Protocol

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/ 03

Compound Number or Name: GSK2982772

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

Study Phase: Phase 1b/2a

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

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 / Amendment 03

Compound Number or Name: GSK2982772

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Date

The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 03	*06-JAN-2021*	*2019N420902_03*
Amendment 02	*14-JUL-2020*	*2019N420902_02*
Amendment 01	*09-APR-2020*	*2019N420902_01*
Original Protocol	*07-JAN-2020*	*2019N420902_00*

Amendment 03 06-JAN-2021

Overall Rationale for the Amendment: To update the skin biopsy sample collection strategy to aid with study recruitment and clarify some operational aspects of COVID-19 testing.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Objectives and Endpoints Section 3 Objectives and Endpoints Section 4.2 Scientific Rationale for Study Design Section 9.1 Statistical Hypotheses Section 9.2 Sample Size Determination	Clarification on description of binary endpoints so they relate to an individual's response Deletion of pharmacokinetics objective related to investigating trough skin concentrations of GSK2982772	Clarification Updated based on revised skin biopsy collection strategy
Section 1.3 Schedule of Activities	Updated to clarify requirement and options for COVID-19 testing. Also updated to reflect revised skin biopsy collection strategy	Updates made to aid study recruitment
Section 4.1 Overall Design	Updated to reflect revised skin biopsy collection strategy	Update made to aid study recruitment
Section 6.2 Measures to Minimize Bias: Randomization and Blinding	Updated to allow off-site dosing at Weeks 2, 4 and 8 in order to avoid an overdose, and provide instructions on follow-up with the study participant	Operational Update

Section # and Name	Description of Change	Brief Rationale
Section 6.3 Study Intervention Compliance		
Section 6.4 Concomitant Therapy	Clarified wording to define stable usage of allowed medications.	Clarification
Section 8.5 Pharmacokinetics	Removal of Section 8.5.3 and Section 8.5.4 related to skin PK.	Updated based on revised skin biopsy collection strategy
Section 8.8 Biomarkers	Updated to remove reference to target engagement using skin biopsies.	Updated based on revised skin biopsy collection strategy
Section 9.1 Statistical Hypotheses	Clarified language to reflect objective of estimating efficacy response (removal of reference to hypothesis testing).	Clarification
Section 9.3 Populations for Analyses	Added COVID-19 population and description to table.	Updated to reflect new analysis population to be used for a subset COVID outputs
Section 9.4 Statistical Analyses	Added minor clarification to Bayesian analysis. Removal of reference to CPMS model in SAP.	Clarification

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

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

Rationale: GSK2982772 is a first-in-class, highly selective, receptor-interacting protein 1 kinase (RIP1) inhibitor being developed for the treatment of psoriasis. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including tumour-necrosis factor (TNF) family cytokines, ligands for toll-like receptor (TLR)-3 and TLR4, sensors of viral infection and interferons. To date, approximately 303 participants have been exposed to active treatment (IR formulation) of GSK2982772 at doses that ranged up to 960 mg, including healthy volunteers and three patient populations (mild to moderate plaque psoriasis, moderate to severe rheumatoid arthritis and moderate to severe ulcerative colitis).

Plaque psoriasis is a chronic relapsing inflammatory skin disease that is characterized by keratinocyte hyperproliferation and epidermal hyperplasia. Standard treatment for psoriasis generally requires long-term use of topical therapies, psoralen and ultraviolet A (PUVA), ultraviolet B (UVB) and/or systemic immunosuppressant therapies to achieve and maintain adequate disease control.

In the last decade, biological therapies targeting TNF or Th17/ interleukin (IL)12/IL22/IL23 pathways have demonstrated significant clinical efficacy for those patients who had inadequate response to standard topical, UV, and/or oral therapy. However, biologic therapies have several limitations: high cost, risk for loss of response, side effects, development of anti-drug antibodies (ADAs) and require parenteral administration, which can limit patient acceptability and treatment compliance. In addition, apremilast (Otezla), a PDE4 inhibitor, has been recently approved as an oral psoriasis treatment but its efficacy is modest in moderate to severe patients. GSK2982772 may fill a niche in the treatment of plaque psoriasis.

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 CCI (0) or CCI (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 (AEs) • 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)

Objectives	Endpoints
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.

Additional exploratory endpoints are included to further investigate the clinical effect of GSK2982772, and the effect of GSK2982772 on pathways in the skin and blood and target engagement in blood.

Overall Design: This is a multi-centre, randomised, double-blind, placebo-controlled study in participants with moderate to severe psoriasis. The study is designed to assess the efficacy and safety of GSK2982772 administered as a QD MR oral tablet. Participants will receive 960 mg of GSK2982772 or placebo for 12 weeks. In addition, blood and skin biopsy samples will be collected to explore the pharmacokinetics, target engagement in blood, and pharmacodynamic effects in blood and in the skin.

An interim futility analysis will be conducted when at least six participants receiving GSK2982772 have completed the Week 12 visit or discontinued study treatment.

Disclosure Statement: This is a randomized, double-blind, placebo-controlled trial.

Number of Participants: Approximately 32 participants will be screened to achieve 21 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.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration: Following Screening and successful completion of Baseline measurements, participants will be centrally randomised and will receive study intervention administered as oral tablets once daily for 12 weeks. Participants will be randomised (2:1) to receive 960 mg GSK2982772 or placebo as shown in study schematic in Section 1.2.

The duration of the study, including Screening and follow-up, is not expected to exceed 21 weeks for each participant.

Participants will receive their first dose on Day 1 at the investigational site. On defined visit days, participants will administer study intervention after completion of their pre-

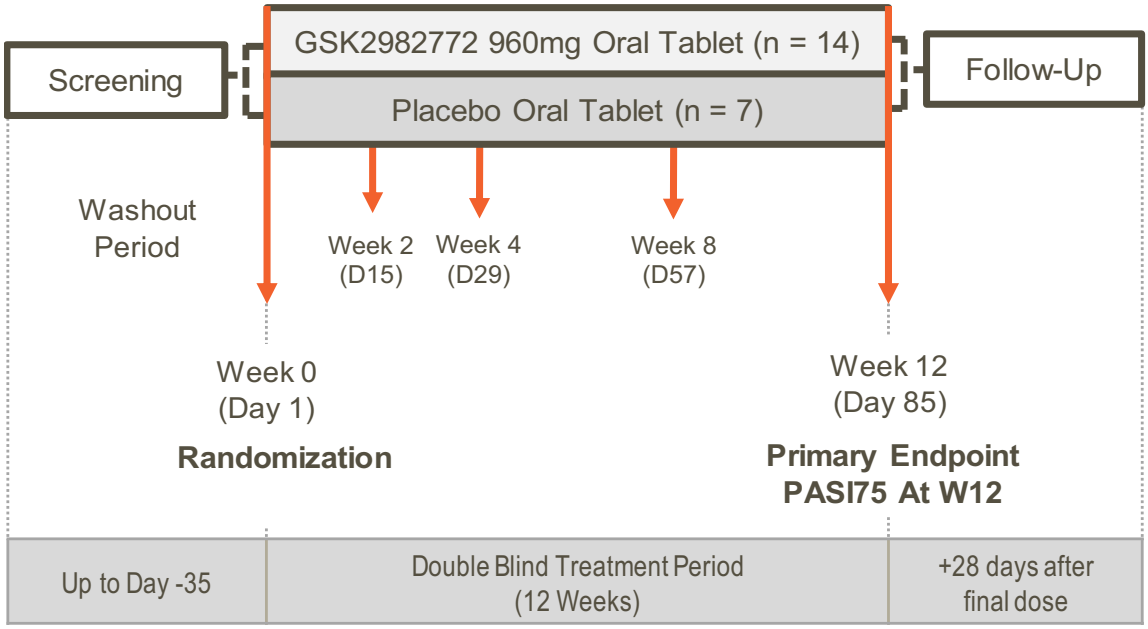
dose assessments. On all other days, participants will self-administer study intervention at home.

A completed participant is one who has completed all planned study assessments including the follow-up visit.

The end of the study is defined as the last participant's last visit.

Data Monitoring or Other Committee: Yes

1.2. Schema



1.3. Schedule of Activities (SoA)

This section lists the procedures and parameters of each planned study assessment.

Screening Visit

Procedures	**Screening** (up to -35 days)
Informed Consent[1]	X
Inclusion/Exclusion Criteria Review	X
Demography	X
Medical History[2]	X
QuantiFERON-TB Gold Plus Test[3]	X
HIV, Hep B and Hep C Screen[4]	X
Pregnancy Test[5]	X
FSH & Oestradiol[6]	X
Safety Assessments	
Full Physical Exam[7]	X
12-lead ECG[8]	X
Vital Signs[9]	X
COVID-19 test (SARS-CoV-2)[10]	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X
Clinical Laboratory (Haematology, Chemistry and Urinalysis)	X
Concomitant Medication Review	X
SAE - commencing from time of informed consent	X
Register Visit in Randomization and Medication Ordering System New Generation (RAMOS NG)	X
Severity of Disease	
Psoriasis Area and Severity Index (PASI)	X
Psoriatic Body Surface Area (BSA)	X
Static Investigator Global Assessment of Psoriasis Severity (sIGA)	X

Footnotes:

1. Includes study specific consent (which must be obtained before Screening activities commence) and a separate optional consent for Pharmacogenetics (PGx) (which may be collected at any time before PGx sample collection).
2. Includes past and current conditions, medication history, and family history of premature CV disease.
3. In cases where the QuantiFERON-TB Gold Plus test is indeterminate, the participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative or they have a negative tuberculin skin test.
4. If hepatitis C antibody is positive, a hepatitis C Ribonucleic Acid Polymerase Chain Reaction (RNA PCR) assay will be performed on a fresh sample to confirm the result.
5. For women of child-bearing potential only: Serum pregnancy test must be performed at Screening.
6. For women whose postmenopausal status is in doubt only. Refer to Appendix 4.
7. Includes height at Screening visit.
8. Triplicate ECGs will be taken at Screening and at Day 1 (Baseline). At all other specified time points single ECGs are acceptable. However, if QTc prolongation is detected triplicate ECGs will be performed. Fridericia's formula (QTcF) must be used for the QTc correction.
9. Blood pressure (systolic and diastolic), heart rate, respiratory rate and temperature to be assessed, as well as COVID-19 symptoms check.

10. This test should be performed at the screening visit and will be analysed by the central laboratory. If the screening visit is more than 14 days before the Week 0 (Day 1) visit, the test must be repeated, The 2nd COVID test may be run by the central laboratory (7-9 days before the Day 1 visit), done at a local testing facility (test must be performed within 9 days of Day 1, with documented results prior to dosing), or via completion of a COVID point of care test at the site (within 9 days of or on Day 1).

Treatment Period

Procedures	**Treatment Period**					**Follow-up**	**Early Withdrawal**
	Week 0 (Day 1) Baseline	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Week 16 (Day 113)	
	N/A	±3D	±3D	±3D	±3D	±7D	NA
Inclusion/Exclusion Criteria Review[1]	X[3]						
Pregnancy Test[2,3]	X		X	X	X	X	X
Safety Assessments							
Full Physical Exam						X	X
Brief Physical Exam[3]	X	X	X	X	X		
12-lead ECG[3, 4]	X	X	X	X	X	X	X
Vital Signs[3, 5]	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)[3]	X	X	X	X	X	X	X
Clinical Laboratory[3] (Haematology, Chemistry and Urinalysis)	X	X	X[6]	X[6]	X	X	X
Fasting Lipids, Glucose and Insulin[3, 7]	X		X		X		
Concomitant Medication Review	continuous throughout study						
AE/SAE Review	continuous throughout study						
Study Treatment							
Randomisation	X						
Study Treatment[8]	←----------				----------→		
Dispense Study Treatment	X	X	X	X			
Collect Study Treatment		X	X	X	X		X
Assess Study Treatment Compliance		X	X	X	X		X
Register Visit in RAMOS NG	X	X	X	X	X	X	X
Clinical Outcomes Assessments							
Psoriasis Area and Severity Index (PASI)[3]	X	X	X	X	X	X	X
Psoriatic Body Surface Area (BSA)[3]	X	X	X	X	X	X	X

Procedures	**Treatment Period**					**Follow-up**	**Early Withdrawal**
	Week 0 (Day 1) Baseline	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Week 16 (Day 113)	
	N/A	±3D	±3D	±3D	±3D	±7D	NA
Static Investigator Global Assessment of Psoriasis Severity (sIGA) [3]	X	X	X	X	X	X	X
Other Assessments and Procedures							
PK Blood Sample[3]		X	X	X	X		X
Pharmacogenetic (PGx) Sample	X[9]						
Skin Biopsy Sample[3,10]	X		X[11]		X		X[12]
PD / Biomarker Blood Samples[3]	X		X		X		X

Footnotes:

1. All inclusion/exclusion criteria will be reviewed on Day 1 (Baseline) prior to randomization. In addition, physical exam (brief), ECG, vital signs, C-SSRS, and disease severity criteria (PASI, BSA and sIGA) will be re-assessed.
2. For women of child-bearing potential only: Serum pregnancy test must be performed at Screening. At all other visits other than Week 2, a urine pregnancy test will be performed. If a urine test result is positive or ambiguous, a confirmatory serum test must be performed.
3. Perform pre-dose during treatment period (NB excludes Week 12/Day 85 visit as Day 84 is the last day of dosing).
4. Triplicate ECGs will be taken at Screening and on Day 1 (Baseline). At all other specified time points single ECGs are acceptable. However, if QTc prolongation is detected triplicate ECGs should be performed. Fridericia's formula (QTcF) must be used for the QTc correction.
5. Blood pressure (systolic and diastolic), heart rate, respiratory rate and temperature to be assessed at all time points, as well as COVID-19 symptoms check.
6. Urinalysis not required on Days 29 and 57.
7. Blood samples will be taken after overnight fast for fasting lipid, glucose and insulin analysis.
8. Following Day 1, participants will take study medication at home. At the Week 2, 4, and 8 visits, the dose should not be taken before the clinic visit. Instead, the dose should be taken either on site, after all pre-dose study assessments have been completed (preferred), or after the visit (at home) if the timing of the on-site dosing would result in the dose being less than 20 hours after the last dose (i.e. overdose). There is no dose administered at Week 12/Day 85.
9. PGx sample collected at Day 1, after randomization and if the participant provides additional, optional informed consent. If sample is not collected at Day 1, it can be collected at any time post-randomization.
10. Mandatory skin biopsy samples will be collected from all participants: one non-lesional and one lesional biopsy will be collected on Day 1 (Baseline) before 1st dose of study medication. One additional lesional biopsy sample from the same plaque will be collected pre-dose at Week 12/Day 85.
11. One optional lesional skin biopsy sample will also be collected at Week 4/Day 29 from consenting participants only. A separate consent must be obtained.

12. Collection of 1 lesional skin biopsy sample required at Early Withdrawal visit if study withdrawal occurs prior to Week 12 and if the participant has completed at least 14 days of treatment. If biopsy has already been obtained within the last 14 days, then another biopsy will not be collected.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

GSK2982772 is a first-in-class, highly selective, receptor-interacting protein 1 kinase (RIP1) inhibitor being developed for the treatment of psoriasis.

2.1. Study Rationale

This is a Phase 1b/2a study in participants with moderate to severe plaque psoriasis. The study is designed to assess the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of 960 mg GSK2982772 administered as a once daily modified release (MR) formulation.

This is the second study performed in participants with plaque psoriasis.

The first study (203167) was an experimental medicine (EM) study designed to understand the mechanism of action and potential for clinical efficacy of GSK2982772 in participants with mild to moderate plaque psoriasis. GSK2982772 was administered as 60 mg BID and 60 mg TID of an immediate release (IR) tablet formulation. Both dose levels were shown to be well tolerated. A small reduction in Psoriatic Lesion Severity Sum (PLSS) and improvement in Psoriatic Area and Severity Index (PASI) was observed for the BID versus placebo cohort but not for the TID cohort versus placebo. This is believed to be due to the unexpectedly large response observed in the placebo TID treatment group. In addition, a reduction in histopathological markers (epidermal thickness, cluster of differentiation 3 (CD3)+ T-Cells, CD11+ myeloid dendritic cells) in both cohorts in comparison to placebo was observed. Exposure-response relationship (E-R) analyses of the combined BID and TID regimens showed an improved PLSS score with increasing tertiles of GSK2982772 trough plasma concentrations and participants with highest GSK2982772 skin concentrations tended to have better PLSS score. Based on the observed E-R, it is hypothesised that 60 mg BID/TID dosing regimens did not provide sufficient exposure to achieve clinically relevant efficacy. In the current study, a once daily dose of 960 mg MR provides ~15-fold higher trough plasma concentrations than was achieved with the 60 mg TID IR regimen in study 203167. This magnitude of increase should result in a significant shift in the pharmacological response, and hence efficacy response, thereby determining proof of concept for receptor-interacting serine/threonine-protein kinase 1 (RIPK1) inhibition in moderate to severe psoriasis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK2982772 can be found in the Investigator's Brochure (IB).

2.2. Background

RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including tumour-necrosis factor (TNF) family cytokines, ligands for toll-like receptor (TLR)-3 and TLR4, sensors of viral infection and interferons. Through tight regulation by ubiquitylation, deubiquitylation and interaction with its receptors, RIP1 has dual roles as a kinase and a scaffolding protein, and serves as an upstream checkpoint for both cell death and survival [Ofengeim, 2013].

In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and NFκB- signalling [Griffiths, 2017; Humphries, 2015]

Plaque psoriasis is a chronic relapsing inflammatory skin disease that is characterized by keratinocyte hyperproliferation and epidermal hyperplasia. Psoriasis is considered a T helper type 1 and 17 (Th1 and Th17)-mediated disease, with the interleukin 23 (IL-23)/Th17 cell axis playing a crucial role. Keratinocyte activation following a trauma or infection results in plasmacytoid dendritic cell activation to produce type I interferons (IFN). Type I IFNs then activate myeloid dendritic cells, leading to release of IL-23 and IL-12, which then activate Th17, Th1 and Th22 cells to produce an abundance of pro-inflammatory cytokines (e.g. IL-17, IL-22, IFNγ and TNF) leading to an amplification of the inflammation [Lowes, 2014].

Standard treatment for psoriasis generally requires long-term use of topical therapies, psoralen and ultraviolet A (PUVA), ultraviolet B (UVB) and/or systemic immunosuppressant therapies to achieve and maintain adequate disease control.

In the last decade, biological therapies targeting TNF or Th17/IL22/IL23 pathways have demonstrated significant clinical efficacy for those patients who had inadequate response to standard topical, UV, and/or oral therapy. However, biologic therapies have several limitations: high cost, risk for loss of response, side effects, development of anti-drug antibodies (ADAs) and require parenteral administration, which can limit patient acceptability and treatment compliance.

Although apremilast, a phosphodiesterase-4 inhibitor (PDE4) inhibitor, has been approved as an oral psoriasis treatment, its efficacy is modest in patients with moderate to severe plaque psoriasis [Otezla drug label, 2019]. There remains a high unmet need for novel oral therapies that can achieve maximal sustained clearance of skin lesions and improvement in quality of life, balanced by favourable safety and tolerability profiles. Furthermore, an effective oral therapy could prevent transition to the use of biologic therapy, provide an option for patients to come off biologics or allow patients to have greater flexibility with dose modulation.

GSK2982772, an inhibitor of RIP1 kinase activity, may address this unmet need in the treatment of plaque psoriasis. To date, approximately 303 participants have been exposed to active treatment (IR formulation) of GSK2982772 at doses that ranged up to 960 mg, including healthy volunteers and three patient populations (mild to moderate plaque psoriasis, moderate to severe rheumatoid arthritis and moderate to severe ulcerative colitis). GSK2982772 will now be investigated in patients with moderate to severe psoriasis.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK2982772 may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2982772]		
Central Nervous System (CNS) effects	Non-clinical data: In initial 4-week nonclinical toxicology studies, neurological-related events (uncoordinated movement, irregular gait, trembling, hunched appearance and decreased activity) were observed in some rats and monkeys. In 13-week nonclinical toxicology studies, no neurological-related events were observed in rats or monkeys. In the 39-week good laboratory practice (GLP) toxicology study, there were no CNS findings observed in monkeys administered 6, 20 or 60 mg/kg/day. Clinical data: No drug-associated CNS adverse events reported in clinical studies.	Participant Selection: • Participants with known history of significant neurologic disorders including but not limited to progressive multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS), Alzheimer's and dementia will be excluded. • Individuals with potentially increased susceptibility for neurologic effects will be excluded based on medical history at Screening. Participant Monitoring: • Participants will be monitored for standard CNS-related AEs.
CNS suicidality	GSK2982772 is considered to be a CNS-active drug based on pre-clinical studies. Clinical data:	Participant selection: • Participants with a current history of Suicidal Ideation Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	To date in the GSK2982772 clinical programme, there have been some reports of lethargy, abnormal dreams, and depressed mood. In the Phase IIa psoriasis study (201367), one serious adverse event (SAE) of accidental overdose with ecstasy/ methylenedioxymethamphetamine (MDMA) was reported in a participant who received GSK2982772 60 mg BID. There was no evidence to suggest that this was a suicide attempt. Also, in this study, there was a participant who received GSK2982772 60 mg BID, who reported suicidal ideation at the Day 43 visit via C-SSRS. The participant reported that he had these thoughts on and off prior to joining the study and did not plan to take action on these feelings. No further suicidal ideation was reported by this participant. In the open-label modified release formulation study in healthy participants (205017), a completed suicide (by hanging) was reported 28 days after a single dose of GSK2982772. This individual had a prior undisclosed suicide attempt. Given the short half-life of GSK2982772, there is no temporal relationship	history of attempted suicide will be excluded from the study. Participant Monitoring: • Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. • Baseline and treatment emergent assessment of suicidality will be conducted by trained site personnel using the (C-SSRS in all participants. • Any participant in the study who experiences signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	to support a causal relationship between the completed suicide and GSK2982772.	
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in participants taking other immunomodulating drugs or corticosteroids. Clinical data: In the first time in human (FTiH) study, no SAEs were reported. One participant experienced an AE herpes zoster approximately 27 days after receiving his last dose with GSK2982772. The blinded Investigator determined this to be potentially drug-related. In the Psoriasis study (203167), one participant receiving GSK2982772 experienced an AE of herpes zoster on study Day 9. The blinded Investigator considered the AE to be of moderate severity and not related to study drug. AEs of genital herpes and oral herpes (one participant each) were reported in participants who received GSK2982772 60 mg TID in the Phase II Rheumatoid Arthritis (RA) study (203168).	Participant Selection: ● Participants with recurrent, chronic or active infections will be excluded from the study. Participants will be screened for tuberculosis (TB), human immunodeficiency Virus (HIV), Hepatitis B and C, and excluded from the study if positive. ● Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in participants with Psoriasis. Participant monitoring ● After administration of GSK2982772, participants will be monitored carefully for signs of infection and asked to report any signs of infection for investigation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Vaccinations	There is a theoretical risk that GSK2982772 could decrease an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	Participant Selection: • Attenuated or live vaccines should not be administered to participants from 30 days prior to the first dose of GSK2982772, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK2982772 is discontinued. • If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit: risk (e.g., risk of theoretical decreased responsiveness). • Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in participants with Psoriasis.
Respiratory effects	Non-clinical data: In the single dose Safety Cardiovascular and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14 day repeat oral dose respiratory function study, no respiratory effects on respiratory	Participant Monitoring: • Participants should be monitored for standard respiratory-related AEs. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	function (e.g., tidal volume, minute volume or respiratory rate) were observed at doses of 1 or 10 mg/kg/day. Clinical data: No respiratory SAEs were reported, nor were there any drug associated respiratory related AEs identified in the clinical programme to date.	
Drug interaction	In vitro studies investigating the induction and/or inhibition properties of GSK2982772 with cytochromes P450 (CYP) and uridine glucoronyltransferase (UGT) enzymes, as well as p-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and some uptake transporters have been completed. There is a moderate risk that GSK2982772 could be an inducer of CYP3A4 and may lower circulating levels of concomitant medications that are metabolized by CYP3A4 (e.g. oral contraceptives) when co-administered with GSK2982772. GSK2982772 is a Pgp substrate and co-administration of GSK2982772 with concomitant medications that are Pgp inhibitors could increase the circulating levels of GSK2982772.	Participant selection: • Participants who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. • Participants (WOCBP) who are taking oral contraceptives will be asked to use an additional non-hormonal form of contraception. Participant monitoring: • Concomitant medication usage will be reviewed and monitored prior to inclusion and during study duration. • Clinical laboratory results (e.g. liver function tests) will be routinely monitored throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	There is a low risk that GSK2982772 could be a perpetrator of organic anion transporter 3 (OAT3) substrate. However, methotrexate (MTX) (OAT3 substrate) exposures in participants in study 203168 were monitored before and after GSK2982772 treatment (60 mg BID or TID) and showed no discernible change. There is a moderate risk that GSK2982772 could be an inhibitor of CYP3A4 and may increase circulating levels of concomitant medications that are metabolized by CYP3A4 when co-administered with GSK2982772.	
Reproductive toxicity	Non-clinical data: • The no observed adverse effect level (NOAEL) for female fertility and early embryonic development and for reproductive performance and male-mediated developmental toxicity in rats and for embryofetal development in rabbits was considered to be 200 mg/kg/day. Based on the findings in pre-and postnatal development and embryofetal development studies in rats, the NOAEL for maternal F0 reproductive function and pre- and postnatal development of the F1 offspring is 100 mg/kg/day; although the	Participant selection: • Male and female participants of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 2 days after the last administration of study drug (Appendix 4). • Females of childbearing potential will undergo serum pregnancy test at Screening and then urine pregnancy testing monthly during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	NOAEL from the embryofetal development study was 10 mg/kg/day due to decreased fetal weights, decreased pup weights were not observed at 100 mg/kg/day in the pre- and postnatal development. In the rat, at higher doses (>200 mg/kg/day) that were toxic to the female (decreased body weight and food consumption and/or clinical signs), decreased corpora lutea, implantations, litter size and increased post-implantation loss were observed in the female fertility study, decreased fetal/uterus weight in the embryo-fetal development rat study and decreased pup viability and pup weight in the pre-and postnatal development study.	• Pregnant and lactating females are not eligible for inclusion in the study. Withdrawal criteria: • If a female participant, or female partner of a male participant, should become pregnant during the study, study medication should be discontinued. The participant will be followed to determine the outcome of the pregnancy. • Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE (Section 10.4)
Study Procedures		
Punch skin lesion biopsies	Potential risks of the procedure include discomfort, infection or bleeding.	Participant selection: • Participants with history of hypertrophic or keloid scarring, or known allergy to lidocaine or other local anaesthetics will not be included in the study. • Participants with a platelet count <100x 10^9/L will be excluded from participation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Participant management: • A local anaesthetic will be administered before each skin biopsy is taken (as per local practice) to reduce the risk of pain. The biopsy procedure will be done only by experienced personnel to reduce the risk of bleeding and scarring. Aseptic technique will be utilized to reduce the risk of infection. • The risk of infection, although low given the low invasiveness of the procedure, will be reduced by dressing the site after biopsy. • Participants will be advised to keep the site covered and dry for 24-48 hours before leaving open to the air. Participants will be instructed as to the signs and symptoms of infection, and to contact site personnel should they develop. This information will also be contained in the patient information leaflet. • Biopsy site healing will be monitored during the study as part of AE review.

2.3.2. Benefit Assessment

There are additional treatment options available for participants who have an inadequate response to current therapies for psoriasis. It is possible that treatment with GSK2982772 may be effective in the treatment of psoriasis, as the FTiH study demonstrated that the drug engaged with the target and produced *ex vivo* PD effects in RIP1-dependent cytokines macrophage inflammatory protein 1 alpha (MIP1α) and macrophage inflammatory protein 1 beta (MIP1β). There may be limited direct benefit to the participant for taking part in this trial. However, participants will indirectly benefit through their contribution to the process of developing new therapies in an area of unmet need.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded to participants with psoriasis by contributing to the understanding of the disease and the development of new therapies for patients with these conditions in the future.

3. 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 CCI (0) or CCI (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,	• Adverse events

Objectives	Endpoints
compared with placebo in participants with moderate to severe plaque psoriasis.	• 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, compared with placebo in participants with moderate to severe plaque psoriasis.	Additional PASI parameters: • PASI75 response (achievinge ≥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

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

4. STUDY DESIGN

4.1. Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled, repeat dose study to investigate the efficacy, safety and tolerability, PK and PD and of GSK2982772 960 mg MR QD in participants with active plaque-type moderate to severe psoriasis.

Each participant will participate in the study for no more than 21 weeks. This includes a Screening period up to 35 days, an 84 day (12 week) treatment period, and a 28 day follow-up period after the last dose.

Participants will attend the clinical site to be consented and, if eligible for the study, Screening assessments will be completed. Participants who have completed Screening assessments and are eligible will be randomized in a 2:1 ratio (active to placebo) to one of the following treatments and be dosed (Day 1) within 35 days of the Screening visit:

- 960 mg GSK2982772 QD

- Placebo QD

Punch skin biopsies will be performed on all participants: 1 non-lesional and 1 lesional biopsys will be collected at Baseline (predose). At Week 12 (D85), 1 lesional biopsy from the same plaque will be collectedat . An additional, optional lesional biopsy may also be collected at Week 4 (D29).

An interim analysis is planned to occur when at least six participants on GSK2982772 have completed the Week 12 visit or discontinued study treatment to aid internal decision making around subsequent GSK2982772 trials. 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 interim. The data will be reviewed by an internal Data Review Committee. The details of the planned analyses, data to be reviewed, Data Review Committee (DRC) membership and results dissemination will be given in an interim analysis charter.

The Post-Treatment Period is 28 days (4 weeks) long.

4.2. Scientific Rationale for Study Design

This study has been designed to evaluate the efficacy, safety, PK, and PD profiles of GSK2982772 in participants with moderate to severe plaque psoriasis.

Efficacy Endpoints

The PASI score is a clinician reported outcome which provides a single score combining the assessment of skin lesions (redness, thickness and scaling), weighted by the body surface area involvement in four anatomical regions (head, trunk, arms and legs). It is widely agreed that a 75% improvement in PASI (PASI75) is a clinically relevant endpoint for patients with moderate to severe plaque psoriasis. PASI75 has been used extensively in clinical trials and formed the basis for regulatory drug approvals.

The primary endpoint used to evaluate the efficacy of GSK2982772 in this study is the PASI75 response at Week 12 relative to Baseline. Week 12 was chosen since it represents the timepoint of near maximal response for previous psoriasis medicines in development [Checchio, 2017]. Additional PASI endpoints (e.g. PASI50, PASI90, PASI100 and PASI score) will be collected to support the secondary objectives of this study. Additional secondary efficacy endpoints incorporated in this study include the static sIGA and an assessment of BSA affected by psoriasis.

Patient Population

This study will evaluate GSK2982772 in participants with moderate to severe plaque psoriasis, defined as PASI (≥12), sIGA (≥3) and psoriasis BSA (≥10%). The moderate to severe population is considered optimal for demonstrating the efficacy and safety of GSK2982772 and reflects the population in which a potential new oral treatment may be utilised in the treatment of plaque psoriasis.

Placebo Rationale

The study includes a placebo arm to maintain the integrity of the study, preventing inflation of PASI75 scores which has been seen in some psoriasis (PsO) studies without placebo control [Griffiths, 2017]. Placebo use is minimized with a randomization ratio of 2:1.

Biomarker Rationale

Downstream pharmacology will be evaluated using a panel of histologic, transcriptomic, and proteomic endpoints including some in the RIP1 pathway. The disease biomarker strategy includes both site of action biomarkers assessed in skin biopsies as well as systemic inflammation biomarkers in blood for evidence of change with therapeutic intervention. Keratinocyte hyperproliferation and immune infiltrate will be evaluated by immunohistochemistry. Pharmacodynamic effect on other inflammation pathways will be evaluated using transcriptomic and proteomic analysis. Impact on metabolism will also be evaluated by measuring metabolic related endpoints. These measurements will allow for understanding of the mechanism of action of the drug.

4.3. Justification for Dose

In the study of participants with mild to moderate plaque psoriasis (203167), the magnitude of change in PLSS score was small with a treatment difference vs placebo of ~15% at Day 43. Since the E-R assessment showed an improved PLSS score with increasing tertiles of GSK2982772 trough plasma concentrations and participants with highest GSK2982772 skin concentration tended to have better PLSS score [GSK Document Number 2018N363258_01, it is hypothesised that 60 mg BID/TID dosing regimens did not provide sufficient exposure to achieve clinically relevant efficacy. In the current study, a once daily dose of 960 mg MR provides ~15-fold higher trough plasma concentrations than was achieved with the 60 mg TID IR regimen in the previous 203167 study. This magnitude of increase should result in a significant shift in the pharmacological response, and hence efficacy response, thereby determining proof of concept for RIPK1 inhibition in moderate to severe psoriasis.

The MR formulation (DiffCORE™) was developed to provide a once daily dosing regimen for GSK2982772 (study 209261). The MR dose of 960 mg (to be administered as 2 x 480 mg QD) was selected based on a balance of maximising GSK2982772 trough concentrations and staying within previously explored human GSK2982772 systemic exposure levels.

In study 209261, MR doses of 120, 240, 480 and 960 mg were evaluated. The systemic exposure to GSK2982772 was approximately linear over the dose range 240 to 960 mg (2x480 mg MR tablets). The bioavailability of the MR formulation in the fasted state relative to the IR formulation was approximately 60%. For the MR dose of 960 mg, the predicted steady-state geometric mean area under the concentration-time curve from 0 to 24 h ($AUC_{[0-24]}$) and maximum concentration (Cmax) values are 29.9 µg.h/mL and 1.75 µg/mL when administered in the fasted state and 40.2 µg.h/mL and 3.80 µg/mL when administered with a high fat meal. These values are within the observed geometric mean $AUC_{(0-24)}$ (48.5 ng.h/mL) and C_{max} (6.3 ug/mL) values observed for the 240 mg IR

TID dose in study 205184. In the 39 week monkey toxicology study the $AUC_{(0-24)}$ and C_{max} at the NOAEL (60 mg/kg/day) were 182 µg.h/mL and 23.2 µg/mL, respectively, resulting in approximate 4.6-fold and 5-fold safety margins for $AUC_{(0-24)}$ and C_{max} compared to the highest predicted exposures following administration of 960 mg with a high-fat meal.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosis of plaque psoriasis for at least 6 months before Screening visit.
3. Evidence of moderate to severe psoriasis, at Screening and Baseline before the first dose of study treatment, with:
    - PASI score ≥12, AND
    - Psoriasis plaques involving BSA ≥10%, AND
    - sIGA ≥3
4. Candidate for systemic therapy or phototherapy (includes naïve or previously treated), in the opinion of the Investigator.
5. Agrees to avoid any prolonged exposure to natural or artificial sources of ultraviolet (UV) radiation (e.g. sunlight, tanning beds or phototherapy) from 28 days before Day 1 until the follow-up visit, which may potentially impact the participant's psoriasis in the opinion of the Investigator (see Section 5.3.3).

Weight

6. Body mass index (BMI) within the range of 18.5 to 40.0 kg/m^2 (inclusive).

Sex

7. Male and Female participants:

Preclinical data has not identified risk of clinically relevant genotoxicity, however there is demonstrated/suspected risk of teratogenicity/fetotoxicity. Accordingly, the following contraceptive advice must be adhered to for male and female participants.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 2 days (i.e. 5 terminal half-lives of GSK2982772) after the last dose of study intervention:

- Refrain from donating sperm

  Plus either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below

- Agree to use a male condom and will also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

b. Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a WOCBP

    OR

Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4, during the intervention period and for at least 28 days (i.e. until resolution of potential drug interaction with combined hormonal contraceptives) after the last dose of study intervention. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Non-plaque forms of psoriasis (e.g. erythrodermic, guttate, or pustular), in the opinion of the Investigator.
2. Drug-induced psoriasis (e.g. a new onset of psoriasis or an exacerbation from beta blockers, calcium channel blockers, lithium or anti-TNF therapies).
3. Diagnosis of psoriatic arthritis, uveitis, inflammatory bowel disease, or other immune-mediated conditions that are commonly associated with psoriasis for which a participant requires current systemic (oral, subcutanous [SC], or intravenous [IV]) (including corticosteroids and biologics) immunosuppressant medical treatment.
4. Current SIB as measured using the C-SSRS or a history of attempted suicide at Screening and before first dose of study treatment.
5. Active infection, or a history of infections as follows:
    - Hospitalisation for treatment of infection within 60 days before Day 1.
    - Current use of any suppressive therapy for a chronic infection (such as *pneumocystis jirovecii*, cytomegalovirus, herpes simplex virus, herpes zoster virus and atypical mycobacteria).
    - Use of parenteral (IV or intramuscular) antibiotics (antibacterials, antivirals, antifungals, or antiparasitic agents) within 60 days before Day 1.
    - History of opportunistic infections within 1 year of Screening (e.g. *pneumocystis jirovecii*, CMV pneumonitis, aspergillosis). This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or recurrent nature.
    - History of recurrent, chronic or other active infection that in the opinion of the Investigator may put the participant at unacceptable risk or interfere/confound the integrity of study data.
    - Positive test for SARS-CoV-2 at screening or interaction with known COVID-19 positive contacts within 14 days prior to Day 1.
    - History of latent or active TB, irrespective of treatment status.
    - A positive diagnostic TB test at Screening defined as a positive QuantiFERON-TB Gold plus test.

      Please note: In cases where the QuantiFERON-TB Gold Plus test is indeterminate, the participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative, or they have a negative tuberculin skin test (defined as skin induration <5 mm at 49 to 72 hours, regardless of Bacillus Calmette-Guerin or other vaccination history). There must be no other clinical evidence of TB on physical examination of the participant at Screening.
6. Current or history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. Current or history of renal disease.

8. Significant unstable or uncontrolled cardiovascular disease including uncontrolled hypertension.
9. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
10. History of major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
11. Planned surgical procedure that makes the participant unsuitable for the study, in the opinion of the Investigator.
12. History of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell carcinoma) or carcinoma in situ of the uterine cervix that has been fully treated and shows no evidence of recurrence after at least 12 months following treatment.
13. History of significant progressive neurologic disorders including, but not limited to, progressive MS, ALS, Alzheimer's and dementia.
14. History of a medical condition other than plaque psoriasis, or other considerations, which may confound interpretation of efficacy or safety study data, or put the participant at unacceptable risk, in the opinion of the Investigator.

Prior/Concomitant Therapy

15. History of lack of primary response to anti-TNF biologic therapies (either approved or experimental) at approved doses (or at the doses received if experimental therapies) after at least 3 months of therapy.
16. Participant has previous exposure to 3 or more biologic therapies of any mechanism of action.
17. Treatment with the prohibited therapies listed in Section 6.4.1, or changes to those treatments, within the specified timeframe. If in doubt, or the therapy is not listed please consult with the medical monitor.
    - Other medications (including vitamins, herbal and dietary supplements) will be considered on a case-by-case basis and will be allowed if the medication will not interfere with the study procedures or compromise participant safety, in the opinion of the Investigator.

Prior/Concurrent Clinical Study Experience

18. Participation in a clinical trial and has received an investigational product within 30 days or 5 half-lives whichever is longer (or 12 weeks for biologic therapies), before the first dose of study medication, or plans to take part in another clinical trial at the same time as participating in this clinical trial.
19. Exposure to more than four investigational products within 12 months prior to the first dosing day.

Diagnostic assessments

20. Average QT Duration Corrected for Heart Rate (QTc) >450 msec or QTc>480 msec in participants with bundle branch block at Screening and before first dose of study treatment.

    NOTES:

    - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine-read or manually over-read.

21. Alanine transferase (ALT) >2 × upper limit of normal (ULN)
22. Bilirubin >1.5 × ULN at Screening (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
23. Estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) <60 mL/min/1.73 m2
24. Haemoglobin <10 g/dL; haematocrit <30 %, white blood cell count ≤3000 /mm3 (≤3.0 x 109/L); platelet count ≤ 100,000 /µL (≤ 00 x 109/L); absolute neutrophil count ≤1500 /mm (≤1.5 x 109/L).
25. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb).
26. Presence of hepatitis C antibody at Screening. Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained.
27. Positive serology for HIV 1 or 2.
28. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.

Other Exclusions

29. History of alcohol or drug abuse, that would interfere with the ability to comply with the study or interfere with interpretation of the study, in the opinion of the Investigator.
30. History of sensitivity to any of the study treatments, or components thereof, or a history of drug or other allergy that contraindicates their participation (including lidocaine or other local anaesthetic), in the opinion of the Investigator or Medical Monitor.
31. History of receiving a live or attenuated vaccine within 30 days of randomization OR plan to receive a live or attenuated vaccination during the study until completion of the follow-up visit.
32. History of hypertrophic or keloid scarring.

5.3. Lifestyle Considerations

Participants must adhere to the contraceptive requirements listed in Appendix 4.

5.3.1. Meals and Dietary Restrictions

There are no meal or dietary restrictions except on the Day 1, 29 and 85 visits when participants should fast overnight prior to these visits.

5.3.2. Alcohol Consumption

Participants must abstain from alcohol for 24 hours before all study visits.

5.3.3. Sun Exposure and Activity

Participants must not sunbathe or use a tanning device (sun bed or solarium) for 28 days prior to Day 1 until the follow-up visit (Day 113). Participants will be advised that when they are outdoors they must wear protective clothing (e.g. sun hat, long sleeves) as well as use a broad spectrum UVA/UVB sunscreen and lip balm (sun protection factor [SPF] ≥30) on exposed areas.

Participants will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

Retesting in case of spurious results or sample handling error at Screening is allowed.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if there is reasonable possibility that the individual would be eligible, in the opinion of the Investigator. Participants should be assigned a new participant number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s) to be administered to a study participant according to the study protocol.

ARM Name	GSK2982772	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	480 mg	NA
Dosage Level(s)	960 mg QD	NA
Route of Administration	Oral	Oral
Use	Experimental	Placebo- comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.

6.1. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual (SRM).

    - Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be

provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

6.2. Measures to Minimize Bias: Randomisation and Blinding

Randomisation

At Screening, a unique Participant Number will be assigned to any participant who has at least one Screening procedure performed, other than informed consent. The unique Participant Number will be used to identify individual participants during the course of the study.

Participants who meet Screening eligibility criteria will be randomised to a treatment group through an Interactive Web Response System (IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each site. The IWRS will confirm the participant's case report form (CRF) number (Participant Number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Once assigned, this number must not be reassigned to any other participant in the study. The randomisation is centrally controlled by the IWRS.

Participants will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio. The randomisation will be stratified by prior biologic use.Participants will take study medication every day, once a day for 12 weeks, at approximately the same time each day.

Participants will be administered the first daily dose of study medication by site staff during the site visit for Day 1 (Week 0). At subsequent visits, the dose should be taken either on site (preferred) after the pre-dose assessments, or after the visit at home only if the participant dosing at site would result in a treatment overdose (refer to Section 8.4). Participants will self-administer all other doses of study medication and will record the date and time in the diary cards provided to them. Returned study intervention should not be re-dispensed to the participants.

See the SRM for further details.

Blinding

This will be a double-blind study.

Access to participant-level unblinded data will be restricted to the GSK Biostatistics and CPMS members of the study team for the purpose of conducting analyses for the planned interim analysis. Summary-level data will be shared with the internal DRC at the interim analysis, membership of which will be listed in a data review charter. Results of the interim will not be shared outside of this committee, only the decision and its

implications will be communicated to the study team to minimise bias to the remainder of the trial.

All other members of the GSK study team will remain blinded throughout the study.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form as appropriate.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy.

6.3. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
- If participants are not dosed at the site at the Week 2 (Day 15), Week 4 (Day 29) and/or Week 8 (Day 57) visit(s), the time the dose is taken on those visit days must be confirmed by the site staff through follow-up with the participant, and time and date of dose information will be recorded in the CRF.
- When participants self-administer study intervention(s) at home, compliance with study treatment will be assessed by reviewing the information from the returned diary cards at the study visits, and documenting compliance in the source documents and CRF.
- A record of the number of study treatment tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the CRF.

6.4. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Any allowable medication should be stably maintained prior to enrolment to the study. Usage should be approximately stable and consistent throughout the study intervention and follow-up. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Selected medications for the treatment of psoriasis may be taken, with specific requirements listed in Table 1, and as long as they are not prohibited (Section 6.4.1).

Table 1 Specific Requirements for Permitted Medications During the Study

Therapy	Requirement
Emollients (excluding those containing salicylic acid)	• Omit on day of study visits until after all skin assessments have been performed. • May be used at other times.
Low or least potent (Class 6 or 7) topical corticosteroids[1]	• Only on palms, soles, face, and intertriginous areas • Hydrocortisone 1% and hydrocortisone acetate 1% are the only topical corticosteroids permitted • Omit on day of study visits until after all skin assessments have been performed.
Medicinal shampoos that contain tar and/or salicylic acid (but not corticosteroids)	• Permitted at any time on scalp area.

1. Usage should be approximately stable for 14 days prior to dosing.

6.4.1. Prohibited Medicines

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a

potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless the medication will not interfere with the study, in the opinion of the Investigator and sponsor.

Table 2 lists prohibited medications for defined periods of time before and during the study until after the follow-up visit (Day 113).

Participants who start prohibited medications or therapies as a treatment for PsO or other reasons during the study may be withdrawn from study treatment for safety reasons. If in any doubt, Investigators are advised to discuss medications with the medical monitor.

Table 2 Prohibited Medications

Prohibited Therapy	Washout Period (from before D1 until follow-up)
Biologic Agents (including but not limited to: adalimumab, etanercept, infliximab, certolizumab, ustekinumab, guselkumab, ixekizumab, secukinumab, risankizumab)	4 weeks for etanercept; 8 weeks for infliximab; 12 weeks or 5 half-lives (whichever is longer) for other biologics
Oral retinoids (including but not limited to: acitretin or isotretinoin)	12 weeks
Systemic immunosuppressive or immunomodulating agents. (including but not limited to: cyclosporin, interferon, methotrexate, apremilast)	8 weeks
Systemic corticosteroids or adrenocorticotropic hormone (ACTH) analogs	4 weeks
Phototherapy (PUVA, UVB or self-treatment with tanning bed)	4 weeks
Topical Treatments (including but not limited to: corticosteroids [low potency corticosteroids permitted for certain areas, see permitted medications], immunomodulators, anthralin [dithranol], Vitamin D derivatives, retinoids, or coal tar [used on the body])	2 weeks

Prohibited Therapy	Washout Period (from before D1 until follow-up)
Live or attenuated Vaccinations • If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered whilst receiving GSK2982772 based on an assessment of the benefit: risk (e.g. risk of decreased responsiveness). • Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against pneumococcus and influenza, in participants with PsO.	30 days for live or attenuated vaccinations
Pgp Inhibitors (including but not limited to: amiodarone, azithromycin, clarithromycin, conivaptan, erythromycin, felodipine, itraconazole [FDA, 2012])	4 weeks
Narrow therapeutic index (NTI) CYP3A4 substrates. (including but not limited to: alfentanil, astemizole, cisapride, fentanyl, pimozide, quinidine, sirolimus, terfenadine [FDA, 2012])	4 weeks
Sensitive substrates of CYP2B6 (including but not limited to: bupropion)	4 weeks
Sensitive substrates of CYP2C8 (including but not limited to: repaglinide)	4 weeks
OAT3 inhibitors (including but not limited to: probenecid, teriflunomide)	4 weeks

Paracetamol/acetaminophen, at licensed doses, is permitted for use. Other concomitant medication may be considered on a case by case basis by the Investigator, in consultation with the medical monitor if required.

6.5. Dose Modification

No dose modifications will be allowed.

6.6. Intervention after the End of the Study

There will be no intervention offered at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for efficacy and safety, unless consent is withdrawn. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

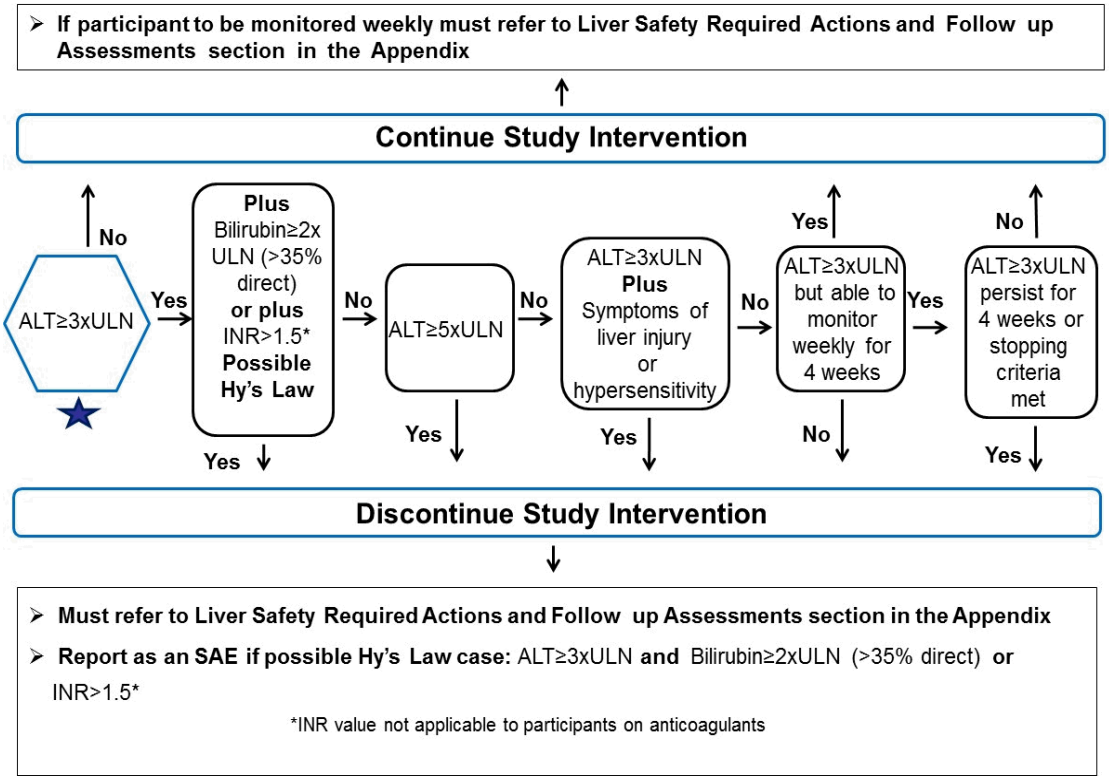
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the Investigator believes study intervention discontinuation is in the best interest of the participant.

Phase 2 Liver Chemistry Stopping and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

7.1.2. QTc Stopping Criteria

A participant with an average triplicate measurement meeting either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec or uncorrected QT >600 msec
- Change from Baseline (Day 1 pre-dose) of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria below:

Day 1 pre-dose QTc with bundle branch block	Discontinuation QTc with bundle branch block
<450 msec	>500 msec
450-480 msec	≥530 msec

- The *Fridericia's* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study.
- The QTc should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period at Screening and at Day 1 (Baseline). At all other specified time points single ECGs are acceptable. However, if QTc prolongation (as defined in the same way as the withdrawal criteria) is detected, triplicate ECGs will be performed and the QTc must be based on the average of triplicated ECG readings.

7.1.3. Rechallenge

7.1.3.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- A participant may be withdrawn from the study at any time if deemed to be demonstrating suspected, probable or confirmed COVID-19 infection. Specific details are in the SRM.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section

1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for Screening or Baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).
    - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Clinical Disease Assessments

8.1.1.1. Psoriasis Area Severity Index (PASI)

Psoriatic lesions will be assessed using the PASI scoring system [Fredriksson, 1978]. Erythema, induration, and scale are each graded on a 5-point scale (0-4), and the % BSA affected is scored on a 7-point scale (0-6) for each of the 4 specified body regions (head, upper extremities, trunk, and lower extremities). The body region scores are each multiplied by a weighted factor; and the sum of the region scores give the overall PASI score. Higher scores indicate more severe disease. PASI is a static measurement made without reference to a previous score (see SRM for full details).

The PASI assessment will be performed by the Investigator or suitably trained delegate, and whenever possible, the PASI assessments for an individual participant should be completed by the same assessor at all time points.

8.1.1.2. Psoriasis body Surface Area (BSA)

The BSA affected with psoriasis will be evaluated at all study visits by the Investigator or suitably trained delegate. In order to be eligible for the study, BSA must be ≥10%. As a reference, the area of the whole palm is counted as 1% BSA.

8.1.1.3. Static Investigator's Global Assessment of Disease Activity (sIGA)

The Investigator or physician designee only will complete a global assessment of disease activity using the physician global assessment item. A 5-point scoring system will be used to measure the severity of psoriatic lesions over the entire body at the time of evaluation (see SRM for full details).

Note:

- The Investigator or physician designee should complete the Investigator's global assessment independently of the participant.
- Ideally, the same Investigator or physician designee should perform all global assessments for each participant for the duration of the study.

8.2. Safety Assessments

Blinded safety data will be reviewed by the safety review team (SRT) details of which can be found in the SRT charter.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, joint, lymph nodes, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. Height will be measured at the screening visit only.
- A brief physical examination will include, at a minimum, weight and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses or that could be related to infection (e.g. COVID-19).
- At each visit, the participant should be asked whether they have had COVID-19 symptoms, or exposure to anyone with COVID-19 positive test in the past 14 days. These symptoms include, but are not limited to, a high temperature and dry cough. Guidance on how to manage participants who develop COVID-19 symptoms during the study are described in the SRM. Participants with exposure to anyone with COVID-19 infection should not be included in the study until 14 days after the last exposure.

8.2.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

8.2.3. Electrocardiograms

- Triplicate and single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required (Screening and Day 1 [Baseline]), 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5-10 minutes) recording period.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed andto the SoA (Section 1.3) for the timing and frequency.

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered significantly abnormal by the Investigator or medical monitor.
- If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.2.5. Suicidal Ideation and Behaviour Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with PsO. Although this drug has not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to healthy volunteers, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Families and caregivers of participants being treated with GSK2982772 should be alerted regarding the need to monitor participants for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study Investigator.

Participants being treated with GSK2982772 must be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. Participants that experience signs of suicidal ideation or behavior must be withdrawn from study treatment.

At Screening, the ‘Baseline/Screening C-SSRS’ will be completed. At each subsequent study visit, the ‘Since Last Visit C-SSRS’ will be completed. GSK Version 4.1 of both rating scales will be used.

Participants who answer ‘yes’ to any suicidal behaviour or ‘yes’ to suicidal ideation Questions 4 or 5 will be referred to their general practitioner (GP) or appropriate psychiatric care. The medical monitor will be notified. If appropriate, an AE or SAE must be reported (see Section 8.3- AE and SAE). In addition, the Investigator must complete a Possible Suicidality Related Adverse Event (PSRAE) form to collect detailed information on the circumstances of the reported AEs which, in the Investigator’s opinion, are

possibly suicidality-related. These may include, but are not limited to, an event involving suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) to the site staff.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- For all studies except those utilizing medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose.
- If a pregnancy is reported, the Investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will

be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV medical dictionary for regulatory activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4. Treatment of Overdose

For this study, any dose of GSK2982772 greater than 960 mg within a 20-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor in conjunction with clinical pharmacologist (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection

Blood samples for PK analysis of GSK2982772 will be collected prior to dosing at the time points indicated in SoA, Section 1.3. The actual date and time (24-hour clock) of each blood sample collection will be recorded. Details of blood sample collection, processing, storage and shipping procedures are provided in the SRM.

8.5.2. Plasma Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of In vitro/ In vivo Translation (IVIVT), GlaxoSmithKline (GSK). Concentrations of GSK2982772 will be determined in plasma samples using the currently

approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM). Once the plasma has been analysed for GSK2982772 any remaining plasma may be analysed for other compound-related material and the results reported under a separate IVIVT, GlaxoSmithKline protocol.

8.6. Pharmacodynamics

Pharmacodynamic parameters are being evaluated in this study using biomarkers as detailed in Section 8.8.

8.7. Genetics

A 6 mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Q2 Solutions laboratory manual and the Study Reference Manual.

8.8. Biomarkers

Collection of samples for biomarker research is part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3):

- Blood (target engagement, proteomic, and metabolic analyses)
- Skin biopsies (histology and transcriptomic analyses)

Biomarkers will be analysed in samples taken at visits described in the SoA (Section 1.3), to evaluate the effect of GSK2982772 as below:

- Target engagement – TEAR1 assay (target engagement assay RIP1) in blood samples.
- Transcriptome – see Section 8.8.2 transcriptomic analysis of mRNA, including but not limited to RNA-seq, isolated from skin biopsy samples. Also, if transcriptomic data dictate, mRNA expression of inflammatory gene transcripts in the skin biopsies which may include, but are not limited to IL-4, IL-10, IL-17, IL-21, IL-22, TNF and IFNγ see Section 8.8.3
- Disease and inflammatory biomarkers – histopathological scoring including, but not limited to, epidermal thickness, K16, Ki67, CD3 and CD11c, in skin biopsy samples. Protein markers in blood samples which may include but are not limited to IL-17, CCL20, IL-6, IL-8, IL-4, CXCL10, see Section 8.8.4.
- Metabolic biomarkers – HOMA, HbA1c and lipid panel may be analysed in blood, see Section 8.8.5.

8.8.1. Skin Biopsy

All biopsies will be 4 mm punch biopsies and will be taken using standard methodology only by suitable experienced personnel, trained in aseptic technique.

At Baseline (pre-dose Day 1), a target lesion for biopsy will be identified (≥3 cm^2) on the trunk or extremities. The same target lesion will be used for all subsequent timepoints. Lesions on palmar surfaces of the hands and feet, scalp, knees, elbows and intertriginous areas will not be used as the target lesion site. At Baseline only, a non-lesion biopsy will be taken from an unaffected area close to the target lesion.

Lesional biopsies will be taken from the outer third of the selected biopsy lesion at timepoints defined in the SoA (Section 1.3). The sites on the outer third of the same lesion should be at least 1.5 cm from each other.

Biopsy tissue taken from the psoriatic skin lesions will be divided for histological and gene expression (summarised in Section 8.8).

Details of biopsy processing will be in the SRM.

8.8.2. RNA Transcriptome Research

Transcriptome studies will be conducted using RNA-seq, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each skin sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to psoriasis and medically related conditions or the action of GSK2982772.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.3. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcriptase polymerase chain reaction (RT-qPCR), and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a RNA expression profile for each skin sample. The RNAs assayed may be those involved with the pathogenesis of psoriasis; the absorption, distribution, metabolism, or excretion of GSK2982772; or in the participant's response to GSK2982772. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to GSK2982772 or the pathogenesis of psoriasis. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to psoriasis and medically related conditions or the action of GSK2982772.

8.8.4. Proteome Research

Plasma proteome studies may be performed by 2-D gel separation, and/or peptide mass mapping, or an alternative equivalent procedure. Proprietary algorithms and standard statistical techniques, such as analysis of variance (ANOVA) and analysis of covariance (ANCOVA), will be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. These differentially expressed proteins will be identified by mass spectrometry or equivalent technology. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to psoriasis and medically related conditions or the action of GSK2982772.

The samples may also be used to confirm findings by application of alternative technologies.

8.8.5. Metabolome Research

Blood plasma and/or serum metabolome studies will be performed by nuclear magnetic resonance (NMR), mass spectrometry (MS), liquid chromatography – mass spectrometry (LC-MS), gas chromatography – mass spectrometry (GC MS), and/or Fourier transform mass spectrometry (FTMS), and equivalent methods. This may include analysis of identified or uncharacterized metabolites and lipids that are known to be or emerge in the future as important in the pathogenesis of psoriasis or a related medical condition, the participant's response to GSK2982772, or AE.

8.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of this study is to determine 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.

9.2. Sample Size Determination

Approximately 32 participants will be screened to achieve 21 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. The sample size is based on the difference in PASI75 response rates between GSK2982772 960 mg and placebo.

At Week 12, the expected PASI75 response rate on placebo is approximately 7%. This value represents typical responses seen in this indication [Papp, 2018; Checchio, 2017].

The study will leverage historical placebo data to reduce the uncertainty in the placebo response rate and thus improve operating characteristics of the trial. The historical placebo data will be combined with the trial data via a Bayesian analysis.

With a sample size of 21 participants there is approximately 99% probability of achieving a >97.5% posterior probability that the true treatment difference over placebo >0%, based on an assumed placebo response of 7% and 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 with an effective sample size of 50 participants was used. For the active arm a vague Beta (1/3, 1/3) prior is used.

An equivalent power calculation, assuming placebo response of 7% and using a two-sided significance level of 0.05, the proposed sample size of 21 participants gives >90% power to detect a 55% difference in PASI75 response rates between GSK2982772 960 mg versus placebo at Week 12 using a Newcombe score test [Newcombe, 1998] (assuming no historical data is borrowed).

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

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who signed the ICF, passed screening and were eligible for randomisation (regardless of whether the participant went on to be randomised).
Randomised	All participants who were randomly assigned to study intervention in the study. Participant must have signed ICF and passed screening. Data will be reported according to the randomised study intervention.
Intent to Treat (ITT)	All randomised participants who received at least one dose of study treatment. Data will be reported according to the randomised study intervention.
Safety	All randomized participants who receive at least 1 dose of any study treatment. Data will be reported according to the actual study intervention received.
COVID-19	All participants in the Safety set who had a confirmed, probable or suspected COVID-19 case diagnosis.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to the first unblinded data look (interim analysis) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Analyses

Efficacy analyses will be based on the ITT population unless stated otherwise in the SAP. The primary analysis will assess the difference in PASI75 response rates between GSK2982772 960 mg and placebo at Week 12. A Bayesian logistic regression analysis of the difference in PASI75 response rates at Week 12 will be conducted to calculate posterior probabilities that the true effect of GSK2982772 relative to placebo is greater than a range values of interest.

An informative prior will be used for the placebo arm to leverage relevant historical placebo data into the analysis. It is expected that this prior will be a Beta (3.5, 46.5)

distribution, giving the historical data an effective sample size of 50 participants. Further emerging placebo data may be incorporated into the prior distribution for the placebo arm prior to breaking the study blind. A non-informative prior will be used for the PASI75 response rate on GSK2982772.

Participants who discontinue early or have missing PASI data at any visit will be treated as PASI75 non-responders at that time point (regardless of their response at previous visits). Sensitivity analyses will be conducted to investigate the impact of this approach to handling missing data.

9.4.2. Secondary Analyses

Secondary analyses will be based on the ITT population unless stated otherwise in the SAP.

The proportion of participants achieving additional PASI responder endpoints of interest (PASI50/90/100) will be summarised by treatment arm and visit.

Differences between treatment groups and associated confidence intervals at each visit will be presented. Newcombe score confidence intervals will be calculated.

Change from Baseline in both PASI score and BSA over time will be analysed using a mixed model repeated measures (MMRM) approach to account for the repeated visits per participant. Log transformations will be applied if appropriate. Summary statistics by treatment and visit will also be provided.

The sIGA scores will be summarised as categorical data with the proportion of participants achieving each result being presented by treatment group and visit.

A population analysis will be implemented 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 at Week 16 (additional time point of interest for comparison to competitors)The model structure will be dependent on the emerging data.

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9.4.2.1. Pharmacokinetic Analysis

GSK2982772 plasma concentrations will be summarised descriptively by visit.

9.4.2.2. Pharmacokinetic/Pharmacodynamic Analysis

Exploratory plots will be presented for individual and/or pooled plasma concentration versus change from Baseline and/or absolute PASI score. If data permit, potential association between systemic exposure of GSK2982772 and PASI score may be studied using linear or non-linear models, as appropriate. Exposure-response may also be evaluated for other efficacy or PD biomarkers.

9.5. Interim Analyses

An interim analysis is planned to occur when at least six participants on GSK2982772 have completed the Week 12 visit or discontinued study treatment to aid internal decision making around subsequent GSK2982772 trials. 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 interim. There is no plan to stop the trial early based on positive efficacy data.

The data will be reviewed by an internal DRC. The committee will include the study statistician, the study pharmacokineticist and a limited number of GSK individuals. The charter will identify the specific individuals 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.

The interim will focus on efficacy data including, but not limited to, PASI response rates and change in PASI score from Baseline.

The SAP and data review charter will describe the planned interim analyses in greater detail.

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.

9.6. Data Review Committee (DRC)

An internal DRC will review data from the Interim Analysis as detailed in Section 9.5.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 code of federal regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK2982772 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK2982772 approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The Investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate tick box will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of

disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

GSK will have a DRC to review data at the interim analysis and a SRT to review ongoing blinded safety data, refer to Section 9.5 for more details.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the Investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study

results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.
- Data reported on the CRF or entered in the electronic case report form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for Screening pregnancy criteria.
  - Pregnancy testing will be conducted as appropriate per Section 1.3 Schedule of Activities.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red blood cell (RBC) Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH)	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic	Total Protein

Laboratory Assessments	**Parameters**			
			Transaminase (SGPT)	
	Glucose[2]	Calcium	Alkaline phosphatase	Albumin
	Triglycerides[2]	Total cholesterol[2]	High Density Lipoproteins (HDL) cholesterol[2]	Low Density Lipoproteins (LDL) cholesterol[2]
	Glycated haemoglobin (HbA1c)	Insulin[2]		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• COVID-19 (SARS-CoV-2) • HIV • Hepatitis B surface antigen (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis C (Hep C antibody) (and hepatitis C RNA in participants with positive Hepatitis C antibody due to prior resolved) • QuantiFERON-TB Gold Plus test • Tuberculin skin test (if QuantiFERON-TB Gold Plus test is indeterminant) • Follicle-stimulating Hormone (FSH) and estradiol (as needed in women of non-child bearing potential only) • Serum human chorionic gonadotropin (hCG - as needed for women of child bearing potential) to be done at Screening and if urine test positive or ambiguous at other timepoints in study. Estimated glomerular filtrate rate (eGFR) will be calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6. All events of ALT ≥3 ×ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Overnight fasting required. Any abnormal result for glucose or lipids may be repeated at the discretion of the Investigator.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
○ Results in death
○ Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Other measures to evaluate AE and SAE may be utilized (e.g. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Assessment of Causality
• The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The Investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section). • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Email transmission of the scanned SAE paper CRF is the preferred method to transmit this information to GSK. • GSK Contacts and instructions for paper SAE reporting can be found in the Study Reference Manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods [b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should will be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. ,Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive GSK2982772.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the Investigator, will be reported to GSK as described in Appendix 3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2982772 (or study interventions of this drug class), and psoriasis (or immune-inflammatory and related diseases). They may also be used to develop tests/assays including diagnostic tests related to GSK2982772 (or study interventions of this drug class), and psoriasis (or immune-inflammatory and related diseases). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome as appropriate.
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2982772 (or study interventions of this class), and psoriasis (or immune-inflammatory and related diseases). The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2982772 in psoriasis (or study interventions of this drug or drug class in immune-inflammatory and related diseases) continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 2 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase 2 liver chemistry stopping criteria and required follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5
Cannot Monitor	ALT ≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver chemistry event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within Baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and GSK Medical Governance approval **is** granted (see below). • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study intervention and continue	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, with timing to be guided by clinical pharmacokinetics representative on a case by case basis, after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia

participant in the study for any protocol specified follow-up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within Baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within Baseline	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A Immunoglobulin M (IgM) antibody; HbsAg and HBcAb; Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to pk blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot

be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Reference

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.7. Appendix 7: COVID-19 Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.
These measures will remain in place until until study completion.

STUDY PROCUDURES DURING COVID-19 PANDEMIC

During the special circumstances caused by the COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants. Guidance on how to deal with participants who develop COVID-19 symptoms during the study are described in the SRM.

As outlined in Section 8, protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. However, when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

Missing protocol required data/visits due to COVID-19 should be noted in participant notes, captured in the eCRF and recorded as a COVID-19 protocol deviation.

Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.

Study Interventions:

- If allowed by country regulation/ethics, then study intervention (including rescue study medication and ancillary supplies related to IMP administration) can be shipped direct-to-patient (DTP) from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will

provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation.

- The Principal Investigator assumes Good Clinical Practice (GCP) responsibilities for IMP handling and the medical control for dispensing to patients. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.
- Compliance with study intervention administration will be verified through observation by study staff or trained home healthcare professionals.
- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- Diary cards may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of completed diaries are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

µg	Microgram
ACTH	Adrenocorticotropic Hormone
ADA	Anti-drug Antibody
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
$AUC_{[0-24]}$	Area Under Concentration-Time Curve from 0 to 24 h
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
BMI	Body mass index
BSA	Body Surface Area
BUN	Blood urea nitrogen
CCL20	Chemokine Ligand 20
CD3	Cluster of Differentiation 3
CD11c	Cluster of Differentiation 11c
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum Concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronovirus Disease 2019
CPK	Serum Creatine Phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CXCL10	C-X-C Motif Chemokine 10
CYP	Cytochromes P450
DNA	Deoxyribonucleic Acid
DRC	Data Review Committee
DTP	Direct to Patient
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtrate rate
EM	Experimental Medicine
E-R	Exposure Response Relationship
FDA	Food and Drug Administration

FSH	Follicle-stimulating Hormone
FTiH	First Time in Human
FTMS	Fourier Transform Mass Spectrometry
GC MS	Gas Chromatography Mass Spectrometry
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GP	General Practitioner
GSK	GlaxoSmithKline
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoproteins
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HOMA	Homeostatic Model Assessment of Insulin Resistance
HPLC	High performance liquid chromatography
hr	Hour(s)
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IFNγ	Interferon Gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INR	International Normalized Ratio
IP	Investigational Product
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
IVIVT	In vitro/ In vivo Translation
IWRS	Interactive Web Response System
K16	Keratin 16
kg	Kilogram
kg/m^2	Kilogram per meter square
Ki67	Antigen KI-67
LAM	Lactational Amenorrhoea Method
LC-MS	Liquid Chromatography – Mass Spectrometry

LDH	Lactate Dehydrogenase
LDL	Low Density Lipoproteins
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitre
mm	Millimetre
MIP1α	Macrophage inflammatory protein 1 alpha
MIP1β	Macrophage inflammatory protein 1 beta
MMRM	Mixed Model Repeated Measures
MR	Modified Release
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
MS	Mass Spectrometry
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTX	Methotrexate
MV	Minute Volume
NOAEL	No Observed Adverse Effect Level
NMR	Nuclear Magnetic Resonance
NTI	Narrow Therapeutic Index
OAT3	Organic Anion Transporter 3
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PDE4	Phosphodiesterase-4 inhibitor
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PI	Principle Investigator
PK	Pharmacokinetics
PLSS	Psoriatic Lesion Severity Sum
PsO	Psoriasis
PSRAE	Possible Suicidality Related Adverse Event
PUVA	Psoralen and Ultraviolet A
QD	Once Daily
QTc	QT Duration Corrected for Heart Rate
QTcF	QT Duration Corrected for Heart Rate by Fridericia's Formula
QTL	Quality Tolerance Limit
RA	Rheumatoid Arthritis
RAMOS NG	Randomization and Medication Ordering System New Generation
RBC	Red Blood Cell
RIP1	Receptor-Interacting Protein 1
RIPK1	Receptor-interacting serine/threonine-protein kinase 1
RNA	Ribonucleic acid
RNA-seq	Ribonucleic Acid sequencing

RNA PCR	Ribonucleic Acid Polymerase Chain Reaction
RT-qPCR	Reverse Transcriptase Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Related Coronavirus 2
SIB	Suicidal Ideation Behavior
sIGA	Static Investigator's Global Assessment of Disease Activity
SC	Subcutanous
SDR	Source Document Review
SDV	Source Data Verification
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of Activities
SPF	Sun Protection Factor
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAR1	Target Engagement Assay RIP1
TH1	T Helper Type 1
TH17	T Helper Type 17
TH22	T Helper Type 22
TID	Three Times a Day
TLR	Toll-like Receptor
TNF	Tumor-Necrosis Factor
UGT	Uridine Glucoronyltransferase
ULN	Upper Limit of Normal
UV	Ultraviolet
UVB	Ultraviolet B
WBC	White Blood Cells
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DiffCORE
RAMOS NG

Trademarks not owned by the GlaxoSmithKline group of companies
Otezla
QuantiFERON-TB Gold PLUS

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [02]: (14-JUL-2020)

Overall Rationale for the Amendment: To include additional safety monitoring for participants in the study in response to the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Study Synopsis Section 9.2 Sample Size Determination	Revised the allowable number of replacement participants to be randomised (from up to approximately 3 to up to approximately 6) to ensure that approximately 21 have completed the Week 4 visit.	Amended due to anticipated impact of COVID pandemic on participant retention
Section 1.3 Schedule of Activities	Updated to add COVID-19 testing and monitoring of COVID-19 signs and symptoms.	Additional safety monitoring
Section 5.2 Exclusion Criteria	Added exclusion criteria to exclude study participants who have a positive test for SARS-CoV-2 at screening or interaction with known COVID-19 positive contacts within 14 days prior to Day 1. In addition, expanded exclusion criteria to exclude study participants that may have any other considerations (not just medical conditions) that, in the opinion of the Investigator, would put the participant at unacceptable risk.	Additional safety monitoring

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Participation Discontinuation/Withdrawal from the Study	Added new information to include that a participant may be withdrawn from the study at any time if deemed to be demonstrating suspected, probable or confirmed COVID-19 infection.	Additional safety monitoring
Section 8.2.1 Physical Examination	Added text to remind Investigators to pay special attention to clinical signs related to previous serious illnesses or that could be related to infection (e.g. COVID-19).	Additional safety monitoring
Section 8.2.5 Suicidal Ideation and Behavior Risk Monitoring	Correction to clarify that the 'Baseline/Screening' version of the C-SSRS questionnaire is used at the Screening visit, and the 'Since Last Visit' version of the C-SSRS questionnaire is used at the Week 0/Day 1 visit.	Correction
Section 10.2 Clinical Laboratory Tests	COVID-19 (SARS-CoV-2) test added to list of Other Screening Tests.	Additional safety monitoring
Section 10.7 Appendix 7	Added to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.	To outline measures that may be applicable for any site impacted by the COVID-19 pandemic.
Section 10.8 Abbreviations and Trademarks	Updated accordingly with new terminology.	Administrative Update

Amendment [01]: (09-APR-2020)

Overall Rationale for the Amendment: To address a request from Health Canada for clarification of contraception requirements and the QTc formula to be used in the study. In addition, some administrative corrections have been made to the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Brand name for apremilast added.	Clarification
	Grammatical corrections made.	Correction
	Wording updated to indicate that the interim futility analysis will be conducted when at least six participants receiving GSK2982772 have completed the Week 12 visit **or discontinued study treatment**.	Clarification
Section 1.3 Schedule of Activities (SoA)	Footnotes updated to indicate that Day 85 is a non-dosing day.	Clarification
	Text added to describe the circumstances in which biopsies would not be required at the Early Withdrawal visit.	Clarification
	Text added to indicate that Fridericia's formula (QTcF) must be used for QTc correction.	Restricted protocol to use of Fridericia's formula only in response to Health Canada feedback.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design	Correction to duration of treatment period. Wording updated to indicate that the interim futility analysis will be conducted when at least six participants receiving GSK2982772 have completed the Week 12 visit **or discontinued study treatment**.	Correction Clarification
Section 5.1 Inclusion Criteria	The Female Participants Decision Tree has been removed from inclusion criterion 7 and replaced with text to improve clarity for the justification of contraceptive use in this study.	Clarification
Section 5.2 Exclusion Criteria Section 7.1.2 QTc Stopping Criteria	The option to use Bazett's formula for QTc has been removed.	In response to Health Canada feedback, restricted protocol to use of Fridericia's formula only.
Section 2.2 Background Section 2.3 Benefit/Risk Assessment Section 3 Objectives and Endpoints Section 4.3 Justification of Dose Section 5.3.1 Meal and Dietary Restrictions Section 6.3 Study Intervention Compliance Section 8.8 Biomarkers	Minor typographical errors have been corrected.	Corrections

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Measures to Minimise Bias: Randomisation and Blinding	Addition of text to make clear that randomisation will be stratified by prior biologic use.	Clarification
Section 8.2.1 Physical Examinations	Addition of text to indicate that height is measured at screening only.	Clarification
Section 8.2.3 Electrocardiograms	Approximate time to complete triplicate ECG readings has been updated.	To align with information in Section 7.1.2
Section 9.3 Population for Analysis	Addition of the definition of randomised population and clarification of other populations.	Clarification
Section 9.5 Interim Analyses	Wording updated to indicate that the interim futility analysis will be conducted when at least six participants receiving GSK2982772 have completed the Week 12 visit **or discontinued study treatment**.	Clarification
Section 10.1.7 Data Quality Assurance	Language added to indicate that quality tolerance limits have been pre-defined for the study.	Confirmation that Quality Tolerance Limits have been defined, to comply with ICH E6 R2 guidelines.
Section 10.2 Clinical Laboratory Tests	Pregnancy testing language has been updated to align with the Schedule of Activities (SoA).	Clarification
Section 10.7 Abbrevations and Trademarks	Otezla has been added to Trademark Information table.	Clarification

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