Statistical Analysis Plan

Study ID: 208022

Official Title of Study: A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of GSK2982772 in participants with moderate to severe plaque psoriasis

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Title Page

Protocol Title: A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of GSK2982772 in participants with moderate to severe plaque psoriasis

Protocol Number: 208022

Compound Number: GSK2982772

Short Title: A study to evaluate the benefit and safety of GSK2982772 in moderate to severe psoriasis patients

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Version history

This Statistical Analysis Plan (SAP) for study 208022 is based on the protocol dated 06-JAN-2021.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	27MAR2020	1 (07JAN2020)	Not Applicable	Original version
2		3 (06JAN2021)	Clarification that statistical analyses will use a Bayesian approach and expected covariates updated.	Increased consistency in results being reported from the trial, given the primary analysis is using a Bayesian approach. Updated model text to include all expected covariates.
			Sensitivity analysis for binary missing data updated.	Since the time of writing, the impact of COVID-19, and therefore the chance of dropouts unrelated to trial activities, has increased. To assess this, the team have decided to include imputing missing PASI response with the response at the previous timepoint (LOCF approach) as a sensitivity to NRI.
			Clarification of endpoint and hypothesis text	Updated text to match current protocol wording.
			Addition of COVID and	COVID population added to reflect internal

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Modified ITT analysis populations	standards for reporting COVID data. Modified ITT included to assess efficacy on participants who have completed Week 4 assessment (first timepoint of interest) as a supplementary population for efficacy assessments.
			Placebo prior	Clarification on the prior distribution to be used in primary analysis.
			Revision of planned analyses of skin biopsy data for PK and target engagement	Skin biopsy to be collected for PK and target engagement assays is no longer required under Protocol Amendment 3. The planned MMRM analysis of skin target engagement is not required but may be conducted if sufficient data available.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 208022. Details of the planned interim analysis are also provided.

Additional exploratory analyses of inflammatory, metabolic and transcriptomic markers; data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Changes to the Protocol Defined Statistical Analysis Plan

There are no changes to the originally planned statistical analysis specified in the protocol.

1.2. Objectives, Endpoints and Estimands

1.2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of GSK2982772 960 mg modified release (MR) once daily (QD) for 12 weeks, compared with placebo in participants with moderate to severe plaque psoriasis.	• PASI75 response (achieving ≥75% improvement from Baseline in PASI score) at Week 12.
Secondary	
• To further evaluate the efficacy of GSK2982772 960 mg MR QD for 12 weeks, compared with placebo in participants with moderate to severe plaque psoriasis.	Further PASI parameters: • PASI50, PASI90 and PASI100 response (achieving ≥50%, ≥90% and 100% improvement from Baseline in PASI score, respectively) at Week 12. • Change from Baseline PASI scores at Week 12. Static Investigator's Global Assessment (sIGA): • sIGA response (achieving a sIGA score of [redacted] (0) or [redacted] (1)) at Week 12. Psoriasis Body Surface Area (BSA): • Change from Baseline in psoriatic BSA at Week 12.
Safety	
• To evaluate the safety and tolerability of GSK2982772 960 mg MR QD for 12 weeks, compared with placebo in participants with moderate to severe plaque psoriasis.	• Adverse events • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead electrocardiogram (ECG) monitoring • Columbia Suicide Severity Rating Scale (C-SSRS)
Pharmacokinetics	
• To assess trough plasma concentrations of GSK2982772 960 mg MR QD for 12 weeks, in participants with moderate to severe plaque psoriasis.	• Trough plasma concentrations of GSK2982772 at Weeks 2, 4, 8, 12.
Exploratory	
• To investigate the efficacy of GSK2982772, 960 mg MR QD over time,	Additional PASI parameters:

Objectives	Endpoints
compared with placebo in participants with moderate to severe plaque psoriasis.	• PASI75 response (achieving ≥75% improvement from Baseline in PASI score) at Weeks 2, 4, and 8. • PASI50, PASI90 and PASI100 response (achieving ≥50%, ≥90% and 100% improvement from Baseline in PASI score respectively) at Weeks 2, 4, and 8. • Change from Baseline PASI scores at Weeks 2, 4, 8. Static Investigator's Global Assessment (sIGA): • sIGA response (achieving a sIGA score of CCI (0) or CCI (1)) at Weeks 2, 4, and 8. • sIGA score category at Weeks 2, 4, 8, 12. Body Surface Area (BSA): • Change from Baseline in BSA at Weeks 2, 4, and 8.
• To investigate effect of GSK2982772 960 mg MR QD for 12 weeks, on pathway and target engagement, transcriptomic profiling, inflammatory, and metabolic biomarkers in the skin and blood of participants with moderate to severe plaque-type psoriasis.	Pharmacology biomarker endpoints: • Target Engagement Assay RIP1 (TEAR1) in blood at Weeks 0, 4, and 12. Transcriptomic profiling: • Transcriptomic analysis, including but not limited to ribonucleic acid sequencing (RNA-seq), of messenger ribonucleic acid (mRNA) isolated from skin at Weeks 0, 4, and 12, with any changes in specific inflammatory gene transcript levels (e.g. IL-4, IL-10, IL-17, IL-21, IL-22, TNF and IFNγ) possibly being evaluated. Inflammatory and Keratinocyte biomarkers: • Change from Baseline in histopathological scoring of psoriatic lesional biopsies, which may include, but are not limited to the following at Weeks 0, 4, and 12: epidermal thickness, keratin 16 (K16), antigen KI-67 (Ki67), CD3, cluster of differentiation 11c (CD11c). • Change from Baseline in inflammatory protein markers in blood which may include but are not limited to the following at Weeks 0, 4, and 12: IL-17, chemokine ligand 20 (CCL20), IL-6, IL-8, IL-4, C-X-C motif chemokine 10 (CXCL10). Metabolic biomarkers • Change from Baseline in metabolic markers in fasting blood which may include but are not limited to the following at Weeks 0, 4, and 12:

Objectives	Endpoints
	homeostatic model assessment of insulin resistance (HOMA) (glucose and insulin), glycated hemoglobin (HbA1c), lipid panel.

Derivations of key primary and secondary endpoints (PASI, sIGA, BSA) will be given in the accompanying OPS document to this SAP. No rounding will be performed on PASI percentage change values when deriving PASI responder variables.

1.2.2. Estimands

Estimands were not incorporated into the protocol for this study. The missing data handling rules are outlined in analysis sections.

1.3. Study Design

Overview of Study Design and Key Features	

Design Features	• Phase 1b/2a, multicentre, randomised, double-blind, placebo-controlled, parallel, repeat dose study of GSK2982772 in participants with active plaque-type moderate to severe psoriasis.
	• The maximum total duration for each participant in the study will be 21 weeks:
	  • Screening period of up to 35 days
	  • Treatment period of 12 weeks (84 days)
	  • Follow-up period for up to 28 days after last dose

Study intervention	• Participants will receive either GSK2982772 960mg MR QD or placebo for 12 weeks (84 days). • No dose modifications or adjustments are permitted per protocol.
Study intervention Assignment	• Participants will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio. • Randomisation will be stratified by prior biologic use.
Interim Analysis	• One interim analysis is planned to occur when at least six GSK2982772 participants complete the Week 12 visit or withdraw from study treatment.

2. STATISTICAL HYPOTHESES / SUCCESS CRITERIA

The primary objective of this study is to estimate the efficacy of GSK2982772 960 mg MR QD compared with placebo following 12 weeks of treatment, this will be assessed using the estimates of PASI75 response at Week 12.

There will be no adjustment for multiplicity.

3. SAMPLE SIZE DETERMINATION

Approximately 32 participants will be screened to achieve 21 participants randomly enrolled to either GSK2982772 or placebo in a 2:1 allocation ratio. Replacement participants may be randomised (up to approximately 6) into the study at the discretion of the Sponsor, to ensure that approximately 21 have completed the Week 4 visit.

The primary efficacy endpoint is PASI75 response (achieving ≥75% improvement from Baseline in PASI score) at Week 12.
With a sample size of 21 participants there is approximately 99% probability of achieving a posterior probability of at least 97.5 that the true treatment difference over placebo is greater than zero. This is based on an assumed placebo response of 7%, an assumed true treatment difference of 55% and incorporating informative historical placebo data into the analysis. For the placebo arm an informative Beta (3.5, 46.5) distribution is assumed, with an effective sample size of 50 participants. For the active arm a vague Beta (1/3, 1/3) prior is used.

No sample size re-estimation is planned for this study.

4. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who signed the ICF, passed screening and were eligible for randomisation (regardless of whether the participant went on to be randomised). • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Randomised	• All participants who were randomly assigned to study intervention in the study. • Participant must have signed ICF and passed Screening.	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
	• Data will be reported according to the randomised study intervention.	
Intent to Treat (ITT)	• All participants who were randomised to study intervention in the study and who received at least one dose of study intervention. • Data will be reported according to the randomised study intervention.	• Efficacy
Modified Intent to Treat (ITT)	• All participants in the ITT population who completed at least the Week 4 assessment. • Data will be reported according to the randomised study intervention.	• Efficacy
Safety	• All participants in the enrolled population who received at least one dose of study intervention. • Data will be reported according to the actual study intervention received.	• Safety • PD
COVID-19	• All participants in the Safety set who had a confirmed, probable or suspected COVID-19 case diagnosis.	• COVID outputs
Pharmacokinetic (PK)	• All participants in the Safety population who had at least one non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention received.	• PK

Actual treatments are defined as follows: If a participant randomised to the placebo arm receives any amount of GSK2982772 he or she will be included in the corresponding active treatment arm.

4.1. Protocol Deviations

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

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 are captured and categorised in the protocol deviations system independent dataset (DV1).
- This dataset will be the basis for the summaries of important protocol deviations.

Data will be reviewed prior to unblinding and freezing the database to ensure all deviations are captured and categorised in the protocol deviations A&R dataset.

4.1.1. Definitions for Per Protocol Analysis Set

This study will not include a Per Protocol analysis set.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless otherwise specified, the Enrolled or Randomised Analysis Sets will be used for all Study Population analyses (detailed in the OPS), the Intent to Treat Set will be used for all Efficacy analyses, PK Set will be used for PK analyses and Safety Analysis Set will be used for all safety and PD analyses, COVID specific outputs as well as a subset of safety analyses will be produced using the COVID population.

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the electronic case record form (eCRF), not the assigned stratum at randomization.

Credible intervals (CrI) will be equal-tailed and use 95% level unless otherwise specified.

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

- Continuous data (normally distributed):
  n, mean, standard deviation (SD), median, minimum and maximum.

- Continuous data (log-normally distributed):
  n, geometric mean, SD on the log scale (SD (log)), median, minimum and maximum.

- Categorical data:
  number and percentage of participants in each category.

Figures of average responses to primary and secondary endpoints for each treatment group over time will be produced including a suitable measure of uncertainty. Adjusted (posterior) values will be used where available.

5.1.1. Bayesian Analysis

The analyses will be conducted in the Bayesian framework. Models will be fitted by MCMC simulations and informative priors may be used. In that case, a sensitivity analysis using vague priors will also be carried out. Prior distributions are given in the analysis sections below and will be reported in the CSR. Posterior values will be calculated by weighting categorical coefficients level according to the proportions observed in the data and taking the mean value of continuous covariates.

For continuous endpoints, posterior distributions for each arm will be summarized using: posterior mean, SD, 95% CrI, as well as posterior mean and 95% CrI for the difference between arms. Medians may be used in place of medians for skewed posterior distributions.

For categorical endpoints, posterior distributions for each arm will be summarized using: posterior median response rate and 95% CrI, as well as posterior median difference in response rates and odds ratios and associated 95% CrIs.

Posterior probabilities of being greater than thresholds of interest may also be presented.

Any additional requirements for a particular analysis are given alongside the analysis description.

Bayesian Model Checking & Diagnostics
• A minimum burn-in period of 5,000 MCMC samples will be used. • A minimum of 10,000 MCMC samples will be run to generate samples of the posterior distribution. • Convergence will be assessed using visual inspection of trace plots and autocorrelation plots, the ratio of the Monte Carlo Standard Error (MCSE) to the SD of the posterior distribution (ratio should be <0.01). • If the model is not deemed to have converged the following actions will be taken in the order described below: o Increasing the number of MCMC samples and/or the thinning will be explored. The blocking of the parameters will be considered.

5.1.2. Baseline Definition

Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and will be used as baseline.

Screening values may be used if Day 1 data is unavailable for efficacy and safety endpoints. Otherwise, if not Screening data available, baseline will be set to missing.

5.1.3. Multicenter Studies

Due to the small sample size, the number of participants per site will be small. It is anticipated that analyses by centre would unlikely be informative and will not, therefore, be provided.

5.2. Primary Endpoint(s) Analyses

5.2.1. Definition of endpoint(s)

The primary endpoint for this study:

- PASI75 response at Week 12 (Day 85), where PASI75 response is defined as a reduction in PASI score from baseline of at least 75%.

5.2.2. Main analytical approach

The primary analysis will be produced for the ITT population.

The summary measure of interest is the difference in PASI75 response rates at Week 12 (Day 85) between GSK2982772 and placebo. Missing values will be imputed as non-responders.

The primary endpoint will be analysed using a Bayesian logistic regression model, details given in Table 2. Summary statistics will be provided for the posterior distribution of the true difference in PASI75 response rate (GSK2982772 vs placebo) as well as posterior probabilities for a range of thresholds.

A non-informative prior will be used for the PASI75 response rate on GSK2982772 and covariates.

An informative prior will be used for the placebo response rate of the form: 90% weight on Be(5.39, 69) and 10% on Be(1/3,1/3). The prior was derived from historical data from similar clinical trials using meta-analytic predictive prior (MAP) approach, the effective sample size is approximately 63 [Schmidli, 2014].

In the event that the placebo prior is different from what is presented here, this will be documented in the CSR.

Table 2 Statistical Analysis of Primary Endpoint

Endpoint(s)	
• PASI75 response at Week 12 (Day 85)	
Analysis Method	
Bayesian Logistic Regression (using informative prior)	
Model Specification	
Outcome	y_i = Response (0/1) for participant *i*
Predictors	• Treatment (categorical) • Prior Biologic Use (categorical) • Baseline PASI score (continuous) Unless stated otherwise the predictors (not including study treatment) will be centered around their estimated mean prior to inclusion in the model
Model	$y_i \sim Ber(p_i)$ $logit(p_i) = (Treatment=Placebo)\times\beta_1 + (Treatment=GSK)\times\beta_2 + (Prior\ Biologic\ Use^*)\times\beta_4 + (Baseline\ PASI\ score^*)\times\beta_5$
Prior distributions for coefficients (**β**)	**β** = fixed effect parameters associated to predictors • β_1: informative prior such that $logit^{-1}(\beta_1) \sim$ mixture of Betas* • β_2: non-informative prior such that $logit^{-1}(\beta_2) \sim Beta(1/3, 1/3)$ • Other β_k: non-informative priors of N(0, SD=100) *Expected prior is a mixture of Be(5.39, 69) and Be(1/3,1/3), weighted to 90% and 10% respectively. Final prior will be reported in the CSR.
Model Checking & Diagnostics	
See Section 5.1.1	
Results Presentation	
• Posterior medians and 95% CrI of true response rate for each treatment group. • Posterior medians and 95% CrI for the true difference in proportion of responders (GSK2982772 – placebo) and odds ratios of GSK2982772 to placebo. • Probabilities that the true treatment difference is greater than a range of values of interest (e.g. 0%, 20%, 45%, 55%). See OPS outputs list for details. • Probabilities that the true response rate on active is greater than a range of values of interest (e.g. 0%, 30%, 55%). See OPS outputs list for details.	
Interim Analysis	
The interim analysis will estimate the predictive probability of meeting various decision criteria including: - >55% probability that true difference in PASI75 response (GSK2982772 – Placebo) above 45% - >97.5% probability that true difference in PASI75 response (GSK2982772 – Placebo) above 0%	

Predictive probabilities will be calculated via simulation assuming a total sample size of 21 (14:7 for GSK2982772:Placebo).

The parameter posterior distributions from the Bayesian logistic regression analysis of interim data will be used to simulate predicted PASI75 responses for remaining trial subjects. For participants yet to be enrolled, average covariate values will be assumed.

The predicted data will be combined with the observed interim data and the Bayesian logistic model applied to assess the decision criteria. This process will be repeated for each run of the MCMC procedure. The proportion of times the decision criteria is met will be the predicted probability.

5.2.3. Sensitivity analyses

Where informative priors have been used, a sensitivity analysis using vague priors (no historical borrowing) will also be produced.

Additional sensitivity analyses to assess the impact the missing data handling for binary data may be produced, such as using a LOCF approach to missing data.

5.2.4. Supplementary analyses

A supplementary analysis where the primary analysis is repeated using the Modified ITT population may be produced to assess the treatment effect in subjects able to complete at least 4 weeks of treatment. A frequency table of PASI response using this population would also be produced.

Off-treatment PASI data, collected following treatment discontinuation prior to Week 12, may be used for additional supplementary analyses if available.

5.2.5. Subgroup analyses

No formal subgroup analysis is planned. Descriptive statistics in the form of a frequency table of PASI75 response by prior biologic use will be produced.

5.3. Secondary Endpoint(s) Analyses

5.3.1. Definition of endpoint(s)

The secondary efficacy endpoints are:

Categorical endpoints

- PASI50, PASI90 and PASI100 response at Week 12 (Day 85), where PASI*X* response is defined as a reduction in PASI score from baseline of at least *X*%.
- sIGA response at Week 12 (Day 85), defined as [redacted] (0) or [redacted] (1).

Continuous endpoints

- Change from Baseline in PASI scores at Week 12 (Day 85)
- Change from Baseline in psoriatic BSA at Week 12 (Day 85).

5.3.2. Main analytical approach

Categorical endpoints

The proportion of participants achieving additional PASI responder endpoints of interest (PASI50/90/100) will be summarised by treatment arm and visit. Missing values will be imputed as non-responders. Credible intervals for response rates will be included (using Be(1/3, 1/3) prior for all treatment arms and visits).

The sIGA scores will be summarised as categorical data with the proportion of participants achieving each sIGA score being presented by treatment group and visit. The proportion of sIGA [redacted] (0) or [redacted] (1) will also be presented, with missing values imputed as non-responders. Credible intervals for response rates will be included (using Be(1/3, 1/3) prior for all treatment arms and visits).

Line plots of proportion of responders (with 95% CrI) over time by treatment group will be produced for both PASI and sIGA responder endpoints.

A Bayesian logistic regression approach will be used to assess response rates at Week 12, details given in Table 3.

Continuous endpoints

Both secondary and exploratory objectives of BSA and PASI score will be investigated using the same Bayesian repeated measures model (MMRM) analysis.

Summary statistics by treatment and visit will be provided for change from baseline in both PASI score and BSA. A summary of percentage change in PASI will also be provided.

A Bayesian MMRM approach will be used to account for the repeated visits (details given in Table 4). This approach assumes missing values are MAR.

Line plots of posterior means (±SD) from the MMRM analysis over time by treatment group will be provided.

Table 3 Statistical Analysis of Categorical Secondary Endpoint(s)

Endpoint(s)	
• Proportion of PASI50, PASI90 and PASI100 responders at Week 12 (Day 85) • Proportion of sIGA CCI (0) or CCI (1) at Week 12 (Day 85)	
Analysis Method	
Bayesian Logistic Regression	
Model Specification	
Outcome	y_i = Response (0/1) for participant *i*
Predictors	• Treatment (categorical) • Prior Biologic Use (categorical) • Baseline score (sIGA to be treated as continuous) Unless stated otherwise the predictors (not including study treatment) will be centered around their estimated mean prior to inclusion in the model
Model	$y_i \sim Ber(p_i)$ $logit(p_i) = (Treatment=Placebo)\times\beta_1 + (Treatment=GSK)\times\beta_2 + (Prior\ Biologic\ Use^*)\times\beta_4 + (Baseline\ PASI\ score^*)\times\beta_5$
Prior distributions for coefficients (**β**)	**β** = fixed effect parameters associated to predictors • β_1 & β_2: non-informative prior such that $logit^{-1}(\beta_k) \sim Beta(1/3, 1/3)$ • Other β_k: non-informative priors of N(0, SD=100)
Model Checking & Diagnostics	
See Section 5.1.1	
Results Presentation	
• Posterior medians and 95% CrI of true response rate for each treatment group. • Posterior medians and 95% CrI for the true difference in proportion of responders (GSK2982772 – placebo) and odds ratios of GSK2982772 to placebo. • Probabilities that the true treatment difference is greater a range of values of interest (e.g. 0, 20, 40). See OPS outputs list for details.	

Table 4 Statistical Analysis of Continuous Secondary Endpoint(s)

Endpoint(s)	
• Change from Baseline PASI scores at Week 12 (Day 85) • Change from Baseline in psoriatic BSA at Week 12 (Day 85)	
Analysis Method	
Bayesian GLMM with natural link (MMRM equivalent)	
Model Specification	
Outcome	$\mathbf{y}_i$ = vector of change from baseline for participant *i*
Predictors	• Treatment (categorical) • Visit (categorical) • Treatment*visit (categorical) • Prior Biologic Use (categorical) • Baseline (continuous) • Baseline*visit (continuous) Unless stated otherwise the predictors (not including study treatment or visit) will be centered around their estimated mean prior to inclusion in the model
Model	$\boldsymbol{y}_i \sim MVNormal(\boldsymbol{\mu}_i, \boldsymbol{\Sigma})$ $\boldsymbol{\mu}_i = X_i \boldsymbol{\beta}$
Prior distributions for coefficients (**β**)	**β** = fixed effect parameters associated to predictors • β_k : non-informative prior of N(0, SD=100)
Prior distributions for random effects (**b**)	• **Σ** ~ Inverse Wishart (J, S), with J = number of visits (degree of freedom), S = identity matrix Note: 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 5.1.1	
Results Presentation	
• Posterior mean, SD and 95% CrI will be presented for each treatment by timepoint interaction. • Posterior mean treatment differences (GSK2982772 – placebo) and associated 95% CrI will be produced for each timepoint. • Probabilities that the true treatment difference at each visit is greater a range of values of interest (e.g. 0, 100) may be provided. See OPS outputs list for details. • Outputs produced will include results for earlier timepoints in addition to the objective specified timepoint of Week 12 (Day 85).	

5.3.3. Sensitivity analyses

No sensitivity analyses are planned for secondary efficacy endpoints.

5.3.4. Supplementary analyses

No supplementary analyses are planned for secondary efficacy endpoints.

5.3.5. Subgroup analyses

No subgroup analyses are planned for secondary efficacy endpoints.

5.4. Safety Analyses

Displays will be based on GSK Core Data Standards. No formal statistical testing will be performed on Safety data.

5.4.1. Extent of Exposure

Descriptive summaries of exposure data will be provided, including the average dose taken, duration of exposure and cumulative actual dose. Study intervention compliance will be reported in exposure listings and will be defined in the OPS.

The following definitions will be used for exposure:

- Duration of exposure (days) is defined as time between first and last dose dates (last dose-first dose +1).
- Cumulative actual dose (mg) is defined as the total actual dose received (mg) during the 12-week treatment period (total number of active tablets taken x 480mg).
- The average daily dose (mg) taken is defined as the cumulative actual dose divided by the duration of exposure.

Cumulative actual dose will be determined from the number of tablets in dispensed and returned bottles.

5.4.2. 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 following AE categories will be provided:

- AE
  - Any AEs
  - Common* non-serious AEs
  - AEs related to study intervention
  - AEs leading to permanent discontinuation of study intervention

- SAE
  - Any SAEs
  - SAEs related to study intervention
  - Fatal SAEs

*For disclosure purposes, common is defined as AEs occurring in at least 5% of any treatment arm. Due to the small sample size of this study this table will include all non-serious AEs.

A summary of number and percentage of participants with any adverse events by maximum intensity will be produced. The AE summaries will be sorted by System Organ Class (SOC) and Preferred term (PT) in descending order. The summary will use the following algorithms for counting the participant:

- **Preferred term row**: Participants experiencing the same AE preferred term several times with different severities will only be counted once with the maximum severity.

- **Any event row**: Each participant with at least one adverse event will be counted only once at the maximum severity no matter how many events they have.

A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. Similarly, a study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing.

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

Summaries tables may be omitted if the number of events is sufficiently low.

5.4.2.1. Adverse Events of Special Interest

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

5.4.3. Laboratory Data

Separate summary tables for haematology and chemistry laboratory tests as well as urine concentration parameters will be produced. Liver function laboratory tests and lipid 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 (criteria are listed in the OPS)
- 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.
An e-DISH plot of maximum post-baseline total bilirubin versus maximum post-baseline ALT will be created.

5.4.4. Vitals Signs

A summary of change from baseline vital sign values will be provided by visit and treatment group, including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, weight, BMI and temperature.

Blood pressure and heart rate values will be categorized into clinical concern ranges (listed in the OPS).

5.4.5. ECG

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

- 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.
- Summary of change from baseline in ECG values. In the case of triplicate ECG measurements, summaries will use the average of the triplicate, listings will present all individual measurements.

The clinical concern ranges for ECG parameters are defined in the OPS. The absolute and change from baseline ECG values will be rounded to the nearest integer before being categorized according to the clinical concern ranges.

The following summaries of participants

- A summary of QTcF absolute values will display the number and percentage of participants with a post-baseline increase to a value within each clinical concern range for the worst-case post-baseline only.
- A summary of change from baseline QTcF values will display the number and percentage of participants with a change within each range for the worst-case post-baseline. Participants with missing baseline values will be excluded from this summary.

5.4.6. C-SSRS

A summary of C-SSRS data may be produced if there are multiple cases (>3) of suicidal ideation or behaviour, otherwise the data will be listed only.

5.5. Pharmacokinetic

Pharmacokinetic analyses will be conducted using the PK population.

Pharmacokinetic blood samples will be collected pre-dose at Week 2 (Day 15), 4 (Day 29), 8 (Day 57) and 12 (Day 85) visits to measure trough plasma concentrations of GSK2982772. Skin biopsies will be taken pre-dose at Week 4 (Day 29) and Week 12 (Day 85) to measure trough concentrations of GSK2982772 in the skin.

Summaries of trough plasma and skin GSK2982772 concentrations by visit will be produced as well as for PK predicted target engagement (the formula for this derivation is provided in the OPS).

Line plots of individual participant trough plasma and skin concentrations by visit will be produced as well as a plot for the treatment group average by visit.

Scatter plot of trough skin concentration versus trough plasma concentration at Week 4 (Day 29) and Week 12 (Day 85) will be produced.

5.5.1. Pharmacokinetic/Pharmacodynamic

The relationship between trough concentration of GSK2982772 and target engagement in both plasma/blood and skin (data permitting) will be investigated graphically using scatter plots.

Exploratory plots may be presented for individual and/or pooled plasma concentration versus change from baseline and/or absolute PASI score.

A population analysis will be implemented by CPMS to describe the PASI score (change from baseline and absolute) versus time course (up to Week 12) using a longitudinal model in order to predict the PASI score and the derived PASI75 at Week 16 (additional time point of interest for comparison to competitors). The model structure will be dependent on the emerging data.

If data permit, potential relationship between trough concentration of GSK2982772 and PASI score will be studied. PASI scores (change from baseline and absolute) over time (up to Week 12 (Day 85)) will be modelled in order to predict the PASI score at Week 16 using a non-linear mixed effect approach. Exposure-response may also be evaluated for other efficacy or PD biomarkers. This work will be conducted by the GSK DMPK group and will not form part of the CSR delivery.

5.6. Exploratory Endpoint(s) Analyses

5.6.1. Pharmacodynamic

Pharmacodynamic analysis will be conducted on the Safety population.

Target engagement of RIP1 kinase is defined as the percentage reduction of Free/Total relative to baseline. Target engagement in both blood and skin will be summarized by treatment group and visit.

Line plots of both individual and average target engagement by treatment group will be presented over time for both skin and blood. Boxplots of the target engagement data by visit and treatment may also be produced.

A Bayesian MMRM analysis of the log difference in ratio of free to total RIP1 will be used to analyse target engagement in the blood and skin over time (details given in Table 5).

Following the implementation of Protocol Amendment 3, skin biopsies to be used to assess target engagement in the skin are not required. The MMRM analysis of skin target engagement outlined above may not be produced if only limited skin data is available.

Table 5 Statistical Analysis of Continuous Exploratory Endpoint(s)

Endpoint(s)	
• Log(Ratio) – Baseline log(Ratio) in the blood at Week 12 (Day 85) • Log(Ratio) – Baseline log(Ratio) in the skin at Week 12 (Day 85). Where Ratio = Free RIPK1/Total RIPK1	
Analysis method	
Bayesian GLMM with natural link (MMRM equivalent)	
Model Specification	
Outcome	$\mathbf{y}_i$ = vector of change from baseline for participant *i*
Predictors	• Treatment (categorical) • Visit (categorical) • Treatment*visit (categorical) • Prior Biologic Use (categorical) • Baseline (on log scale) (continuous) • Baseline (on log scale)*visit (continuous) Unless stated otherwise the predictors (not including study treatment or visit) will be centered around their estimated mean prior to inclusion in the model
Model	$\boldsymbol{y}_i \sim MVNormal(\boldsymbol{\mu}_i, \boldsymbol{\Sigma})$ $\boldsymbol{\mu}_i = X_i \boldsymbol{\beta}$
Prior distributions for coefficients (**β**)	**β** = fixed effect parameters associated to predictors β_k : non-informative prior of N(0, SD=100)
Prior distributions for random effects (**b**)	**Σ** ~ Inverse Wishart (J, S), with J = number of visits (degree of freedom), S = identity matrix Note: 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 5.1.1	
Results Presentation	
• Adjusted ratios to baseline and 95% CrI will be derived using the following transformation: exp(posterior mean) for each treatment group • Percentage target engagement will be calculated using the formula: (1 – Adjusted ratio)*100%. • Ratios to placebo and 95% CrI will be calculated by back-transforming (exp()) the difference in posterior means and associated 95% CrI. This will be used to derive the percentage reduction in Free/ Total for GSK2982772 compared to placebo. • Summary tables and figures produced will include results for earlier timepoints in addition to Week 12 (Day 85).	

5.7. Other Analyses

Additional analyses will be conducted on exploratory biomarkers including: proteomic and metabolic biomarkers in the blood, histopathological markers in the skin and transcriptomic RNA-seq data in the skin. Details of these analyses are given in the OPS.

5.8. Interim Analyses

An interim analysis (IA) is planned to occur when at least six participants on GSK2982772 have completed the Week 12 (Day 85) visit or withdrawn from study treatment. The purpose of the IA is for internal decision making about future GSK2982772 trials and assess futility. The study may be stopped for futility if the probability of a positive outcome at the end of the trial is low based on the data available at the IA. The trial cannot be stopped early based on positive efficacy data.

Predictive probabilities will be calculated via simulation. The parameter posterior distributions from the Bayesian logistic regression analysis of interim data will be used to repeatedly simulate PASI75 response for remaining trial subjects. The predicted data will be combined with interim data to assess end of study criteria and calculate the proportion of times the decision criteria are met.

The data will be reviewed by an internal Data Review Committee. The committee will include the study statistician, the study pharmacokineticist and a limited number of GSK staff. A DRC charter will identify the specific staff to form part of the DRC, as well as detail the data to be reviewed, planned analyses, guidelines for the decision rules to be followed and a dissemination plan for interim decisions.

A subset of the outputs for the end of study will be produced for the IA. These will focus on efficacy data including, but not limited to:

- Summaries of PASI response data and change from baseline in PASI score by treatment and visit as outlined in Section 5.3.2 (Modified ITT population).
- Bayesian analysis of PASI75 response at Week 12 (Day 85) as outlined in Section 5.2.2 (Modified ITT population).
- Summaries of PK data and predicted target engagement as outlined in Section 5.5 (PK population).
- Summary of longitudinal model used to predict PASI score and the derived PASI75 at Week 16, outlined in Section 5.5.1, (conducted by CPMS on the ITT population).
- Summaries of disposition and psoriatic baseline characteristics (Randomised population).

Safety monitoring of blinded data will be conducted by the internal GSK Safety Review Team (SRT) at regular intervals throughout the study, see Section 8.2 of Protocol.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
AE	*Adverse Event*
A&R	*Analysis and Reporting*
BSA	*Psoriasis body Surface Area*
CI	*Confidence Interval*
CrI	*Credible Interval*
CSR	*Clinical Study Report*
C-SSRS	*Columbia Suicide Severity Rating Scale*
DRC	*Data review committee*
eCRF	*Electronic Case Record Form*
GSK	*GlaxoSmithKline*
IA	*Interim Analysis*
ITT	*Intent-To-Treat*
LS Mean	*Least Squares Mean (or marginal mean)*
MAR	*Missing At Random*
MMRM	*Mixed Model Repeated Measures*
MR	*Modified Release*
OPS	*Output and Programming Specification*
PASI	*Psoriasis Area Severity Index*
PCI	*Potential Clinical Importance*
PD	*Pharmacodynamic*
PK	*Pharmacokinetic*
PT	*Preferred Term*
QD	*Once Daily*
QTcB	*Bazett's QT Interval Corrected for Heart Rate*
QTcF	*Frederica's QT Interval Corrected for Heart Rate*
RNA-seq	*Ribonucleic Acid Sequencing*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SD	*Standard Deviation*
SE	*Standard Error*
sIGA	*Static Investigator's Global Assessment of Disease Activity*
SOC	*System Organ Class*
TEAR1	*Target Engagement Assay RIP1*
TMF	*Trial Master File*
ULN	*Upper Limit of Normal*

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
None

7. REFERENCES

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