the predictors	• Placebo at Week 12: robust MAP prior: mixture prior has 28.5% weight on a Normal (-31.56, SD=5.67), 21.5% weight on a Normal (-31.21, SD=11.00) and 50% weight on a Normal (-30, SD = 50) • GSK1070806 at Week 12: vague prior Normal(-30, SD=50) • All other parameters: vague priors Normal(0, SD = 10^6)
Prior distribution for residual covariance matrix	• **Σ**: unstructured residual covariance matrix of dimension 4×4 ~ Inverse Wishart (J, S), with J = number of visits (degree of freedom), S = identity matrix If convergence issues occur, an alternative covariance matrix structure may be used, for example a compound symmetric structure, to help improve convergence.
Model Checking & Diagnostics	
See Section 4.1.1	
Results Presentation	
• Adjusted posterior median, and 95% CrI for each treatment by timepoint interaction (table). • Posterior median treatment differences (GSK1070806 – placebo) and associated 95% CrI for each timepoint (table and figure). • Probabilities that the true treatment difference (GSK1070806 – placebo) at each visit is < 0%, -15%, -25%, and -40% (table), e.g., Prob(GSK1070806 – placebo < -15%) • Outputs will include results for earlier timepoints in addition to the objective specified timepoint of Week 12.	

For the PCFB in the EASI at Week 12 in the placebo arm, data from 16 previous trials in AtD were included to derive an informative prior using a meta-analytic predictive (MAP) method [Schmidli, 2014]. A vague mixture component was added to allow for prior-data conflicts.

Data were extracted from the following publications: [Beck, 2014], [Bissonnette, 2019], [Gooderham, 2019], [Guttman-Yassky, 2019], [Guttman-Yassky, 2020a], [Guttman-Yassky, 2020b], [Ruzicka, 2017], [Simpson, 2016], [Simpson, 2018], [Simpson,2019], [Simpson, 2020], [Thaçi, 2016].

4.2.3. Sensitivity analyses

As a sensitivity analysis, a vague prior of Normal (-30, SD=50) will be applied instead of the robust MAP prior for placebo at Week 12.

4.2.4. Additional estimands

An additional estimand for the primary endpoint is defined: the intercurrent event of the use of Rescue Therapy will be handled with the treatment policy strategy: data collected after use of Rescue Therapy will be included in the statistical analysis.

Missing data assumption will be MAR, i.e., given the history of a subject, the part that is missing will be distributed similarly as those that are still in the study at that time, whether they have taken Rescue Therapy or not.

The same statistical approach as described in Section 4.2.2 will be used.

Primary endpoint additional analysis due to COVID-19

For the primary endpoint, if >= 6 participants in Group 1 have confirmed COVID-19 up to Week 12, then an additional analysis whereby the intercurrent event of the onset of COVID-19 (confirmed diagnosis only) will be handled with the hypothetical strategy may be conducted.

EASI scores collected after the onset of COVID-19 (confirmed diagnosis only) will be set to missing.

Missing observations will be assumed to be Missing at Random (MAR), i.e. assume that the missing part, given the history, will be like the data observed in the absence of COVID-19.

For the use of Rescue Thearpy, the same method (hypthetical stratgey) as in the primary analysis will be used.

4.3. Secondary Endpoints Analyses

For Safety analysis please refer to Section 4.5.

4.3.1. Clinical secondary endpoints

4.3.1.1. Definition of clinical endpoints

The secondary endpoints for Group 1 are:

- Change from baseline in the EASI at Week 12.
- EASI 50/75/90 responses at Week 12, EASI 50/75/90 response is defined as ≥ 50/75/90% reduction in the EASI from Baseline.
- IGA score of 0 ('clear') or 1 ('almost clear') response at Week 12.

The secondary endpoint for Group 2 is:

- Percent change from baseline in the EASI at Week 12.

4.3.1.2. Main analytical approach

The analyses of the secondary endpoints will be based on the Safety analysis set. Participants will be analysed according to the treatment they received.

Group 1 – continuous endpoints

The approach is the same as that used for the primary endpoint (Section 4.2.2), including up to Week 12 visit. Vague prior of Normal(0, SD=10^6) will be used for all parameters associated to the predictors. EASI scores will be set to missing after Rescue Therapy. Missing data will be assumed to be MAR.

Group 1 – binary endpoints

Bayesian logistic regression will be used.

Responses collected after use of Rescue Theapy will be set to non-responders.

Missing responses will be imputed as non-reponders.

Binary Endpoints	
• EASI50, EASI75, and EASI90 responses at Week 12 • IGA score of 0 or 1 response at Week 12	
Analysis Method	
Bayesian Logistic Regression	
Model Specification	
Outcome	$y_i = Ry_i$ = response (0/1) for participant *i* at Week 12
Predictors	• Treatment (categorical) • Baseline score (continuous) Baseline score will be centered around its observed mean prior to inclusion in the model
Model	$y_i \sim Ber(p_i)$ $logit(p_i) = (Treatment=Placebo)\times\beta_1 + (Treatment=GSK)\times\beta_2 + (Baseline\ score)\times\beta_3$
Prior distributions for coefficients (**β**)	**β** = parameters associated to predictors • β_1, β_2: vague prior such that $logit^{-1}(\beta_k) \sim Beta(1/3, 1/3)$ • $\beta_3\beta_k$: vague prior N(0, SD=10^6)
Model Checking & Diagnostics	
See Section 4.1.1	
Results Presentation	
• Adjusted posterior median and 95% CrI of true response rate for each treatment group, using the back-transformation of the logit (table). • Posterior median and 95% CrI for the true difference in proportion of responders (GSK1070806 – placebo) (table)	

- Probabilities that the true treatment difference is greater than 0 and 10%.
- Outputs will include results for earlier timepoints in addition to the objective specified timepoint of Week 12.

Group 2 – continuous endpoint

The PCFB in the EASI in Group 2 in the GSK1070806 arm will be analysed using a simplified version of the approach used for the primary endpoint (Section 4.2.2) with only one treatment arm. EASI scores will be set to missing after Rescue Therapy. Missing values are assumed to be Missing at Random (MAR). Vague priors of Normal(0, SD=10^6) will be used for the parameters associated to the predictors.

4.3.1.3. Sensitivity analyses

No sensitivity analyses are planned for secondary efficacy endpoints.

4.3.1.4. Supplementary analyses

Data collected after use of Rescue Therapy may be used.

4.3.2. Immunogenicitiy

The immunogenicity analyses will be based on the Safety analysis set and will be reported for groups 1 and 2 combined.

The immunogenicity of GSK1070806 will be characterized with summary statistics of incidence, i.e. the number of participants with anti-drug antibodies by treatment over time. Immunogenicity testing involves a screening assay and a confirmation assay that together produce 3 results:

- Screening assay result (positive / negative)
- Confirmatory assay result (positive / negative) if positive result in the screening assay
- Titre result (numeric) if positive result in the confirmation assay.

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4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set and reported for groups 1 and 2 combined. Participants will be analysed according to the treatment they received.

No formal statistical testing will be performed on Safety data.

4.5.1. Extent of Exposure

A listing of exposure to study treatment will be produced.

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. Summary tables will include the number of participants with the AE, the percentage of participants with the AE. The definitions of AEs or SAEs will be detailed in OPS.

An AE is considered study intervention emergent if the AE onset date is on or after study intervention start date.

All AE summaries will be based on study intervention emergent events unless otherwise specified.

SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not.

All AE and SAE summaries will be presented by System Organ Class (SOC) & Preferred Term (PT) unless otherwise specified. Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

Summary tables will be produced for the following categories:

1. Adverse events by system organ class and preferred term and maximum intensity
2. Drug-related adverse events by system organ class and preferred term and maximum intensity
3. Serious adverse events by system organ class and preferred term (number of subjects and occurrences)
4. Common (>=0%) adverse events by overall frequency
5. Common (>=0%) non-serious adverse events by system organ class and preferred term (number of subjects and occurrences)
6. Serious adverse events by system organ class and preferred term and maximum intensity
7. Non-serious drug-related adverse events by overall frequency
8. Serious fatal and non-fatal drug-related adverse events by overall frequency

4.5.2.1. Adverse Events of Special Interest

There are no adverse events of special interest identified for this study.

4.5.2.2. COVID-19 Assessment and COVID-19 AEs

COVID-19 assessments for participants with COVID-19 AEs will be summarized.

4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

The impact of the COVID-19 pandemic on the safety results will be assessed, if any.

Adverse Events

A listing of COVID-19 related AEs (SMQ related to COVID to flag all preferred terms related to COVID-19) will be produced.

If >= 10 participants (groups 1 and 2 combined) have confirmed COVID-19, the following tables will be created:

1. Adverse Events by System Organ Class and Preferred Term and Maximum Intensity (AEs before the onset of COVID-19 vs. AEs on and after the onset of COVID-19; Safety Analysis Set)
2. Adverse Events by System Organ Class and Preferred Term and Maximum Intensity (AEs on and after the onset of COVID-19; COVID-19 Analysis Set)
3. Serious adverse events by system organ class and preferred term and maximum intensity (SAEs before the onset of COVID-19 vs. SAEs on and after the onset of COVID-19; Safety Analysis Set)
4. Serious adverse events by system organ class and preferred term and maximum intensity (SAEs on and after the onset of COVID-19; COVID-19 Analysis Set)

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

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. Shift tables of worst-case results post-baseline relative to baseline will be provided for the following tests:

- For lab tests with associated Potential Clinical Importance (PCI) criteria (see Section 6.2.1)
- For categorical urinalysis parameters

Only post-baseline data will be included in these tables. If a participant moves to both a low and a high clinical concern range during the treatment period, then the participant is counted in both categories.

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above. Possible Hy's law cases are defined as any elevated alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5. Total bilirubin ≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. The summary will be produced for worst-case post-baseline only.

4.5.3.2. Vital Signs

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

Shift tables of worst-case results relative to PCI criteria post-baseline relative to baseline will be provided for SBP, DBP and heart rate (see Section 6.2.1).

4.5.3.3. ECG

For all ECG analyses, baseline is taken to be the mean of the triplicate values collected pre-dose Day 1. The following summaries will be provided:

1. Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category
2. Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category
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 average of the triplicate.

The QTc data analysis will use the values based on Fridericia formula. For analysis purposes, if QTcF is not available, it will be derived from QTcB.

Shift tables will be provided for QTcF and will be used to detect any clinically important changes:

- Maximum QTc values post-baseline relative to baseline by category defined as
    - To ≤450msec or No Change
    - Any increase > 450 msec

  - Increase to >450 to <=480
  - Increase to >480 to <=500
  - Increase to >500 msec
- Maximum increase in QTc values post-baseline relative to baseline by category defined as:
  - Increase of ≤ 30 msec
  - Increase between 31 and 60 msec
  - Increase > 60 msec

4.6. Other Analyses

4.6.1. Subgroup analyses

There are no planned subgroup analyses for any of the endpoints.

4.7. Interim Analyses

The details of the planned analysis and timing will be documented in the Interim Analysis Charter.

The decision criteria will be based on predictive probabilities of achieving two decision criteria (at the end of the study) defined in the interim charter, based on the interim data. The prediction of the future data will be based on the posterior distribution of the parameters at interim. The latter will be estimated using the same statistical analysis as described in Section 4.2.2.

4.8. Changes to Protocol Defined Analyses

There is no change or deviation to the originally planned statistical analysis specified in protocol amendment #1 (Dated: 25-FEB-2022).

5. SAMPLE SIZE DETERMINATION

Approximately 64 patients may need to be screened to obtain 48 randomized participants (approximately 30 and 18 participants in Groups 1 and 2, respectively). Participants who have withdrawn from the study, may be replaced at the discretion of the sponsor.

The sample sizes for Groups 1 and 2 are selected to support preliminary assessment of the clinical effect, based on PCFB in the EASI for Groups 1 and 2.

Operating characteristics of some criteria of interest for the both groups of the study have been calculated and presented below.

Group 1:

Based on 30 participants (20 administered GSK1070806 and 10 administered placebo), the probability of different criteria of interest are given in the table below.

A Bayesian linear regression was used, assuming that the PCFB in the EASI follows a Normal distribution. The priors were as follows:

- Placebo arm: a robust meta-analytic predictive (MAP) prior was constructed based on placebo PCFB in the EASI reported in recent clinical trials in AtD. The resulting mixture prior has 28.5% weight on a Normal (-31.56, SD=5.67), 21.5% weight on a Normal (-31.21, SD=11.00) and 50% weight on a Normal (-30, SD = 50), with an effective sample size of 14 participants (expected local-information-ratio (ELIR) method (Neuenschwander, 2020)) assuming a between-participant SD = 50.
- GSK1070806 arm: a vague Normal prior was used, with mean = -30 and SD = 50, corresponding to an effective sample size (ELIR method) of 1 participant assuming a between-participant SD = 50.

Operating characteristics are provided below. A true PCFB in the EASI of -30% in the placebo arm was assumed, based on recent clinical trials in AtD. Various true PCFBs in the EASI for the GSK1070806 arm at Week 12 were assumed, giving various true treatment differences. A between-participant SD of 50% was assumed for both GSK1070806 and Placebo arms.

Criteria	**True treatment difference**			
	-40%	**-25%**	**-15%**	**0%**
Observing a >75% posterior probability that the true difference from placebo is <-15%	82.6%	43.9%	18.4%	2.5%
Observing a >75% posterior probability that the true difference from placebo is <-7.5%	92.8%	66.6%	37.7%	7.8%
Observing a >97.5% posterior probability that the true difference from placebo is < 0%	68.8%	30.3%	10.9%	1.0%

Group 2:

There are no planned statistical analyses comparing GSK1070806 *versus* placebo. The analysis will be conducted on PCFB in the EASI in the GSK1070806 arm.

Based on 15 participants on GSK1070806, the operating characteristics are given below.

A vague Normal prior was used, with mean = 0 and SD = 1×10^6, corresponding to an effective sample size (ELIR method) of 0 participant assuming a between-participant SD=50.

Criteria	True PCFB in the EASI in GSK1070806			
	-70%	-55%	-45%	-30%
Observing a >50% posterior probability that the true PCFB in EASI is <-45%	97.4%	78.1%	50.0%	12.3%
Observing a >50% posterior probability that the true PCFB in EASI is <-37.5%	99.4%	91.2%	71.9%	28.1%
Observing a >50% posterior probability that the true PCFB in EASI is <-30%	99.9%	97.4%	87.7%	50.0%

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

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

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 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.

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

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, race, ethnicity, height, weight, and BMI will be summarized.

A summary of atopic dermatitis history and characteristics will be provided. The summary will include baseline EASI score (continuous), baseline IGA score (categorical), and duration since diagnosis.

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

6.1.3. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study. 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 both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only.

The summary of concomitant medications will be provided by Anatomical Therapeutic Chemical (ATC) classification Level 1 and ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients.

Pre-intervention, Treatment, and Follow up concomitant medications are defined in OPS.

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 summarised, 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. Study Intervention Compliance

Not applicable for this study.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF.

Summary of COVID-19 Assessments for Subjects with COVID-19 Adverse Events and a Listing of Visits impacted by COVID-19 Pandemic will be provided.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

6.2.1.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Potential Clinical Importance**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male	<0.1	>0.54
		Female	<0.1	>0.54
		Δ from BL	>0.075 change from baseline	
Haemoglobin	g/L	Male	<100	>185
		Female	<100	>165
		Δ from BL	>25 change from baseline	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		<100	>999
While Blood Cell Count (WBC)	$x10^9$/ L		<2	

Clinical Chemistry				
Laboratory Parameter	**Units**		**Potential Clinical Importance**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		<30	
Corrected Calcium	µmol/L			
-Ages 18-59 years			<1.5	>3.25
-Ages 60-90 years			<1.5	>3.25
Creatinine	µmol/L			
-Male ≥18 yrs	µmol/L			Change from baseline >44.2
-Female ≥18 yrs	µmol/L			Change from baseline >44.2

Clinical Chemistry				
Laboratory Parameter	**Units**		**Potential Clinical Importance**	
			Low Flag (< x)	**High Flag (>x)**
Potassium	mmol/L		<3.0	>6.5
Sodium	mmol/L		<130	>160
Blood Urea Nitrogen (BUN)	mg/dl			>40

Liver Function			
Laboratory Parameter	**Units**	**Category**	**Potential Clinical Importance**
ALT/SGPT	U/L	High	≥ 3x ULN
AST/SGOT	U/L	High	≥ 3x ULN
Alkaline Phosphatase	U/L	High	≥ 2x ULN
Total Bilirubin	µmol/L	High	≥ 2x ULN
Direct Bilirubin			>35%

Urinalysis
A participant is considered to have urinalysis results of PCI, if there is an increase in Protein or an increase in Occult Blood results during the study, or if microscopy is performed.

6.2.1.2. ECG

ECG Parameter	Units	Potential Clinical Importance	
		Lower Limit	**Upper Limit**
Absolute			
Absolute QTc(F) Interval	msec	> 450	≤ 480
		> 480	≤ 500
		> 500	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc(F)	msec	> 30	≤ 60
		> 60	

6.2.1.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Potential Clinical Importance	
		Low Flag	High Flag
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110
Temperature	°C	≤ 35.5	> 38.0

Vital Sign Parameter (Change from Baseline)	Units	Potential Clinical Importance			
		Decrease from Baseline		Increase from Baseline	
		Lower Limit	Upper Limit	Lower Limit	Upper Limit
Systolic Blood Pressure	mmHg	≥ 20	< 40	≥ 20	< 40
		≥ 40		≥ 40	
Diastolic Blood Pressure	mmHg	≥ 10	< 20	≥ 10	< 20
		≥ 20		≥ 20	
Heart Rate	bpm	≥ 15	< 30	≥ 15	< 30
		≥ 30		≥ 30	

Note: For a Parameter, separate rows denote categories of PCI. For example, for Systolic Blood Pressure, an Increase from Baseline of >= 20 mmHg to < 40 mmHg falls into a lower increase PCI category, and an Increase from Baseline of >=40 mmHg falls into a higher increase PCI category.

6.2.2. Study Period

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

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

Treatment period is defined as time from first dose to and including Week 12 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 on-intervention window, i.e. ≥Week 12 visit + 1 day.

6.2.3. Study Day and Reference Dates

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

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

The study day is calculated as below:

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

6.2.4. Assessment Window

Unscheduled and Early Withdrawal visits will not be remapped. Data from these visits will not be used in summary tables (except for endpoints using any post-baseline data) but will be presented in any relevant listings.

6.2.5. Multiple measurements at One Analysis Time Point

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

6.2.6. Handling of Partial Dates

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

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

6.2.7. Early PK Access Key Activities

Designated independent representative(s) may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development at one or

more time points throughout the trial using scrambled (random reassignment of subject identification numbers) PK and PKPD unblinded datasets.

7. ABBREVIATIONS

Abbreviations	
AtD	Atopic Dermatitis
BN	Biologic Naive
CFB	Change from Baseline
CPSR	Clinical Pharmacology Study Report
DLQI	Dermatology Life Quality Index
Dupi-IR	dupilumab inadequate responder
EASI	Eczema area and severity index
GSVA	gene set variation analysis
IGA	Investigator Global Assessment
MAP	Meta-analytic predictive prior
MAR	Missing at Random
MCMC	Monte Carlo Markov Chain
OPS	Output and Programming Specification
PCFB	Percent Change from Baseline
PP-NRS	Peak Pruritis numerical rating scale
PRO	Patient reported outcomes
TCS	Topical corticosteroid

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