TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled, repeat dose study to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with active plaque-type psoriasis

Compound Number: GSK2982772

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N251765_00	2016-MAR-22	Original
2015N251765_01	2016-MAY-25	Amendment No. 1
Regulatory feedback led to a requirement for additional concomitant medication restrictions. In addition, some administrative clarifications have been made.		
2015N251765_02	2017-APR-12	Amendment No. 2
Addition of a second cohort of subjects in the study to evaluate a 60 mg three times daily (TID) dosing regimen.		

SPONSOR SIGNATORY

PPD

12th April 2017

Caroline Savage, MD

Date

Vice President & Head Experimental Medicine Unit

Immunoinflammation Therapy Area

PPD

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 203167

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 203167

Rationale

This is the first study with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with active, plaque-type psoriasis.

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg twice daily and 60 mg three times daily for 84 days). In addition a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics, pharmacodynamics, and efficacy in subjects with active plaque-type psoriasis (PsO). Although no formal hypothesis will be tested, these endpoints will enable a fuller understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in PsO, by making full use of the information obtained from each subject enrolled.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 in subjects with active plaque-type psoriasis.	• Adverse events • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead ECG monitoring
Secondary	
• To investigate the pharmacokinetics of GSK2982772 in blood following 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 in subjects with active plaque-type psoriasis.	• Pre-dose plasma concentrations of GSK2982772 at Days 43 (Week 6) and 85 (Week 12). • Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours post dose.
• To investigate the effect of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in skin biopsies from psoriatic skin lesions in subjects with active plaque-type psoriasis.	• Change from baseline in histopathological scoring of psoriatic lesional biopsies which may include, but are not limited to the following as data permit: K16, CD3/CD11c, CD161, elastase positive dermal cells and epidermal thickness. • mRNA expression of inflammatory gene transcripts which may include, but are not limited to the following as data permit: IL-4, IL-10, IL-17, IL-21, IL-22, IL-23, TNF and IFNγ on Days 1 (Week 0) and 43 (Week 6).

Objectives	Endpoints
• To investigate the effect of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Percentage change from baseline and actual Psoriatic Lesion Severity Sum (PLSS) scores in the index lesion.
Exploratory	
• To investigate the effect of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Change from baseline in Psoriasis Area Severity Index (PASI) scores. • The proportion of subjects who achieve PASI ≥ 50%, 75%, and 90% improvement from baseline score. • Change from baseline and actual Physician Global Assessment (PGA). • The proportion of subjects who achieve "clear" (0) or "almost clear" (1) on (PGA). • Change from baseline in body surface area (BSA).
• To investigate the effect of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in the blood of subjects with active plaque-type psoriasis.	• Change from baseline in blood inflammatory markers which may include, but are not limited to the following as data permit: CRP, VEGF, S100A8, S100A9, IL-17, IL-22, and TNF.
• To investigate the effect of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 on transcriptome profiling of both blood and skin of subjects with active plaque-type psoriasis.	• Transcriptomic analysis of mRNA isolated from blood and skin at Day 1 (Week 0) and Day 43 (Week 6).
• To investigate pathway and target engagement following 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 in blood and skin biopsy tissue in subjects with active plaque-type psoriasis.	• Pharmacology biomarker endpoints may include, but are not limited to the following Days 1 (Week 0), 43 (Week 6) and 85 (Week 12), as data permit: o Target Engagement Assay RiP1 (TEAR1) in blood and skin. o Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in skin.
• To investigate the concentration of GSK2982772 in the skin of subjects with active plaque-type psoriasis after 60 mg	• Pre-dose GSK2982772 concentrations in skin biopsies at Days 1 (Week 0) and 43

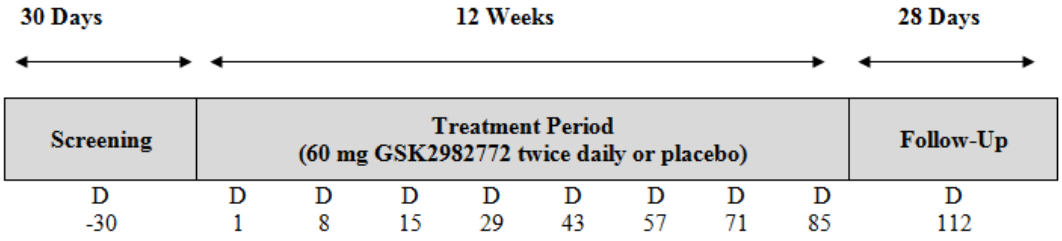
Objectives	Endpoints
twice daily doses and 60 mg three times daily doses of GSK2982772.	(Week 6), as data permit.
• To investigate the effect of 60 mg twice daily doses and 60 mg three times daily doses of GSK2982772 on the patient reported outcomes (PROs) of subjects with active plaque-type psoriasis.	• Change from baseline in Dermatology Life Quality Index (DLQI) score. • Change from baseline and actual Visual Analogue Scale (VAS) itch score.

Overall Design

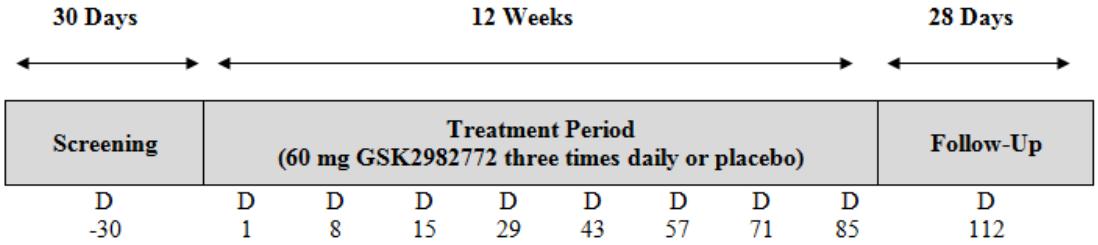
This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled, repeat dose study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with active plaque-type psoriasis. The study design schematic is depicted in Figure 1 below. There will be two cohorts of subjects. Cohort 1 will receive either GSK2982772 60 mg or placebo orally twice daily and Cohort 2 will receive either GSK2982772 60 mg or placebo orally three times daily.

Figure 1 Study Overview

Cohort 1



Cohort 2



Safety assessments, PK samples in skin and blood, PASI, PLSS, DLQI, Itch VAS, PGA assessments, Target engagement, inflammatory biomarkers in skin and blood

Treatment Arms and Duration

Each subject will participate in the study for approximately 20 weeks. This includes a screening period up to 30 days, an 84 day (12 week) treatment period, and a 28 day follow-up visit after the last dose.

Subjects will attend the clinical site to be consented and if eligible for the study, screening assessments will be completed. Subjects will then enter the Treatment Period and be dosed (Day 1) within 30 days of the screening visit.

Punch skin biopsies will be performed on all subjects. Two (2) target lesions will be identified (≥ 3cm x3 cm) on the trunk or extremities. One target lesion will be used for lesion biopsy and the other for PLSS at baseline (pre-dose Day 1) and Day 43 (Week 6). A third biopsy will be performed at baseline only (pre-dose Day 1) from non-lesional skin.

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

In Cohort 1 subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

60 mg GSK2982772 twice daily (BID)

Placebo twice daily (BID)

In Cohort 2 subjects who have completed screening assessments and are eligible will be randomised in a 3:1 ratio (active to placebo) to one of the following treatments:

60 mg GSK2982772 three times daily (TID)

Placebo three times daily (TID)

Type and Number of Subjects

In Cohort 1, a sufficient number of subjects will be screened so that approximately 30 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor, to ensure that approximately 24 evaluable subjects complete the study.

In Cohort 2, a sufficient number of subjects will be screened so that approximately 24 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 32) into the study at the discretion of the Sponsor, to ensure that approximately 20 evaluable subjects complete the study.

For both cohorts, a subject is considered evaluable if they have completed at least one post-treatment biopsy.

Analysis

The safety and tolerability of GSK2982772 following 12 weeks of treatment will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead ECG monitoring.

An ongoing review of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GSK individuals, some of whom are also members of the GSK study team who are not involved in the day-to-day running of the study. The primary purpose of these reviews will be to monitor target engagement, inflammatory markers and the index lesion PLSS for internal decision making. A data review charter will outline in detail the activities of this review and how the integrity of the study will be maintained. An interim analysis will be conducted after the completion of Cohort 1.

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in index lesion PLSS will be statistically analyzed using a repeated measures mixed effects model (MMRM) comparing each GSK2982772 arm with placebo at each time point.

The relationship between each of the mechanistic endpoints and also with the clinical endpoints may also be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g., index lesion PLSS score). In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain percentage change in PLSS (i.e., comparatory rate), based on the data that we have observed in the study. Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

2. INTRODUCTION

2.1. Study Rationale

This is the first study with GSK2982772, a receptor-interacting protein-1 (RIP1) kinase inhibitor, in subjects with active plaque-type psoriasis.

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg twice daily and 60 mg three times daily for 84 days). In addition, a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy in subjects with active PsO. Although no formal hypothesis will be tested, these endpoints will enable a fuller understanding of the mechanism of action and potential for clinical efficacy of GSK2982772 in PsO.

2.2. Brief Background

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

RIP1 is a member of the receptor-interacting Serine/Threonine kinase family containing an amino-terminal kinase domain, an intermediate domain and a carboxy-terminal death domain. RIP1 is a key signalling node which plays an essential role in inflammation and cell death in response to signals including TNF family cytokines, ligands for TLR3/TLR4, sensors of viral infection, and interferons [Ofengeim, 2013]. 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]. Detailed understanding of RIP1 kinase function has not been fully elucidated, but it is known that RIP1 exerts it signalling functions through both its catalytic kinase activity and by acting as a scaffolding protein for signalling complexes. Recent work has demonstrated that RIP1 catalytic kinase activity can regulate TNF-mediated necroptosis [Ofengeim, 2013] and noncanonical apoptosis [Wang, 2008, Dondelinger, 2013]. In addition, the production of certain inflammatory cytokines can be regulated by RIP1 kinase activity [GlaxoSmithKline Document Number 2014N204126_01]. In contrast, RIP1's scaffolding function acts to facilitate other immune processes including TNF mediated classical apoptosis and NF-kB-signalling [Ofengeim, 2013, Humphries, 2015]. With this, an inhibitor of RIP1 kinase activity with GSK2982772 may fill a unique niche in the treatment of inflammatory conditions through multiple mechanisms, including inhibition of inflammation-induced cell death (necroptosis and apoptosis) and inhibition of the production of certain pro-inflammatory cytokines.

Plaque psoriasis (PsO) is a chronic relapsing inflammatory skin disease that is characterized by keratinocyte hyperproliferation and epidermal hyperplasia. In preclinical models, blockade of NFκB or apoptosis pathways results in spontaneous TNF-dependent dermal inflammation that resembles human PsO in murine models [Bonnet, 2011]. In contrast to UC, overt cellular necrosis is not a histologic feature of PsO; however, innate immune responses to DAMPs have been reported in preclinical PsO models [Chen, 2013]. Like Inflammatory Bowel Disease (IBD) and other chronic inflammatory diseases, its pathobiology is incompletely understood. However, a number of inflammatory cytokines, including TNF, IL12/23, and IL17 family members, are thought to play a role in the pathogenesis of PsO, as evidenced by the clinical successes of several biologics targeting these signalling pathways.

Standard treatment generally requires long-term use of topical therapies, followed by systemic immunosuppressant therapies, Psoralen and ultraviolet A (PUVA), and Ultraviolet B (UVB) therapies to achieve and maintain adequate disease control. Novel oral therapies for PsO are becoming more widely used for moderate to severe disease, but may be limited by efficacy (apremilast) and safety/tolerability profiles (tofacitinib). Biologic therapies targeting TNF or Th17/IL22/IL23 pathways have demonstrated significant clinical efficacy for those patients who have had inadequate response to standard topical, UV, and/or oral therapy, but all biologics carry risks for loss of response, side effects, and anti-drug antibodies. There remains a high unmet need for

novel oral therapies which will achieve maximal sustained clearance of skin lesions and improvement in quality of life, balanced by favourable safety and tolerability profiles.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 in subjects with active plaque-type psoriasis.	• Adverse events • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead ECG monitoring
Secondary	
• To investigate the pharmacokinetics of GSK2982772 in blood following 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 in subjects with active plaque-type psoriasis.	• Pre-dose plasma concentrations of GSK2982772 at Days 43 (Week 6) and 85 (Week 12). • Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours post dose.
• To investigate the effect of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 on inflammatory biomarkers in skin biopsies from psoriatic skin lesions in subjects with active plaque-type psoriasis.	• Change from baseline in histopathological scoring of psoriatic lesional biopsies which may include, but are not limited to the following as data permit: K16, CD3/CD11c, CD161, elastase positive dermal cells and epidermal thickness. • mRNA expression of inflammatory gene transcripts which may include, but are not limited to the following as data permit: IL-4, IL-10, IL-17, IL-21, IL-22, IL-23, TNF and IFNγ on Days 1 (Week 0) and 43 (Week 6).
• To investigate the effect of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Percentage change from baseline and actual Psoriatic Lesion Severity Sum (PLSS) scores in the index lesion.
Exploratory	
• To investigate the effect of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Change from baseline in Psoriasis Area Severity Index (PASI) scores. • The proportion of subjects who achieve PASI ≥ 50%, 75%, and 90% improvement from baseline score.

Objectives	Endpoints
	• Change from baseline and actual Physician Global Assessment (PGA). • The proportion of subjects who achieve "clear" (0) or "almost clear" (1) on PGA. • Change from baseline in body surface area (BSA).
• To investigate the effect of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 on inflammatory biomarkers in the blood of subjects with active plaque-type psoriasis.	• Change from baseline in blood inflammatory markers which may include, but are not limited to the following as data permit: CRP, VEGF, S100A8, S100A9, IL-17, IL-22, and TNF.
• To investigate the effect of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 on transcriptome profiling of both blood and skin of subjects with active plaque-type psoriasis.	• Transcriptomic analysis of mRNA isolated from blood and skin at Day 1 (Week 0) and Day 43 (Week 6).
• To investigate pathway and target engagement following 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 in blood and skin biopsy tissue in subjects with active plaque-type psoriasis.	• Pharmacology biomarker endpoints may include, but are not limited to the following Days 1 (Week 0), 43 (Week 6) and 85 (Week 12), as data permit: o Target Engagement Assay RIP1 (TEAR1) in blood and skin. o Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in skin.
• To investigate the concentration of GSK2982772 in the skin of subjects with active plaque-type psoriasis after 60 mg twice daily doses, and 60 mg three times daily doses of GSK2982772.	• Pre-dose GSK2982772 concentrations in skin biopsies at Days 1 (Week 0) and 43 (Week 6), as data permit.
• To investigate the effect of 60 mg twice daily doses, and 60 mg three times daily doses, of GSK2982772 on the patient reported outcomes (PROs) of subjects with active plaque-type psoriasis.	• Change from baseline in Dermatology Life Quality Index (DLQI) score. • Change from baseline and actual Visual Analogue Scale (VAS) itch score.

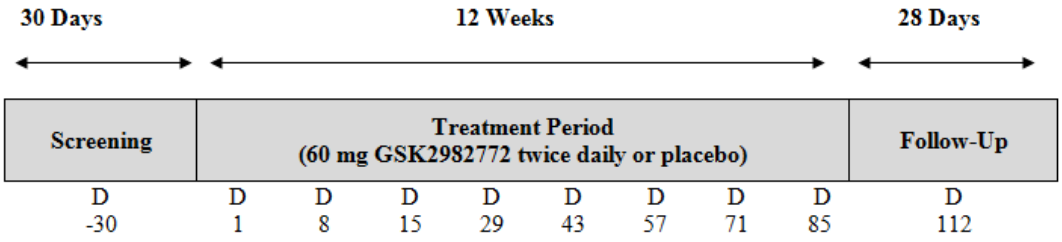
4. STUDY DESIGN

4.1. Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled, repeat dose study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with active plaque-type psoriasis. The study design schematic is depicted in Figure 2 below. There will be two cohorts of subjects. Cohort 1 will receive either GSK2982772 60 mg or placebo orally twice daily and Cohort 2 will receive either GSK2982772 60 mg or placebo orally three times daily.

Figure 2 Study Overview

Cohort 1



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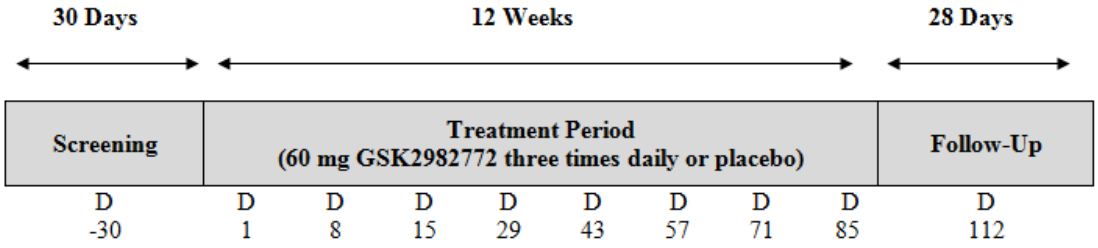


Safety assessments, PK samples in skin and blood, PASI, PLSS, DLQI, Itch VAS, PGA assessments, Target engagement, inflammatory biomarkers in skin and blood

4.2. Treatment Arms and Duration

It is anticipated that the total duration of participation in the study will be approximately 20 weeks from screening to the last study visit.

4.2.1. Screening

Subjects will attend the clinical unit for a screening visit and if eligible and consenting may enter the Treatment Period of the study.

4.2.2. Treatment Period

In Cohort 1, subjects will be randomly assigned to either GSK2982772 60mg or placebo orally twice daily (approximately 12 hours apart) for 84 days. In Cohort 2 subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally three times daily (approximately 8 hours apart) for 84 days. Further guidance and information for study treatment and dosing are provided in the Study Reference Manual (SRM).

Punch skin biopsies will be performed on all subjects. Two (2) target lesions will be identified (≥ 3 cm by 3 cm) on the trunk or extremities. One target lesion will be used for lesion biopsy and the other for PLSS at baseline (pre-dose Day 1) and Day 43 (Week 6). A third biopsy will be performed at baseline only (pre-dose Day 1) from non-lesional skin. Photographs will be taken by the investigator or designee to illustrate any visible changes in psoriasis target lesions during the course of the study.

During the 12 week treatment period, subjects will return to the clinical site for visits on Days 8, 15, 29 and 43, and then every 2 weeks thereafter until Day 85. At specific visits, subjects must not take study treatment prior to their scheduled visit (see Section 7.1). On Days 22, 36, 50, 64 and 78 each subject will be contacted by telephone and asked about their general health. Subjects will be given a diary card at each visit, in which will they will be instructed to record their daily study medication and concomitant medication administration and any adverse events while away from the clinical site.

4.2.3. Follow-up Period

After the Treatment Period, the subject enters the Follow-up Period for 28 days, to complete follow-up assessments per the Time and Events table (Section 7.1).

4.3. Type and Number of Subjects

In Cohort 1, a sufficient number of subjects will be screened so that approximately 30 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor, to ensure that approximately 24 evaluable subjects complete the study.

In Cohort 2, a sufficient number of subjects will be screened so that approximately 24 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 32) into the study at the discretion of the Sponsor, to ensure that approximately 20 evaluable subjects complete the study.

For both cohorts, a subject is considered evaluable if they have completed at least one post-treatment biopsy.

4.4. Design Justification

As this is the first trial of GSK2982772 in subjects with PsO, the primary endpoint is the safety and tolerability of GSK2982772. In addition, this study will include assessments of target engagement and downstream pathway PD effects of GSK2982772, to understand whether GSK2982772 is inhibiting the pathway of interest in this disease.

Skin biopsies are being taken at pre-dose on Days 1 (Week 0) and 43 (Week 6) to measure PK, target and pathway engagement and effects on inflammatory markers in the skin. It is felt that six weeks of treatment allows adequate time to assess histological improvement in the skin.

The 12 week duration of treatment is based on review of previous proof of mechanism and proof of concept studies in PsO and is limited by the supporting 13 week toxicology studies. It is expected that an effective therapy should cause group level changes in the mechanistic parameters by the 12 week time point.

In Cohort 1 the subjects will be randomised in a 2:1 ratio to GSK2982772 60 mg BID and placebo respectively. In Cohort 2 the subjects will be randomised in a 3:1 ratio to GSK2982772 60 mg TID and placebo respectively. The primary objective of this study is safety and tolerability and assessment of this is most valuable in a placebo controlled, blinded study. The placebo group was deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. Subjects will not be allowed to continue standard of care therapy including topical (not permitted on biopsy areas), oral and biologic therapy. A washout period of specific therapies can be found in Section 6.11.

4.5. Dose Justification

The initial selection of the 60 mg BID dose being tested in this study is based on the safety, PK, and PD data from the GSK2982772 First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was initially selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2 hours). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose was predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects are predicted to have >90% RIP1 target engagement in blood at C_{min} using a novel in-house ex-vivo PD/target engagement assay based solely on the TNF pathway which is believed to be a key component of the RIP1 pathway. Assuming a skin: blood ratio of 0.4 (as observed in the rat), the average RIP1 target engagement in skin is predicted to be 92%. At C_{min}, 44% of subjects are predicted to have >90% RIP1 target engagement in the skin and 90% of subjects are predicted to have >80% RIP1 target engagement in the skin.

However, based on final PK/PD modelling from the full repeat dose part of the Study 200975 (up to 120 mg BID), a 60 mg BID dose is now predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have >85% target engagement at C_{min}. In skin, assuming the same skin: blood ratio of 0.4 as noted

above, the average RIP target engagement at 60 mg BID in skin is predicted to be 96%. At C_{min}, 43% of subjects are predicted to have >90% RIP1 target engagement in the skin and 90% of subjects are predicted to have >70% RIP1 target engagement in the skin.

In review of this final FTiH data, it is believed that the C_{min} target exposure may not be achieved with a 60mg BID dosing regimen. The C_{min} values at 60 mg TID are predicted to be approximately 3.5 fold higher than for 60 mg BID. Therefore, a 60 mg TID cohort is now being proposed.

Using the final PK/PD, a 60 mg TID dose is predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have > 96% target engagement at Cmin. In skin, the average RIP target engagement at 60 mg TID is predicted to be 98%. At Cmin, 91% of subjects are predicted to have >90% RIP1 target engagement in the skin and 90% of subjects are predicted to have >91% RIP1 target engagement in the skin.

In addition, because of the short half-life, a modified release formulation is now being developed with the aim to provide a once daily dosing regimen. By increasing the frequency of dosing to three times daily (TID) with the current immediate release formulation, this will more closely match the PK, safety and efficacy profile of a preferred once daily modified release formulation.

The safety of increasing the dose frequency to 60 mg TID is justified based on nonclinical safety findings to date with GSK2982772. It is anticipated that a human dose of 60 mg TID (180 mg/day) will produce $AUC_{(0-24)}$ and C_{max} values of approximately 9.9 ug.h/mL and 0.8 ug/mL, respectively, which are approximately $1/5^{th}$ and $1/15^{th}$ of the gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01].

Up to 03 Apr 2017, a total of approximately 93 subjects across 4 clinical studies have been randomised to receive GSK2982772. In Study 200975, GSK2982772 administered up to 120 mg BID for 14 days and was well tolerated and no safety concerns were identified. A total of 9 subjects had received 120 mg BID in that study. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01]. In this current study, 203167, approximately 22 of 33 subjects have been randomised to GSK2982772 60 mg BID. In other Phase 2a studies in Rheumatoid Arthritis [(RA); Study 203168] and Ulcerative Colitis [(UC); Study 202152], a total of 4 subjects have been randomised to GSK2982772 60 mg BID. GSK2982772 was well tolerated and no drug-related SAEs have been reported. There was a death of a 19 year old male subject in this current study due to an accidental overdose with 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

The proposed 60 mg TID dose regimen is predicted to have mean C_{max} (0.80 µg/mL) and $AUC_{(0-24)}$ (9.9 µg.hr/mL) that are approximately 10% and 50% higher, respectively than for 60 mg BID (0.70 µg/mL and 6.6 µg.hr/mL). This exposure is well within the observed C_{max} and $AUC_{(0-24)}$ values at 120 mg BID in Study 200975.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. 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 the 4-week GLP toxicology study, CNS findings were observed in 4/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance, and decreased activity. The clinical relevance of these findings in humans is not known. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical data**: A First Time in Human (FTiH) study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date (see Investigators Brochure (IB) [GlaxoSmithKline Document Number 2014N204126_01]. No drug-associated CNS adverse events were identified and no Serious Adverse Effects (SAEs) were reported.	**Subject Selection**: • Subjects 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. **Subject Monitoring**: • Subjects will be monitored for standard CNS-related adverse events.
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 subjects taking other immunomodulating drugs or corticosteroids. **Clinical data**: In the FTiH study, no SAEs were reported. One subject experienced an Adverse Effect (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded investigator determined this to be potentially drug-related.	**Subject Selection**: • Subjects with recurrent, chronic or active infections will be excluded from the study. • Subjects will be screened for TB, 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 subjects with PsO.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Subject Monitoring: • Subjects will be monitored for signs of infection. • See Individual Stopping Criteria for atypical or opportunistic infections (Section 5.4.1).
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.	**Subject Selection**: • Attenuated or live vaccines should not be administered to subjects 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 subjects with PsO.
Respiratory	**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 function (e.g., tidal volume, minute volume or respiratory rate) were observed at doses of 1 or 10 mg/kg/day. See Investigator's Brochure for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_01]. **Clinical data**: In the FTiH study, repeat doses of GSK2982772 were administered x 14 days in 36 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory	**Subject Monitoring:** • Subjects should be monitored for standard respiratory-related adverse events. • Vital signs will be monitored during study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related adverse events were identified.	
CNS/Suicidality	GSK2982772 is considered to be a CNS-active drug based on pre-clinical studies. **Clinical data**: In the FTiH study, there have been some reports of lethargy, abnormal dreams, and depressed mood. No events of suicidal ideation or behaviour or changes in behaviour were reported.	**Subject selection**: • Subjects with a current history of Suicidal Ideation Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** • Subjects 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 Columbia Suicide Severity Rating Scale (C-SSRS) in all subjects. See Section 7.3.7.
Reproductive toxicity	**Non-clinical data:** In the rat embryofetal development study, was no maternal or developmental toxicity at doses ≤200 mg/kg/day. In the rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject selection**: • Male and female subjects 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 30 days (females) and 90 days (males) after the last administration of study drug (Appendix 5). • Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Withdrawal criteria: • If a female subject should become pregnant during the study, study medication should be discontinued. The subject 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.
Drug Interaction	**Non-clinical data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (Pgp) inhibitors were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772. There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772. GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772. See Section 4.3.6 of GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01].	**Subject Selections**: • Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. See Section 6.11.2 for a comprehensive list of medications. **Subject Monitoring:** • Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.
Study Procedures		
Punch skin lesion biopsies	Potential risks of the procedure include discomfort, infection or bleeding.	**Subject selection:** • Subjects with history of hypertrophic scarring or keloid, or known allergy to lidocaine or other local anaesthetics will not be included in the study. • Subjects 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
		Subject 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. Subjects will be advised to keep the site covered and dry for 24-48 hours before leaving open to the air. Subjects 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.

4.6.2. Benefit Assessment

There are additional treatment options available for subjects who have an inadequate response to current therapies for PsO. It is possible that treatment with GSK2982772 may be effective in the treatment of PsO, as the FTiH study demonstrated that the drug engaged with the target and produced *ex vivo* PD effects in RIP1-dependent cytokines MIP1α and MIP1β [GlaxoSmithKline Document Number 2014N204126_01]. There will be limited direct benefit to the subject for participating in this trial. However, subjects will indirectly benefit through their contribution to the process of developing new therapies in an area of unmet need.

4.6.3. Overall Benefit: Risk Conclusion

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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number 2014N204126_01].

In addition, investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus, in subjects with PsO.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

For both cohorts, a subject will be eligible for inclusion in this 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 SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects that do not have any medical conditions, other than active plaque-type psoriasis, that in the opinion of the Investigator put the subject at unacceptable risk or interfere with study assessments or integrity of the data. All medical conditions must be stable for the duration of the study. 3. Presence of active chronic plaque-type psoriasis as determined by the Investigator for at least 6 months (confirmed by the subject or medical record) before first dose of study treatment (Day 1). 4. Subject has psoriasis plaques involving Body Surface Area (BSA) ≥ 3% assessed at Screening and before dosing on Day 1. 5. Physician Global Assessment (PGA) ≥3. 6. Subject must agree to avoid prolonged exposure to natural sunlight, tanning beds or phototherapy devices for the duration of the study. See Section 6.11.2. 7. Subject has at least two stable plaques assessed at Screening and before dosing on Day 1. • Both must be of a suitable size (≥ 3 cm by 3 cm) and one in a site suitable for repeat biopsy, and one in a site suitable for index lesion Psoriatic Lesion Severity Sum (PLSS) scoring. • Both plaques must have a PLSS lesional score ≥2 for the induration component (moderate or above), ≥1 for erythema and scaling with a total score of ≥5. • The biopsy lesion must not be on the face, groin, scalp, knees, elbows, or on the palmar/plantar surfaces of the hands/feet, and must be shielded from natural light with clothing. 8. Subject is naive to any biologic therapies for PsO, OR has had previous exposure to a single anti-TNF biologic agent in the context of a previous clinical trial. The anti-TNF biologic agent must have been discontinued more than 8 weeks prior to screening visit (12 weeks or 5 half lives whichever is longer from first dose).

WEIGHT
9. A body mass index BMI within the range of 18.5 – 35 kg/m^2 (inclusive).

SEX
10. Male and Female subjects **Males:** Male subjects with female partners of child bearing potential must comply with the contraception requirements in Appendix 5. **Females**: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 5) from 30 days prior to the first dose of study medication and until 30 days after the last dose of study medication and completion of the follow-up visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
11. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

For both cohorts, a subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Subjects with clinically overt concurrent psoriatic arthritis who are receiving chronic DMARD therapy (other than NSAIDs), as judged by the Investigator.
2. Has nonplaque forms of psoriasis (e.g. erythrodermic, guttate, or pustular), as judged by the Investigator.
3. Has current drug-induced psoriasis (e.g., a new onset of psoriasis or an exacerbation

from beta blockers, calcium channel blockers, or lithium).

4. Subject with current history of Suicidal Ideation Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide.
5. An active infection, or a history of infections as follows:
    - Hospitalisation for treatment of infection within 60 days before first dose (Day 1).
    - Currently on any suppressive therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    - Use of parenteral (IV or intramuscular) antibiotics (antibacterials, antivirals, antifungals, or antiparasitic agents) within 60 days before first dose.
    - A 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.
    - Recurrent or chronic infection or other active infection that, in the opinion of the investigator might cause this study to be detrimental to the patient.
    - History of TB, irrespective of treatment status.
    - A positive diagnostic TB test at screening defined as a positive QuantiFERON-TB Gold test or T-spot test.
        - In cases where the QuantiFERON or T-spot test is indeterminate, the subject may have the test repeated once, but they will not be eligible for the study unless the second test is negative.
        - In cases where the QuantiFERON or T-spot test is positive, but a locally-read follow up chest X-ray, shows no evidence of current or previous pulmonary tuberculosis, the subject may be eligible for the study at the discretion of the Investigator and medical monitor.
6. QTc >450msec or QTc >480msec in subjects with bundle branch block.
    - The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual over read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
7. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
8. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

9. Current or history of renal disease or estimated glomerular filtrate rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) <60 mL/min/1.73 m^2.
10. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
11. A major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
12. A planned surgical procedure that, in the opinion of the investigator, makes the subject unsuitable for the study.
13. A 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.
14. A history of hypertrophic scarring or keloid formation, or known allergy to lidocaine or other local anaesthetics.

CONCOMITANT MEDICATIONS

15. The subject has received treatment with the therapies listed in Section 6.11, 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 in the opinion of the investigator the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS

16. History of alcohol or drug abuse that would interfere with the ability to comply with the study.
17. Subject intends to sunbathe or use a tanning device (sun bed or solarium) within 14 days prior to Day 1 and until completion of the follow up visit (Day 112).

CONTRAINDICATIONS

18. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
19. Received a live or attenuated vaccine within 30 days of randomization OR plan to receive a vaccination during the study until completion of the follow-up visit.
20. The subject has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer 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. Subjects who were randomized into Cohort 1 are not eligible to be re-randomized into Cohort 2.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
21. Haemoglobin <11 g/dL; haematocrit <30%, white blood cell count ≤3000/mm^3 (≤3.0 x 10^9/L); platelet count ≤ 100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤1.5 x 10^9/L at the screening visit.
22. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. As potential for and magnitude of immunosuppression with this compound is unknown, subjects with presence of hepatitis B core antibody (HBcAb) should be excluded. Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
23. A positive serology for human immunodeficiency virus (HIV) 1 or 2 at screening.
24. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.
25. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5).

Subjects who do not qualify to participate in the study due to a screening laboratory value or ECG abnormality can repeat the test once within the original screening time window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

Subjects can be re-screened only on approval of the GSK Medical Monitor and only once. Re-screening is allowed when a subject failed inclusion/exclusion criteria or some other screening condition initially, but the Investigator believes there is a reasonable probability that the subject would be eligible if re-screened.

5.4. Withdrawal/Stopping Criteria

Subjects may be withdrawn from the study for any of the following reasons:

- A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. The reason for withdrawal should be documented in the Case Report Form (CRF).

- The Sponsor may request a subject withdraw for reasons such as significant protocol deviations (after discussion with the investigator).
- If a subject is withdrawn from study treatment, this subject is also considered to be withdrawn from the study.
- Study is terminated by the Sponsor.

If a subject is withdrawn, the Sponsor may decide to replace that subject and this will be done through the Interactive Response Technology System (IRTS).

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

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

If a subject chooses to withdraw from the study after dosing, the investigator must make every effort to complete the follow up assessments detailed in the Time and Events Table (Section 7.1).

5.4.1. Individual Safety Stopping Rules

Study medication will be discontinued in the event of any of the following:

- If a subject experiences a serious or severe clinically significant AE that in the clinical judgement of the investigator, after consultation with the medical monitor, there is a reasonable possibility that the AE is related to investigational product.
- The subject becomes pregnant.
- The subject initiates treatment with any prohibited medication for the treatment of PsO as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.
- If the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or haematologic stopping criteria (Section 5.4.5) are met.

- The subject experiences any signs of suicidal ideation or behaviour (Section 7.3.7).

5.4.2. Group Safety Stopping Rules

In addition to the criteria specified above, AEs, SAEs, laboratory abnormalities, ECG abnormalities and changes in vital signs occurring across all randomised subject will be regularly reviewed by the Sponsor Safety Review Team (SRT) in order to ensure appropriate subject safety. Any changes to the study due to safety reasons will be promptly communicated to the appropriate Regulatory Authorities.

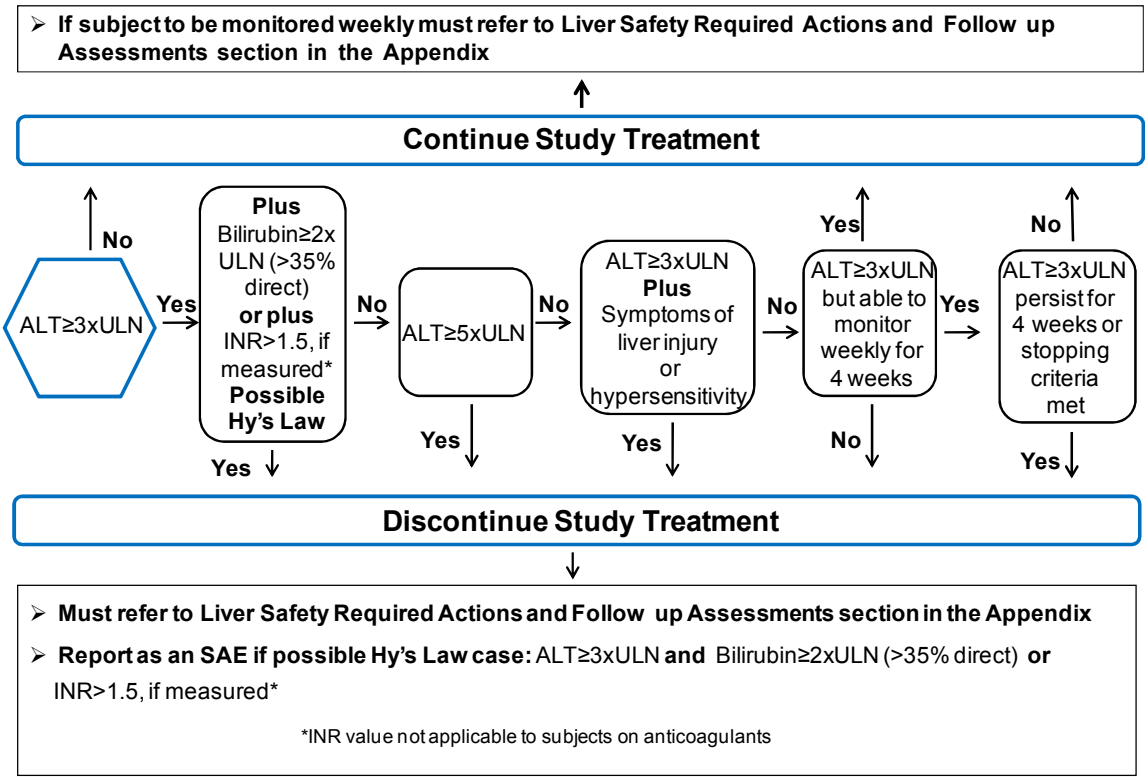
5.4.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Figure 3 Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.3.1. Study Treatment Restart or Rechallenge

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

5.4.4. QTc Stopping Criteria

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec or Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
<450 msec	>500 msec
450–480 msec	≥530 msec

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
- For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
- Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The decision to withdraw a subject will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.4.5. Haematologic Stopping Criteria

Study treatment will be stopped for a subject if any of the following haematological stopping criteria is met:

- Haemoglobin <9 g/dL or an absolute decrease of ≥3 g/dL from baseline (pre-dose Day 1)
- Platelets $<50 \times 10^9$/L

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions for Cohort 1:	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Dosing instructions for Cohort 2:	Take TWO tablets THREE times daily as directed by your physician	Take TWO tablets THREE times daily as directed by your physician
Physical description	White to almost white, round, film coated tablet	White to almost white, round film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

6.2. Treatment Assignment

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

Subjects who meet screening eligibility criteria will be randomised to a treatment group through Interactive Response Technology System (IRTS). The IRTS will confirm the subject's CRF number (Subject 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 subject in the study.

The randomisation is centrally controlled by the IRTS.

In Cohort 1, subjects will take study medication every day, twice a day, approximately 12 hours apart. Subjects will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio. In Cohort 2, subjects will take study medication every day, three times a day, with approximately 8 hours between each dose. Subjects will be randomised to receive either GSK2982772 or placebo in a 3:1 ratio.

Subjects will be administered the first daily dose of study medication by site staff during the site visit for Day 1 (week 0) and Day 43 (week 6). Subjects will self-administer all other doses of study medication and will record the date and time in the diary cards provided to them.

6.3. Planned Dose Adjustments

No dose adjustments are allowed.

6.4. Blinding

This will be a double blind (sponsor unblind) study and the following will apply.

- Sponsor unblinded refers only to the Data Review Committee (DRC) consisting of the GSK Project Physician Lead (PPL), the study statistician, the study pharmacokineticist, Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head, the Early Development Leader (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.
- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator. Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject 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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment 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.

6.7. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment 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 treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When subjects self-administer study treatment(s) at home, compliance with GSK2982772 will be assessed through querying the subject during the site visits and documented in the source documents (diary cards) and CRF. A record of the number of GSK2982772 or placebo tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 >120 mg daily will be considered an overdose in Cohort 1 and any dose of GSK2982772 >180 mg daily will be considered an overdose in Cohort 2. GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

In the event of an overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days for GSK2982772).
3. Obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (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 subject.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.10. Lifestyle and/or Dietary Restrictions

- Subjects must adhere to the contraceptive requirements listed in Appendix 5.
- Subjects must abstain from alcohol for 24 hours before all clinic visits.

6.10.1. Sun Exposure and Activity

Subjects must not sunbathe or use a tanning device (sun bed or solarium) for 14 days prior to Day 1 until the follow up visit (Day 112). Subjects will be advised that when they are outdoors they should wear protective clothing (e.g. sun hat, long sleeves) covering the selected target lesions for biopsy and PLSS scoring as well as use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥30) on exposed areas when outdoors.

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

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Selected medications for the treatment of PsO may be taken, with specific requirements listed in Table 1, and as long as they are not prohibited (Section 6.11.2). All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name and dates of administration are recorded.

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.
Medicinal shampoos that contain tar and/or salicylic acid (but not corticosteroids)	Permitted at any time on scalp area.

6.11.2. Prohibited Medications and Non-Drug Therapies

Table 2 lists prohibited medications for defined periods of time before and during the study until after the follow up visit (Day 112).

Subjects 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

Therapy	Time period
Biologic therapies for the treatment of chronic plaque-type psoriasis • **Exception**: Can have only been exposed to one anti-TNF biologic previously administered in a clinical study setting.	12 weeks or 5 half-lives (whichever is longer) prior to first dose. Otherwise, cannot have been on an anti-TNF biologic treatment at any time during the study.
Photochemotherapy with psoralens and ultraviolet A (PUVA) therapy	4 weeks prior to first dose until after the follow up visit (Day 112).
Phototherapy (e.g., UVB or self treatment with tanning beds)	14 days
Topical therapies (e.g., corticosteroids, cyclosporine, calcineurin inhibitors, coal tar, vitamin A or D analog preparations, anthralin, calcipotrienen, retinoids, tazarotene, methoxsalen, trimethy psoralens).	2 weeks prior to first dose until after the follow up visit (Day 112).
Systemic immunomodulating medications for other medical conditions that are known to affect psoriasis, including but not limited to oral corticosteroids cyclosporine, methotrexate, cyclophosphamide, and beta-adrenergic blockers. Intravenous or oral calcineurin inhibitors (e.g., tacrolimus).	4 weeks prior to first dose until after the follow up visit (Day 112).
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone,	4 weeks prior to first dose until after the follow up visit (Day 112).

Therapy	Time period
erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	4 weeks prior to the first dose until after the follow up visit (Day 112).
Live vaccination	Vaccinations (either live, attenuated) are not permitted within 30 days of randomization or plan to receive a vaccination during the study until follow-up visit. 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 subjects with PsO.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

a. Patient Reported Outcomes (PROs)

b. 12-lead ECG

c. vital signs

d. blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other 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.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- The Institutional Review Board/ Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the Study Reference Manual (SRM).

7.1. Time and Events Table

Procedures	Screening	Treatment Period													Early Withdrawal [14]	Follow Up	Notes
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43 (week 6)	Day 50	Day 57	Day 64	Day 71	Day 78	Day 85 (week 12)			**Visit windows** Screening: up to 30d before Day 1. Treatment Period (except Day 1 & 85): ± 3d. Day 1 NA; Day 85 ± 2d. Early Withdrawal: NA Follow Up: 28d after last dose ± 3d
Screening Procedures	Screening procedures in addition to those listed below are (outpatient visit): informed consent; inclusion/ exclusion criteria; demography; medical history (includes past and current conditions, medication history, and family history of premature CV disease); HIV, Hep B and Hep C screen; serum pregnancy test (WCBP only).																
Site Visit	X	X	X	X		X		X		X		X		X	X	X	1. Full physical exam: height/weight at Screening, height not required at later timepoints. 2. Vitals: BP, HR, RR, temperature. ECG triplicate at Screening only. 3. Urinalysis not required on Days 29, 57 and 71. 4. If urine test is positive, confirmatory serum test must be performed. 5. Pre-dose 6. In Cohort 1, subjects must take study medication twice a day approx. 12h apart. In Cohort 2, subjects must take study medication three times a day approx. 8h apart. Exact time of dosing to be recorded in diary cards. On Days 43 and 85, subjects must not take medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Day 43 only. On Day 85, subjects no longer dosed. 7. Diary card checked by site staff and new diary card dispensed at every study visit. 8. Blood samples for inflammatory
Phone call					X		X		X		X		X				
Safety Assessments																	
Full physical exam[1]	X													X	X	X	
Brief physical exam		X[5]		X		X		X[5]		X		X					
12-lead ECG, vital signs[2]	X	X[5]	X	X		X		X[5]		X		X		X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[5]						X[5]						X	X		
Hematology, chemistry, urinalysis	X	X[5]	X	X		X[3]		X[5]		X[3]		X[3]		X	X	X	
FSH & estradiol (if applicable)	X																
Serum pregnancy (WCBP)	X																
Urine pregnancy test (WCBP only)[4]		X[5]	X	X		X		X[5]		X		X		X	X	X	
Study Treatment																	
Randomisation		X															
Study medication[6]		X	X----------											-----X			
Dispensing of study medication		X				X				X							
Dispensing of diary cards[7]		X	X	X		X		X		X		X					
PROs/ Disease Assessments																	

Procedures	**Screening**	**Treatment Period**													**Early Withdrawal** [14]	**Follow Up**	**Notes**
		Day 1	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43** (week 6)	**Day 50**	**Day 57**	**Day 64**	**Day 71**	**Day 78**	**Day 85** (week 12)			**Visit windows** Screening: up to 30d before Day 1. Treatment Period (except Day 1 & 85): ± 3d. Day 1 NA; Day 85 ± 2d. Early Withdrawal: NA Follow Up: 28d after last dose ± 3d
Psoriatic Body Surface Area	X	X[5]												X	X		biomarkers and mRNA taken pre-dose on Day 1, Day 43 and Day 85.
PASI, PGA, PLSS, Itch	X	X[5]		X		X		X[5]		X		X		X	X		9. PK blood samples taken pre-dose on Day 43. Post-dose serial PK samples taken on Day 1 and Day 43 at 1, 2, 4, and 6 hours post-dose.
DLQI	X	X[5]						X[5]						X	X		
Photograph of lesions		X[5]						X[5]						X	X		
Other Assessments and Procedures																	10. Pre-dose Day 1 one biopsy taken from non-lesional skin and two biopsies taken from biopsy target lesion.
Blood sample for inflammatory biomarkers[8]		X[5]						X[5]						X	X		
Blood sample for mRNA analysis[8]		X[5]						X[5]						X	X		11. On Day 43, two biopsies taken from the same target lesion that was selected at Day 1. Punch biopsies on Day 43 are to be taken pre-dose.
Blood sample for Target Engagement		X[5]						X[5]						X	X		
PK blood samples[9]		X						X[5]						X	X		12. Biopsy only required at Early Withdrawal visit if completed at least 14 days of treatment and prior to Day 43.
Skin punch biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement		X[5,10]						X[11]							X[12]		13. PGx sample collected at Day 1, after randomization and separate informed consent. If sample not collected at Day 1, can be collected at any time post-randomization.
Pharmacogenetic sample (PGx)		X[13]															14. If subject withdraws early, every effort will be made for the subject to complete an Early Withdrawal visit prior to Follow Up.
Con med review & AE/SAE reporting		X----------														----------X	

7.2. Screening and Critical Baseline Assessments

After written informed consent, screening assessments will be performed as outlined in the Time and Events Table (Section 7.1).

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Cardiovascular medical history/risk factors and smoking history (as detailed in the CRF) will be assessed at screening.

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests such as vital signs, physical exams and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The investigator will be responsible for determining the clinical significance of any results the fall outside of the laboratory normal ranges.

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT), which will include 203167 study team members, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- AEs will be collected from the start of study treatment on Day 1 until the follow-up contact (see Section 7.3.1.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 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.

7.3.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 30 days after the last dose.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment 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.
- A brief physical examination will include, at a minimum 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.

7.3.4. Vital Signs

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

7.3.5. Electrocardiogram (ECG)

- Triplicate ECGs will be obtained at screening and single 12-lead ECGs will be obtained at every other time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F or B) intervals. Refer to Section 5.4.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG is to be measured in a supine or semi supine position after 5 minutes rest.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 3, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in times for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**
Haematology	Platelet Count; RBC Count; Hemoglobin; Hematocrit *RBC Indices*: MCV; MCH *WBC count with Differential:* Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils
Clinical Chemistry [1]	BUN; Creatinine; Glucose [2]; Triglycerides [2] Potassium; Sodium; Calcium; Total Cholesterol[2] AST (SGOT); ALT (SGPT); Alkaline phosphatise; HDL cholesterol [2] Total and direct bilirubin; Total Protein; Albumin; LDL cholesterol [2]
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• HIV • Hepatitis B surface antigen (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis C (Hep C antibody) • QuantiFeron Gold test • T-spot (if QuantiFeron is indeterminant) • FSH and estradiol (as needed in women of non-child bearing potential only) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [3]. • Serum hCG (as needed for women of child bearing potential) to be done at screening and if urine test positive at other timepoints in study. • Estimated glomerular filtrate rate (eGFR) will be calculated using the CKD-EPIformula.

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 5.4.3 and Appendix 2.
2. No fasting required. Any abnormal result for glucose or lipids (non-fasted) may be repeated at the discretion of the investigator.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.3.7. Suicidal 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 subjects being treated with GSK2982772 should be alerted about the need to monitor subjects 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.

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

At Screening and baseline (pre-dose Day 1), the 'Baseline/Screening CSSRS' (Columbia Suicide Severity Rating Scale) will be completed. At Days 43 (week 6) and Day 85 (week 12), the 'Since Last Visit CSSRS' will be completed. GSK Version 4.1 of both rating scales will be used.

Subjects who answer 'yes' to any suicidal behaviour or 'yes' to suicidal ideation Questions 4 or 5 will be referred to their GP or appropriate psychiatric care. The medical monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 7.3.1 - AE and SAE). In addition, the investigator should 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.

7.4. Efficacy

7.4.1. Patient Reported Outcomes

Note: Patient Reported Outcomes questionnaires should be completed by subjects before any other assessments at a clinic visit.

7.4.1.1. Itch Visual Analogue Scale

The subject will be asked to rate the intensity of itch over the past week by marking a line on a 10 cm VAS with anchors "0" (no noticeable itching) to "10" (maximum itching sensation).

7.4.1.2. Dermatology Life Quality Index

The DLQI [Finlay, 1994] will be used to assess quality of life. The subject will complete the questionnaire to evaluate how their psoriasis has affected their life over the previous week before the assessment occurs. Each question will be scored out of 0-3 or 0-2, as follows.

0 = Not at all
1 = A little
2 = A lot
3 = Very much

The questionnaire comprises of 10 questions (see SRM for full details).

7.4.2. Clinical Disease Assessments

7.4.2.1. Body Surface Area (BSA)

The BSA affected with psoriasis will be evaluated at Screening and baseline (pre-dose Day 1) and on Day 85 by the investigator or suitably trained delegate. In order to be eligible for the study, BSA must be ≥3%. As a reference, the area of the whole palm is counted as 1% BSA.

7.4.2.2. Selection of Psoriasis Plaques and Plaque Lesion Severity Scoring (PLSS)

Two plaques of at least 3 cm by 3 cm in area will be selected during the Screening period, one for clinical assessment (clinical efficacy skin lesion) and one for skin biopsy (punch biopsies). If at baseline on Day 1, prior to dosing, another lesion appears more suitable, the selected lesion can be changed. Once the lesions have been selected at baseline on Day 1, they must not change.

At a minimum, each plaque will have an induration score of ≥2 (moderate or above) and a score of ≥1 in erythema and scaling. The PLSS is the sum of the erythema, scaling and plaque thickness scores. Each lesion must have a PLSS score of ≥5.

Ideally, the biopsy skin lesion should be the most severe plaque of the two.

Selected lesions should be located on areas (trunk or extremities) that can be shielded to reduce natural exposure to UV light and should not include scalp, inguinal, genital lesions, or the palmar surfaces of the hands and/or feet. Preferably, symmetrical lesions will be chosen, but this is not an absolute requirement.

During the study, the PLSS will be recorded for the clinical efficacy skin lesion (the biopsy lesion is only for biopsy).

7.4.2.3. Psoriasis Area Severity Index (PASI)

The PASI scoring system is a widely-used standard clinical tool for assessing the severity of psoriasis that takes into account the overall severity of erythema (redness), thickness (induration), and scaling, as well as the extent of BSA affected with psoriasis [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 subject will be completed by the same assessor at all time points.

7.4.2.4. Digital Photography

Photographs will be taken by the investigator or designee to illustrate any visible changes in psoriasis target lesions selected on Day 1. For each subject, the investigator or delegate will take photographs of the same area of the body at each time point (i.e., same background, same illuminations, and same distance from the body). Photographs will be taken of the area(s) of the body where the selected lesions are present and should be taken prior to performing the biopsy. Photographs of the face will not be taken. Photographs will be stored electronically, labelled, and collected centrally as explained in the Image Acquisition Guidelines. Photographs will be used to document visual changes in lesions. Date, time and location of the photographs will be captured in the CRF.

Further details are contained in the Image Acquisition Guidelines.

7.4.2.5. Physician's Global Assessment of Disease Activity

The investigator or physician designee only will complete a global assessment of disease activity using the physician global assessment item. A 6-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 physician's global assessment independently of the subject.
- Ideally, the same investigator or physician designee should perform all global assessments for each subject for the duration of the study.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK2982772 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of blood sample collection, processing, storage and shipping procedures are provided in the laboratory manual.

7.5.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technologies and Science In vitro/ In vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. 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 analyzed for GSK2982772 any remaining plasma may be analyzed for other compound-related material and the results reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.5.3. Punch Skin Biopsy for Pharmacokinetic Assay

See Section 7.6.1 for more details on punch skin biopsies. A punch skin biopsy will be taken at baseline (pre-dose Day 1) and Day 43 (Week 6) to measure the concentration of GSK2982772 in the skin (taken from the outer third of the target lesion). Information on processing the biopsies for the skin pharmacokinetic assay will be provided in the SRM.

Once the skin extract has been analyzed for GSK2982772, any remaining skin extract may be analyzed for other compound-related material and the results reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.5.4. Sample Analysis

Skin biopsy sample analysis will be performed under the control of PTS-IVIVT, GlaxoSmithKline. An exploratory analysis of concentrations of GSK2982772 in skin will be conducted.

7.6. Biomarker(s)/Pharmacodynamic Markers

7.6.1. Skin Lesion Biopsy

At baseline (pre-dose Day 1), a target lesion for biopsy will be identified (≥3 cm by 3 cm) on the trunk or extremities. The same target lesion will be used for both the baseline lesion biopsy and at Day 43 (Week 6) even if the lesion has cleared. Lesions on palmar

surfaces of the hands and feet, scalp, knees, elbows and intertriginous areas will not be used as the target lesion site.

- Two 4-mm tissue biopsies will be taken from the outer third of the selected biopsy lesion at baseline (pre-dose Day 1) using standard methodology. The second site on the outer third of the same lesion should be at least 1.5 cm from the first biopsy. Local anaesthetic will be administered before each biopsy, and only suitably experienced personnel, trained in aseptic technique, will obtain the biopsies.
- At baseline only (pre-dose Day 1), a total of 3 biopsies will be taken, 1 from a non-lesional area of skin and 2 biopsies will be taken from the target lesion site. The target lesion biopsy will be taken from the outer third of the lesion. The non-lesional biopsy will be taken from an unaffected area close to the target lesion, and cannot include the palmar surfaces of the hands and feet, scalp, knees, elbows and intertriginous areas
- At Day 43 (Week 6), 2 biopsies will be taken from the same target lesion as identified at baseline even if the lesion has cleared. As above, the biopsies will be taken from the outer third of the lesion.

Biopsy tissue taken from the psoriatic skin lesions will be divided accordingly for pharmacokinetic, target and pathway engagement, histological and gene expression analyses as feasibility dictates. Histologic assessment will include measurement of epidermal thickness, total inflammatory infiltrates, keratin expression (e.g., K16) and specific cell numbers (which may include by not be limited to) CD3+T-cells, CD11c+ myeloid dendritic cells. mRNA may be isolated from skin biopsy tissue, as feasibility dictates, to determine the effect of placebo and GSK2982772 on markers of inflammation and tissue healing (e.g., may include and not be limited to measurement of chemokines, cytokines, and extracellular matrix proteases). Examples of technologies that may be used for analysis include, but are not limited to quantitative PCR, RNAseq, microarray, mass cytometry (CyTOF). See SRM for full details of the division of biopsy tissues.

The baseline nonlesional skin biopsy will be divided accordingly for histologic and gene expression analysis as feasibility dictates. Histologic assessment will include measurement of epidermal thickness, total inflammatory infiltrates, keratin expression (e.g., K16) and specific cell numbers (which may include by not be limited to) CD3+T-cells, CD11c+ myeloid dendritic cells. mRNA expression of inflammatory markers and tissue healing will be assessed in baseline nonlesional skin (as above) as feasibility dictates, using the same technologies as outlined above.

7.6.2. Novel Pharmacodynamic Biomarkers

7.6.2.1. RIP1 Target Engagement in Blood

Blood samples for RIP1 target engagement will be collected at the time points indicated in Section 7.1 to measure levels of free and total RIP1 antibodies.

7.6.2.2. RIP1 Target Engagement in Tissue

Skin punch biopsy samples for RIP1 target engagement will be collected at the time points indicated in Section 7.1 to measure levels of free and drug-bound RIP1 protein if sample quantity and data allow.

7.6.2.3. RIP1 Pathway Markers in Tissue

Skin punch biopsy samples for RIP1 pathway markers will be collected at the time points indicated in Section 7.1 to measure total or phosphorylated RIP1, RIP3, MLKL and cleaved or total caspase 3 and 8 if sample quantity and data allow.

7.6.3. Exploratory Novel Biomarkers

With the subject's consent, tissue, and/or blood sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence disease/condition for study treatment, and/or medically related conditions, as well as the biological and clinical responses to GSK2982772. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Samples will be collected at the time points indicated in Section 7.1. The timing of the collections may be adjusted on the basis of emerging pharmacokinetic or PD data from this study or other new information in order to ensure optimal evaluation of the PD endpoints.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with PsO and/or the action of GSK2982772 may be identified by application of:

- Gene expression array analysis may be conducted on the blood and/or punch skin biopsies using microarray, and/or alternative equivalent technologies such as RNA sequencing, which facilitates the simultaneous measurement (and confirmation) of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each skin sample.
- Soluble inflammatory mediators in the blood may be assayed for cytokine and inflammatory mediators including, but not limited to, pro-inflammatory and anti-inflammatory cytokines, chemokines, and acute phase proteins.
- Phosphoprotein detection in skin tissue and blood may be used to validate RIP1 kinase pathway activation.
- High dimensional CyTOF/Helios based immune profiling of peripheral blood cells including measurement of immune cell phenotypes, intracellular signalling events and key cytokines / chemokines.

These analyses may be reported under separate protocol following the completion of the study. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

7.7. Genetics

In consenting subjects, a blood sample for pharmacogenetics (PGx) research will be drawn on Day 1 (or any time point post randomisation and prior to study completion) to better characterize genetic variability that may affect efficacy or safety endpoints. Information regarding pharmacogenetic (PGx) research is included in Appendix 3.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of the study is to investigate the safety and tolerability of GSK2982772 60 mg BID and 60 mg TID following 12 weeks of treatment. No formal statistical hypotheses will be conducted to assess this objective.

If appropriate, comparisons between the GSK2982772 arms and the placebo arm will be made to investigate the secondary inflammatory, mechanistic and efficacy objectives. Trends over time will be investigated for both treatment arms along with associations between each of the parameters.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

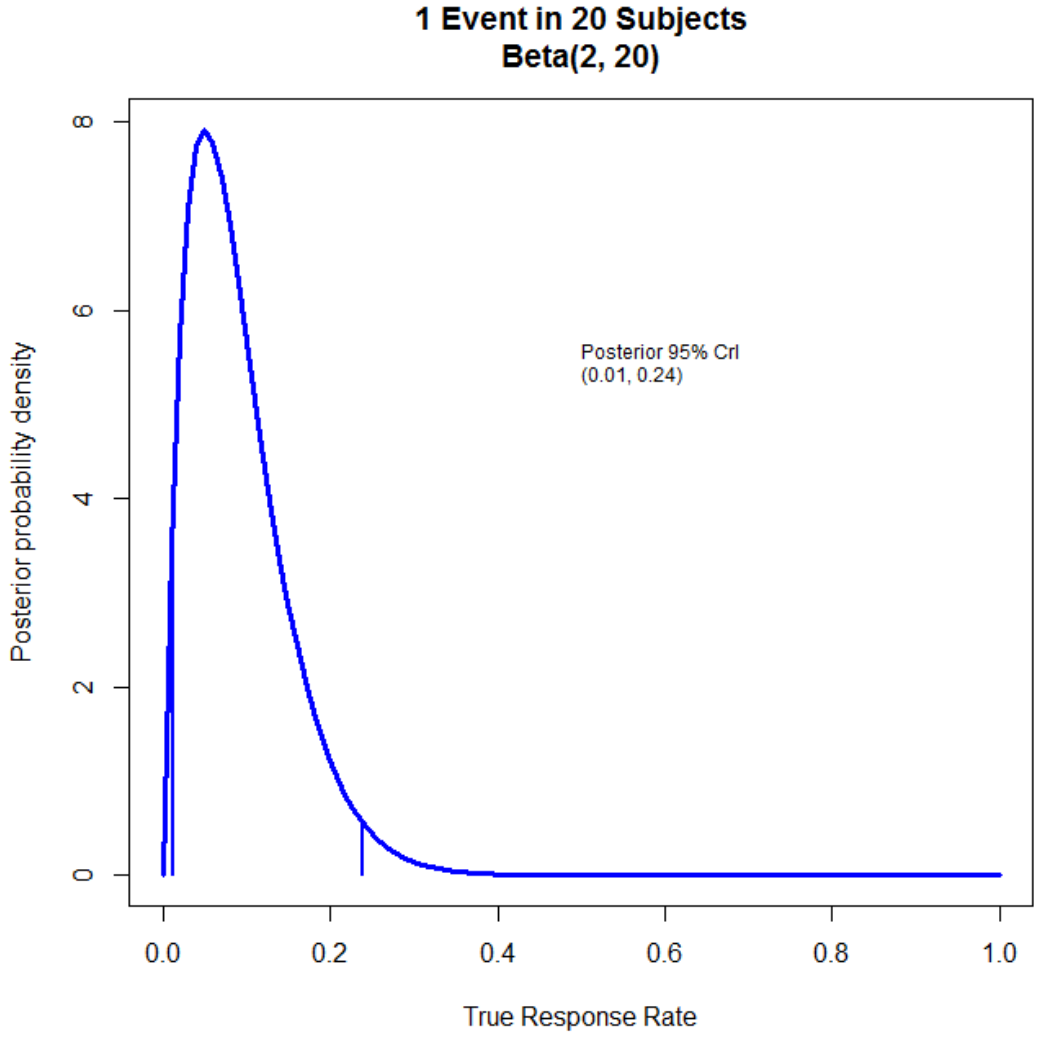
The study is not powered to detect pre-defined differences. In Cohort 1, approximately 30 subjects and up to a maximum of 36, will be randomised into the study to either GSK2982772 or placebo in a 2:1 ratio to ensure that approximately 24 evaluable subjects complete the study.

In Cohort 2, approximately 24 subjects and up to a maximum of 32, will be randomised into the study to either GSK2982772 or placebo in a 3:1 ratio to ensure that approximately 20 evaluable subjects complete the study.

A subject is considered evaluable if they have completed at least one post-treatment biopsy.

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772 60 mg BID and 18 subjects randomised to GSK2982772 60 mg TID. Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 20 then the posterior distribution would be Beta (2, 20), as outlined below in Figure 4.

Figure 4 One Event in 20 Subjects: Beta (2,20) Distribution



Thus, we can be 95% certain that the true probability of the safety event lies between 0.01 and 0.24. Similarly, if we were to observe one safety event in 18 then the posterior

distribution would be Beta (2, 18), thus we can be 95% certain that the true probability of the safety event lies between 0.01 and 0.26.

For supportive information the properties of the secondary endpoint PLSS have also been considered. Assuming a standard deviation of 25%, it is estimated that the lower and upper bounds of the 95% confidence interval for the difference between GSK2982772 60 mg BID (n=20) and placebo (n=10) in percentage change in index lesion PLSS will be within approximately 17.1% of the point estimate, and that the lower and upper bounds of the 95% confidence interval for the difference between GSK2982772 60 mg TID (n=18) and placebo (n=6) in percentage change in index lesion PLSS will be within approximately 17.5% of the point estimate.

9.2.2. Sample Size Sensitivity

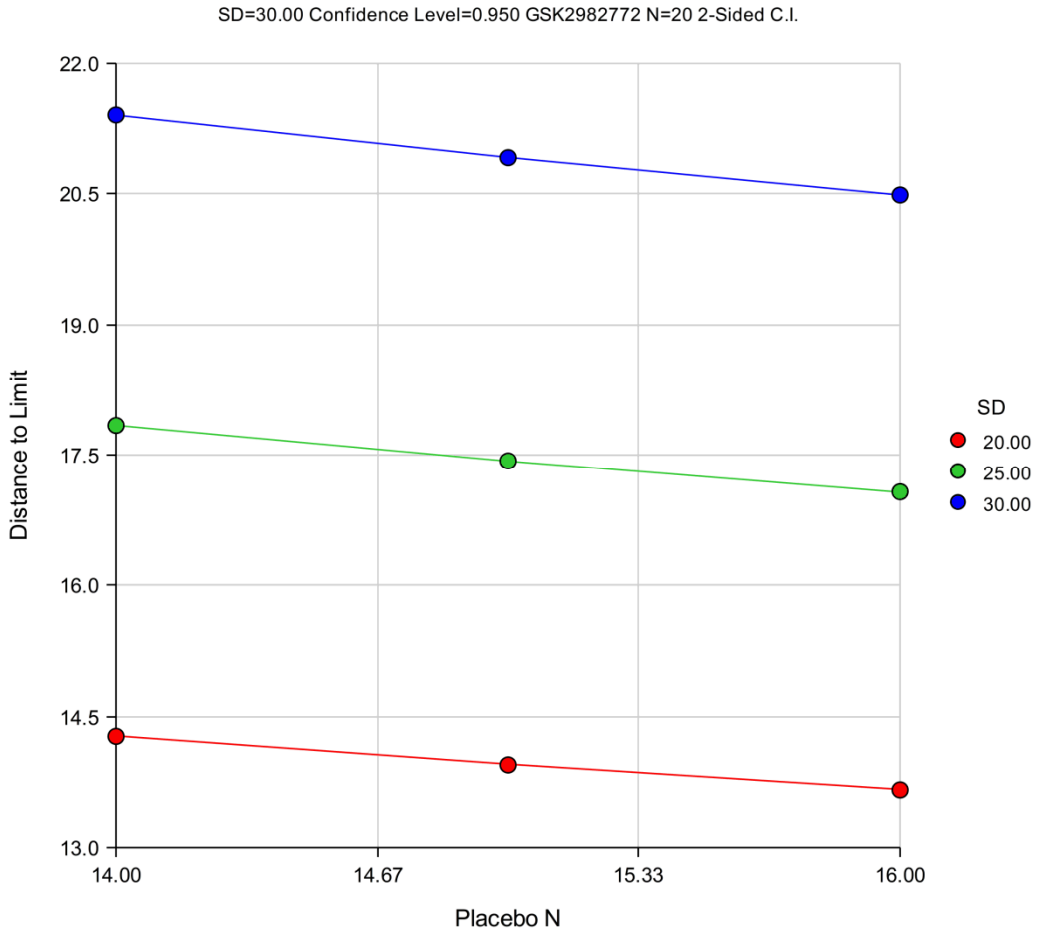
A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is lower than anticipated, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in Table 4.

Table 4 Sample Size Sensitivity

GSK2982772 subjects completing the study	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
20	0	16.1%
20	1	23.8%
20	2	30.4%
18	0	17.6%
18	1	26.0%
18	2	33.1%
16	0	19.5%
16	1	28.7%
16	2	36.4%

Similarly, for supportive information a sensitivity analysis of the precision of the secondary endpoint percentage change in PLSS has been performed to assess the impact of varying variability and numbers of GSK2982772 and placebo subjects Figure 5.

Figure 5 Sample Size Sensitivity for Percentage Change in PLSS



9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be conducted.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All Subjects Population: The 'All Subjects Population' is defined as subjects who were screened for the study. This population is used for the summary of selected accountability data.

Safety Population: The 'Safety Population' is defined as subjects who receive at least one dose of study medication. This population is used for the summary of all data including demography, safety, efficacy and exploratory data but excluding PK data.

Pharmacokinetic Population: The 'PK Population' is defined as subjects in the 'Safety' population who received an active dose and for whom a pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only. Any PKPD analyses will be conducted on the Safety population such that subjects receiving placebo can be included.

9.3.2. Interim Analysis

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT) which will include members of the GSK2982772 project team, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

In both cohorts, once an appropriate number of subjects randomised to GSK2982772 have completed Day 43 (Week 6), the PLSS data will be reviewed in an unblinded manner by a Data Review Committee (DRC) consisting of the GSK Project Physician Lead (PPL), the study statistician, the study pharmacokineticist, the PRR DPU Head, the Early Development Lead (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g., target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data. The primary purpose of these reviews will be to monitor PLSS changes for internal decision making purposes. A data review charter will identify the specific GSK individuals involved, outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted after the completion of Cohort 1 and will only include those subjects randomised to a BID dosing regimen. The purpose of the interim analysis is primarily to provide the project team and key GSK stakeholders with an early indication of the safety and efficacy from the trial, and to facilitate decision making regarding the subsequent clinical development of GSK2982772.

9.3.3. Primary Analyses

All safety evaluations will be based on the Safety population. Clinical interpretation will be based on the review and displays of adverse events, clinical laboratory values, vital sign measurements and 12-lead ECG monitoring.

9.3.4. Secondary Analyses

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in index lesion PLSS be statistically analyzed using a MMRM (repeated measures mixed effects model) comparing each GSK2982772 arm with placebo at each time point. If sufficient numbers of subjects are enrolled with a BSA >5% then the proportion of subjects achieving PASI 50/75/90 at Day 85 (12 Weeks), will be statistically analysed using a Generalised Estimating Equations (GEE) model comparing each GSK2982772 arm with placebo at

each time point if appropriate. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

The relationship between each of the mechanistic endpoints and also with the clinical endpoints may also be graphically presented and analysed using an appropriate statistical model identifying any trends. The model will determine whether the mechanistic effect significantly explains or predicts the effect on the other mechanistic or clinical endpoints (e.g., index lesion PLSS score). This may be conducted through comparing statistical models incorporating different explanatory terms (i.e. mechanistic endpoints) with the 'null' model (no mechanistic endpoints); or if deemed appropriate, multivariate statistical methods may also be applied to determine the relationship between the key endpoints. The consistency in the changes over time between the endpoints will also be assessed.

In addition, based on the data that we observe in the study, probabilities of success will be determined, where the definition of success will be dependent on the endpoint. For example, what is the probability that we would observe a certain percentage change in PLSS (i.e., comparatory rate), based on the data that we have observed in the study.

GSK2982772 plasma concentrations will be summarised descriptively by Day and nominal time point by dosing regimen.

Further details regarding the statistical analysis will be outlined in the Reporting and Analysis Plan (RAP).

9.3.5. Other Analyses

9.3.5.1. Exploratory Analyses

All exploratory endpoints will be descriptively summarized, graphically presented and listed appropriately. Further details can be found in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and

the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche,

scanned, electronic); however, caution needs to be exercised before such action is taken.

- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

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 subjects, 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

11. REFERENCES

Bonnet MC, Preukschat D, Welz P-S, van Loo G, Ermolaeva MA, Bloch W et al. The adaptor protein FADD protects epidermal keratinocytes from necroptosis in vivo and prevents skin inflammation. *Immunity,* 2011;35:572-82.

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464
Gorin MB.

Chen T, Guo Z-p, Li L, Wang L, Jia R-z, Cao N et al. Increased HMGB1 serum levels and altered HMGB1 expression in patients with psoriasis vulgaris. *Archives of Dermatological Research,* 2013;305:263-7.

Dondelinger Y, Aguileta MA, Goossens V, Dubuisson C et al. RIPK3 contributes to TNFR1-mediated RIPK1 kinase-dependent apoptosis in conditions of cIAP1/2 depletion or TAK1 kinase inhibition. *Cell Death and Differentiation*, 2013;20:1381-92.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – A simple practical measure for routine clinical use. *Clin Exp* Dermatol, 1994;19:210-216.

Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. *Dermatologica*, 1978;157(4):238-44.Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. 1978;157:238-44.

GlaxoSmithKline Document Number 2014N204126_01 Investigator's Brochure GSK2982772 PPD 08-MAR-2016.

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. *Mo. Aspects Med*. 2012; 33:467-486.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3 2.

Humphries F, Yang S, Wang B, Moynagh P N. RIP kinases: key decision makers in cell death and innate immunity. *Cell Death & Differ*, 2015;22:225-236.

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

Ofengeim D and Yuan J. Regulation of RIP1 kinase signaling at the crossroads of inflammation and cell death. *Nature Reviews Molecular Cell Biology,* 2013;14:727-36.

U.S. Department of Health and Human Services, Food and Drug Administration (FDA). (2012) Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Center for Drug Evaluation

and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

Wang L, Du F, Wang X. TNF-alpha induces two distinct caspase-8 activation pathways. *Cell*, 2008; 133(4):693-703.

12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMD	Age-related macular degeneration
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BID	Twice a day
BSA	Body Surface Area
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Cmax	Maximum observed concentration
CNS	Central nervous system
CRF	Case Report Form
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-Reactive Protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CYP	Cytochrome P
CyTOF	Mass cytometry
DAMPs	Damage-associated molecular pattern
DRC	Data Review Committee
DLQI	Dermatology Life Quality Index
DMARD	Disease-Modifying Antirheumatic Drugs
DNA	Deoxyribose Nucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDL	Early Development Lead
ETCO2	End-tidal Carbon Dioxide
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTiH	First Time in Human
GCP	Good Clinical Practice
GEE	Generalised Estimating Equations
GFR	Glomerular Filtrate Rate
GSK	GlaxoSmithKline
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus

IB	Investigator Brochure
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin gamma
IP	Investigational Product
IRB	Institutional Review Board
IRTs	Interactive Response Technology System
Kg	Kilogram
L	Litre
LDH	Lactate Dehydrogenase
MCH	Mean corpuscular haemoglobin
MDMA	3,4-methylenedioxy-methamphetamine
MedDRA	Medical Dictionary for Regulatory Activity
mg	Milligram
mL	Millilitre
MLKL	Mixed lineage kinase domain-like protein
mm	Millimeter
mmol	Millimole
MMRM	Repeated measures mixed effects model
MSDS	Material Safety Data Sheet
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	No Adverse Effect Level
NSAID	Non-steroidal Anti-inflammatory Drug
NTI	Narrow therapeutic index
PASI	Psoriasis Area Severity Index
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PGA	Physician Global Assessment
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PI	Principal Investigator
PK	Pharmacokinetic
PLSS	Psoriasis Lesion Severity Score
PPL	Project Physician Lead
PRO	Patient Reported Outcome
PsO	Psoriasis
PSRAE	Possible Suicidality Related Adverse Event
PTS IVIVT	Platform Technologies and Science In vitro/In vivo Translation
PUVA	Psoralen and ultraviolet A
QD	Once a day
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula

QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RIP1	Receptor-interacting protein-1
RIP3	Receptor-interacting protein-3
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SIB	Suicidal Ideation Behaviour
SOP	Standard Operating Procedure
SPF	Sun protection factor
SpO2	Peripheral Capillary Oxygen Saturation
SRM	Study Reference Manual
SRT	Safety Review Team
TB	Tuberculosis
TEAR	Target Engagement Assay RIP1
TID	Three times daily
TLR	Toll-like receptor
TNF	Tumor necrosis factor
UK	United Kingdom
ULN	Upper Limit of Normal
UVB	Ultraviolet B
V	Volume of Distribution
VAS	Visual Analogue Scale

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
QuantiFERON

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study treatment
• 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 event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study</td><td>• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 2 days 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
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications</td></tr>
</table>

treatment and may continue subject 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 perform liver event follow up assessments within **24 hrs** • Monitor subjects 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 perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	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 **<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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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, 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)**; INR measurement is not required and the threshold value stated will not apply to subjects 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 IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; 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 subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject'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.

12.3. Appendix 3 - Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK2982772 or any concomitant medicines;
- Psoriasis susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been

identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK2982772 has been completed and the study data reviewed. In some cases, the samples may not be studied.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's

Events NOT meeting definition of an AE include:
condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.4.2. Definition of Serious Adverse Events

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, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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.
d. Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
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 or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are 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
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. 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

Cardiovascular Events (CV) Definition:
• Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.4.4. Recording of AEs and SAEs

AEs 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) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed PRO questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the PRO questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject 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 the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable):

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 90 days after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
   - Contraceptive subdermal implant
   - Intrauterine device or intrauterine system

- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 will be reported as an AE or SAE.
- A spontaneous abortion 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 treatment by the investigator, will be reported to GSK as described in Appendix 4. 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 subject who becomes pregnant while participating

- Will be withdrawn from the study.
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- 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.

12.6. Appendix 6: Protocol Changes

12.6.1. Protocol Amendment 01

Where the amendment applies

This protocol amendment applies to all countries.

Summary of amendment changes and rationale

Regulatory feedback led to a requirement for additional concomitant medication restrictions. In addition, some administrative clarifications have been made.

List of specific changes (bold indicates text added and strikethrough indicates text removed)

Authors

Author (s): PPD

Section 1 Protocol synopsis for study 203167

An ongoing review of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GSK individuals, some of whom are also members of the GSK study team **who are not involved in the day-to-day running of the study.**

Section 4.5 Dose justification

It is anticipated that a human dose of 60 mg **BID** will produce $AUC_{(0-24)}$ and C_{max} values of approximately 9 ug.h/mL and 1 ug/mL, respectively, which are approximately $1/6^{th}$ and $1/12^{th}$ of the gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the NOAEL dose of 30 mg/kg/day.

Section 4.6.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2982772		
Drug Interaction	**Non-clinical data:** **In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (Pgp) inhibitors were completed. To date, formal drug interaction studies in humans have not been performed with GSK2982772.** **There is a low risk that GSK2982772 could be an inducer of CYP3A4 and therefore may lower circulating levels of concomitant medications that are metabolised by CYP3A4 when co administered with GSK2982772.** **GSK2982772 is a Pgp substrate and therefore co administration with concomitant medications that are Pgp inhibitors could increase circulating levels of GSK2982772.** **See Section 4.3.6 of GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01].**	**Subject Selections:** • **Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. See Section 6.11.2 for a comprehensive list of medications.** **Subject Monitoring:** • **Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study.** **Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.**

Section 6.4 Blinding

This will be a double blind (sponsor unblind) study and the following will apply.

- Sponsor unblinded refers only to the Data Review Committee (DRC) consisting of the GSK study physician, the study statistician, the study pharmacokineticist, **Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head**, the Early Development Leader (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. A data review charter will identify the specific GSK individuals involved; outline in detail the activities of this review, and how the integrity of the study will be maintained. The rest of the core GSK study team will remain blinded.

Section 6.11.2 Prohibited Medications and Non-Drug Therapies

Prohibited Medications

Therapy	Time period
P-glycoprotein (Pgp) inhibitors including but not limited to amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil [FDA, 2012].	**4 weeks prior to first dose until after the follow up visit (Day 112).**
Narrow therapeutic index (NTI) CYP3A4 substrates including but not limited to alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [FDA, 2012].	**4 weeks prior to the first dose until after the follow up visit (Day 112).**

Section 7.1 Time and Events Table

Procedures	Screening	Treatment Period													Early Withdrawal [14]	Follow Up	Notes
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43 (week 6)	Day 50	Day 57	Day 64	Day 71	Day 78	Day 85 (week 12)			**Visit windows** Screening: up to 30d before Day 1. Treatment Period (except Day 1 & 85): ± 3d. Day 1 NA; Day 85 ± 2d. Early Withdrawal: NA Follow Up: 28d after last dose ± 3d
Screening Procedures	Screening procedures in addition to those listed below are (outpatient visit): informed consent; inclusion/ exclusion criteria; demography; medical history (includes past and current conditions, medication history, and family history of premature CV disease); HIV, Hep B and Hep C screen; serum pregnancy test (WCBP only).																
Site Visit	X	X	X	X		X		X		X		X		X	X	X	1. Full physical exam: height/weight at Screening, height not required at later timepoints. 2. Vitals: BP, HR, RR, temperature. ECG triplicate at Screening only. 3. Urinalysis not required on Days 29, 57 and 71. 4. If urine test is positive, confirmatory serum test must be performed. 5. Pre-dose 6. Subjects must take study medication twice a day approx. 12h apart. Exact time of dosing to be recorded in diary cards. On Days 43 and 85, subjects must not take medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Day 43 only. On Day 85, subjects no longer dosed. 7. Diary card checked by site staff and new diary card dispensed at every study visit.
Phone call					X		X		X		X		X				
Safety Assessments																	
Full physical exam[1]	X													X	X	X	
Brief physical exam		**X[5]**		X		X		X[5]		X		X					
12-lead ECG, vital signs[2]	X	**X[5]**	X	X		X		X[5]		X		X		X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	**X[5]**						X[5]						X	X		
Hematology, chemistry, urinalysis	X	**X[5]**	X	X		X[3]		X[5]		X[3]		X[3]		X	X	X	
FSH & estradiol (if applicable)	X																
Serum pregnancy (WCBP)	**X**																
Urine pregnancy test (WCBP only)[4]		**X[5]**	X	X		X		X[5]		X		X		X	X	X	
Study Treatment																	
Randomisation		X															
Study medication (twice daily)[6]		X	X----------											----------X			
Dispensing of study medication		X				X				X							
Dispensing of diary cards[7]		X	X	X		X		X		X		X					

Procedures	Screening	Treatment Period													Early Withdrawal [14]	Follow Up	Notes
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43 (week 6)	Day 50	Day 57	Day 64	Day 71	Day 78	Day 85 (week 12)			**Visit windows** Screening: up to 30d before Day 1. Treatment Period (except Day 1 & 85): ± 3d. Day 1 NA; Day 85 ± 2d. Early Withdrawal: NA Follow Up: 28d after last dose ± 3d
PROs/ Disease Assessments																	8. Blood samples for inflammatory biomarkers and mRNA taken pre-dose on Day 1, Day 43 and Day 85. 9. PK blood samples taken pre-dose on Day 43. Post-dose serial PK samples taken on Day 1 and Day 43 at 1, 2, 4, and 6 hours post-dose. 10. Pre-dose Day 1 one biopsy taken from non-lesional skin and two biopsies taken from biopsy target lesion. 11. On Day 43, two biopsies taken from the same target lesion that was selected at Day 1. Punch biopsies on Day 43 are to be taken pre-dose. 12. Biopsy only required at Early Withdrawal visit if completed at least 14 days of treatment and prior to Day 43. 13. PGx sample collected at Day 1, after randomization and separate informed consent. If sample not collected at Day 1, can be collected at any time post-randomization. 14. If subject withdraws early, every effort will be made for the subject to complete an Early Withdrawal visit prior to Follow Up.
Psoriatic Body Surface Area	X	X[5]												X	X		
PASI, PGA, PLSS, Itch	X	X[5]		X		X		X[5]		X		X		X	X		
DLQI	X	X[5]						X[5]						X	X		
Photograph of lesions		X[5]						X[5]						X	X		
Other Assessments and Procedures																	
Blood sample for inflammatory biomarkers[8]		X[5]						X[5]						X	X		
Blood sample for mRNA analysis[8]		X[5]						X[5]						X	X		
Blood sample for Target Engagement		X[5]						X[5]						X	X		
PK blood samples[9]		X						X[5]						X	X		
Skin punch biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement		X[5,10]						X[11]							X[12]		
Pharmacogenetic sample (PGx)		X[13]															
Con med review & AE/SAE reporting		X----------X															

Section 7.2 Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors **and smoking history** (as detailed in the CRF) will be assessed at screening.

Section 7.3.4 Vital Signs

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

Section 7.5.2 Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technologies and Science ~~In vivo In vitro Technology~~ **In vitro/ In vivo Translation** (PTS IVIVT) and Third Party Resource, GlaxoSmithKline.

Section 9.3.2 Interim Analysis

Once an appropriate number of subjects randomised to GSK2982772 have completed Day 43 (Week 6), the PLSS data will be reviewed in an unblinded manner by a Data Review Committee (DRC) consisting of the GSK study physician, the study statistician, the study pharmacokineticist, **the PRR DPU Head**, the Early Development Lead (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis.

12.6.2. Protocol Amendment 2

Where the amendment applies

This protocol amendment applies to all countries.

Summary of amendment changes and rationale

An additional cohort of subjects is being included in the study in order to evaluate a 60 mg TID dosing regimen. Because of the short half-life, a modified release formulation is now being developed in attempt to increase the C_{trough} and decrease the peak to trough ratio using a once or twice daily dosing regimen. This is considered desirable for improving safety and tolerability and will aid in reduction of PK variability with the current IR formulation. It is believed that by increasing the frequency of dosing to three times daily (TID) with the current formulation, this will closely simulate the PK profile of a preferred modified release formulation.

List of specific changes (bold indicates text added and strikethrough indicates text removed)

Authors

PPD

Medical Monitor Page

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	**Tel** PPD **Email** PPD **Mobile** PPD ~~Tel:~~ PPD ~~Mobile:~~ PPD ~~Email:~~ PPD	**Mobile** PPD ~~Mobile:~~ PPD	**N/A** PPD	**Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom** ~~Pattern Recognition Receptor DPU, UP4440 1250 S Collegeville, PA 19426~~
Secondary Medical Monitor		**Mobile:** PPD **Email** PPD ~~Tel:~~ PPD ~~Mobile:~~ PPD ~~Email:~~ PPD	**Mobile:** PPD PPD ~~Mobile:~~ PPD		**1250S Collegeville Rd. Collegeville PA 19426, USA** ~~Cytokine Chemokine DPU, GSK, Gunnels Wood Road, Stevenage, SG1 2NY, UK~~
SAE contact information	Medical Monitor as above				

Synopsis Rationale

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg twice daily **and 60 mg three times daily** for 84 days). In addition a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics, pharmacodynamics, and efficacy in subjects with active plaque-type psoriasis (PsO).

Synopsis Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg twice daily doses **and 60 mg three times daily** doses of GSK2982772 in subjects with active plaque-type psoriasis.	• Adverse events • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead ECG monitoring
Secondary	
• To investigate the pharmacokinetics of GSK2982772 in blood following 60 mg twice daily doses and **60 mg three times daily** doses of GSK2982772 in subjects with active plaque-type psoriasis.	• Pre-dose plasma concentrations of GSK2982772 at Days 43 (Week 6) and 85 (Week 12). • Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours post dose.
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on inflammatory biomarkers in skin biopsies from psoriatic skin lesions in subjects with active plaque-type psoriasis.	• Change from baseline in histopathological scoring of psoriatic lesional biopsies which may include, but are not limited to the following as data permit: K16, CD3/CD11c, CD161, elastase positive dermal cells and epidermal thickness. • mRNA expression of inflammatory gene transcripts which may include, but are not limited to the following as data permit: IL-4, IL-10, IL-17, IL-21, IL-22, IL-23, TNF and IFNγ on Days 1 (Week 0) and 43 (Week 6).
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Percentage change from baseline and actual Psoriatic Lesion Severity Sum (PLSS) scores in the index lesion.
Exploratory	
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Change from baseline in Psoriasis Area Severity Index (PASI) scores. • The proportion of subjects who achieve PASI ≥ 50%, 75%, and 90% improvement from baseline score. • Change from baseline and actual Physician Global Assessment (PGA). • The proportion of subjects who achieve “clear” (0) or “almost clear” (1) on (PGA). • Change from baseline in body surface area (BSA).
• To investigate the effect of 60 mg twice daily	• Change from baseline in blood inflammatory

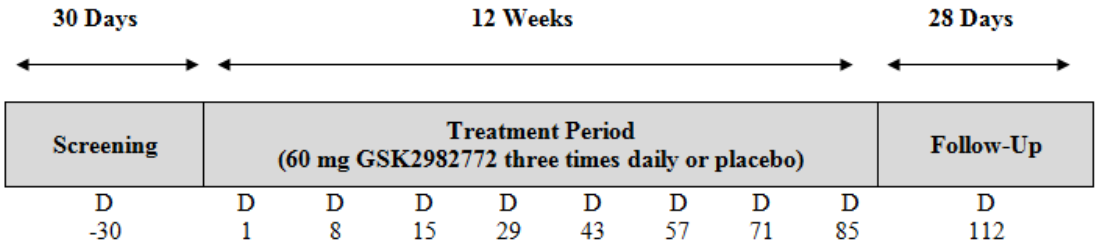
Objectives	Endpoints
doses **and 60 mg three times daily doses** of GSK2982772 on inflammatory biomarkers in the blood of subjects with active plaque-type psoriasis.	markers which may include, but are not limited to the following as data permit: CRP, VEGF, S100A8, S100A9, IL-17, IL-22, and TNF.
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on transcriptome profiling of both blood and skin of subjects with active plaque-type psoriasis.	• Transcriptomic analysis of mRNA isolated from blood and skin at Day 1 (Week 0) and Day 43 (Week 6).
• To investigate pathway and target engagement following 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 in blood and skin biopsy tissue in subjects with active plaque-type psoriasis.	• Pharmacology biomarker endpoints may include, but are not limited to the following Days 1 (Week 0), 43 (Week 6) and 85 (Week 12), as data permit: o Target Engagement Assay RiP1 (TEAR1) in blood and skin. o Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in skin.
• To investigate the concentration of GSK2982772 in the skin of subjects with active plaque-type psoriasis after 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772.	• Pre-dose GSK2982772 concentrations in skin biopsies at Days 1 (Week 0) and 43 (Week 6), as data permit.
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on the patient reported outcomes (PROs) of subjects with active plaque-type psoriasis.	• Change from baseline in Dermatology Life Quality Index (DLQI) score. • Change from baseline and actual Visual Analogue Scale (VAS) itch score.

Synopsis Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled, repeat dose study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with active plaque-type psoriasis. The study design schematic is depicted in Figure 1 below. **There will be two cohorts of subjects. Cohort 1 will receive either GSK2982772 60 mg or placebo orally twice daily and Cohort 2 will receive either GSK2982772 60 mg or placebo orally three times daily**.

Schematic added:

Cohort 2



Synopsis Treatment Arms and Duration

In Cohort 1 subjects who have completed screening assessments and are eligible will be randomised in a 2:1 ratio (active to placebo) to one of the following treatments:

60 mg GSK2982772 twice daily (BID)

Placebo twice daily (BID)

In Cohort 2 subjects who have completed screening assessments and are eligible will be randomised in a 3:1 ratio (active to placebo) to one of the following treatments:

60 mg GSK2982772 three times daily (TID)

Placebo three times daily (TID)

Synopsis Type and Number of Subjects

In Cohort 1, a sufficient number of subjects will be screened so that approximately 30 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor, to ensure that approximately 24 evaluable subjects complete the study.

In Cohort 2, a sufficient number of subjects will be screened so that approximately 24 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 32) into the study at the discretion of the Sponsor, to ensure that approximately 20 evaluable subjects complete the study.

For both cohorts, a subject is considered evaluable if they have completed at least one post-treatment biopsy.

Synopsis Analysis

An ongoing review of available efficacy, pharmacodynamic and mechanistic endpoints will be conducted during the study by a Data Review Committee (DRC), consisting of a limited number of GSK individuals, some of whom are also members of the GSK study

team who are not involved in the day-to-day running of the study. The primary purpose of these reviews will be to monitor target engagement, inflammatory markers and the index lesion PLSS for internal decision making. A data review charter will outline in detail the activities of this review and how the integrity of the study will be maintained. **An interim analysis will be conducted after the completion of Cohort 1.**

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in index lesion PLSS will be statistically analyzed using a repeated measures mixed effects model (MMRM) comparing **each** GSK2982772 **arm** with placebo at each time point.

Section 2.1 Study Rationale

The primary objective will be to investigate the safety and tolerability of repeat oral doses of GSK2982772 (60 mg twice daily **and 60 mg three times daily** for 84 days). In addition, a number of experimental and clinical endpoints will be employed to obtain information on the pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy in subjects with active PsO

Section 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of 60 mg twice daily doses **and 60 mg three times daily** doses of GSK2982772 in subjects with active plaque-type psoriasis.	• Adverse events • Clinical laboratory values (clinical chemistry, haematology and urinalysis) • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) • 12-Lead ECG monitoring
Secondary	
• To investigate the pharmacokinetics of GSK2982772 in blood following 60 mg twice daily doses and **60 mg three times daily** doses of GSK2982772 in subjects with active plaque-type psoriasis.	• Pre-dose plasma concentrations of GSK2982772 at Days 43 (Week 6) and 85 (Week 12). • Post-dose plasma concentrations of GSK2982772 on Days 1 and 43 (Week 6) at 1, 2, 4 and 6 hours post dose.
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on inflammatory biomarkers in skin biopsies from psoriatic skin lesions in subjects with active plaque-type psoriasis.	• Change from baseline in histopathological scoring of psoriatic lesional biopsies which may include, but are not limited to the following as data permit: K16, CD3/CD11c, CD161, elastase positive dermal cells and epidermal thickness. • mRNA expression of inflammatory gene transcripts which may include, but are not limited to the following as data permit: IL-4, IL-10, IL-17, IL-21, IL-22, IL-23, TNF and IFNγ on Days 1 (Week 0) and 43 (Week 6).

Objectives	Endpoints
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Percentage change from baseline and actual Psoriatic Lesion Severity Sum (PLSS) scores in the index lesion.
Exploratory	
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on disease activity in subjects with active plaque-type psoriasis	• Change from baseline in Psoriasis Area Severity Index (PASI) scores. • The proportion of subjects who achieve PASI ≥ 50%, 75%, and 90% improvement from baseline score. • Change from baseline and actual Physician Global Assessment (PGA). • The proportion of subjects who achieve "clear" (0) or "almost clear" (1) on (PGA). • Change from baseline in body surface area (BSA).
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on inflammatory biomarkers in the blood of subjects with active plaque-type psoriasis.	• Change from baseline in blood inflammatory markers which may include, but are not limited to the following as data permit: CRP, VEGF, S100A8, S100A9, IL-17, IL-22, and TNF.
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on transcriptome profiling of both blood and skin of subjects with active plaque-type psoriasis.	• Transcriptomic analysis of mRNA isolated from blood and skin at Day 1 (Week 0) and Day 43 (Week 6).
• To investigate pathway and target engagement following 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 in blood and skin biopsy tissue in subjects with active plaque-type psoriasis.	• Pharmacology biomarker endpoints may include, but are not limited to the following Days 1 (Week 0), 43 (Week 6) and 85 (Week 12), as data permit: o Target Engagement Assay RiP1 (TEAR1) in blood and skin. o Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in skin.
• To investigate the concentration of GSK2982772 in the skin of subjects with active plaque-type psoriasis after 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772.	• Pre-dose GSK2982772 concentrations in skin biopsies at Days 1 (Week 0) and 43 (Week 6), as data permit.
• To investigate the effect of 60 mg twice daily doses **and 60 mg three times daily doses** of GSK2982772 on the patient reported	• Change from baseline in Dermatology Life Quality Index (DLQI) score.

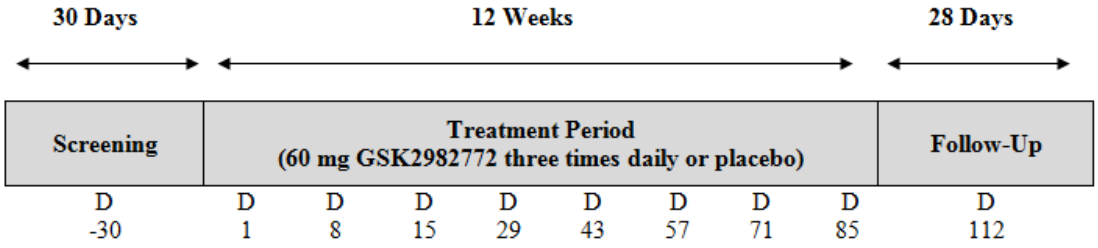
Objectives	Endpoints
outcomes (PROs) of subjects with active plaque-type psoriasis.	• Change from baseline and actual Visual Analogue Scale (VAS) itch score.

Section 4.1 Overall Design

This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled, repeat dose study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with active plaque-type psoriasis. The study design schematic is depicted in Figure 2 below. **There will be two cohorts of subjects. Cohort 1 will receive either GSK2982772 60 mg or placebo orally twice daily and Cohort 2 will receive either GSK2982772 60 mg or placebo orally three times daily**.

Schematic added:

Cohort 2



Section 4.2.2 Treatment Period

In Cohort 1, subjects will be randomly assigned to either GSK2982772 60mg or placebo orally twice daily (approximately 12 hours apart) for 84 days. **In Cohort 2 subjects will be randomly assigned to either GSK2982772 60 mg or placebo orally three times daily (approximately 8 hours apart) for 84 days**.

Section 4.3 Type and Number of Subjects

In Cohort 1, a sufficient number of subjects will be screened so that approximately 30 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 36) into the study at the discretion of the Sponsor, to ensure that approximately 24 evaluable subjects complete the study.

In Cohort 2, a sufficient number of subjects will be screened so that approximately 24 subjects with active PsO are randomised. Additional or replacement subjects may be randomised (up to a maximum of 32) into the study at the discretion of the Sponsor, to ensure that approximately 20 evaluable subjects complete the study.

For both cohorts, a subject is considered evaluable if they have completed at least one post-treatment biopsy

Section 4.4 Design Justification

In Cohort 1 the subjects will be randomised in a 2:1 ratio to GSK2982772 60mg BID and placebo respectively. **In Cohort 2 the subjects will be randomised in a 3:1 ratio to GSK2982772 60 mg TID and placebo respectively**. The primary objective of this study is safety and tolerability and assessment of this is most valuable in a placebo controlled, blinded study. The placebo group was deemed necessary as autoimmune diseases naturally fluctuate in severity. However, the size of the placebo group has been kept to a minimum. Subjects will not be allowed to continue standard of care therapy including topical (not permitted on biopsy areas), oral and biologic therapy. A washout period of specific therapies can be found in Section 6.11

Section 4.5 Dose Justification

The **initial** selection of the 60 mg BID dose ~~to be~~ **being** tested in this study is based on the safety, PK, and PD data from the GSK2982772 First Time in Human (FTiH) study, 200975. GSK2982772 administered at 60 mg BID for 14 days was well tolerated and no safety concerns were identified. A BID dosing regimen was **initially** selected over a QD dosing regimen due to the short half-life of GSK2982772 in humans (~2 hours). Based on preliminary PK/PD modelling of ex-vivo RIP1 target engagement and GSK2982772 concentrations from the multiple dose ascending part of Study 200975, a 60 mg BID dose ~~is~~ **was** predicted to have on average 95% RIP1 target engagement in blood and approximately 90% of subjects are predicted to have >90% RIP1 target engagement in blood at Cmin **using a novel in-house ex-vivo PD/target engagement assay based solely on the TNF pathway which is believed to be a key component of the RIP1 pathway**. Assuming a skin: blood ratio of 0.4 (as observed in the rat), the average RIP1 target engagement in skin is predicted to be 92%. At Cmin, 44% of subjects are predicted to have >90% RIP1 target engagement in the skin and 90% of subjects are predicted to have >80% RIP1 target engagement in the skin.

However, based on final PK/PD modelling from the full repeat dose part of the Study 200975 (up to 120 mg BID), a 60 mg BID dose is now predicted to have on average 99.3% RIP1 target engagement in blood and approximately 90% of subjects will have >96.3% target engagement at C_{min}. In skin, assuming the same skin: blood ratio of 0.4 as noted above, the average RIP target engagement at 60 mg TID in skin in predicted to be 96%. At C_{min}, 43% of subjects are predicted to have >90% RIP1 target engagement in the skin and 90% of subjects are predicted to have >70% RIP1 target engagement in the skin.

In review of this final FTiH data, it is believed that the C_{min} target exposure may not be achieved with a 60mg BID dosing regimen. The C_{min} values at 60 mg TID are predicted to be approximately 3.5 fold higher than for 60 mg BID. Therefore, a 60 mg TID cohort is now being proposed.

Using the final PK/PD, a 60 mg TID dose is predicted to have on average 99% RIP1 target engagement in blood and approximately 90% of subjects will have > 96% target engagement at C_{min}. In skin, the average RIP target engagement at 60 mg TID is predicted to be 98%. At C_{min}, 91% of subjects are predicted to have >90% RIP1 target engagement in the skin and 90% of subjects are predicted to have >91% RIP1 target engagement in the skin.

In addition, because of the short half-life, a modified release formulation is now being developed with the aim to provide a once daily dosing regimen. By increasing the frequency of dosing to three times daily (TID) with the current immediate release formulation, this will more closely match the PK, safety and efficacy profile of a preferred once daily modified release formulation.

~~Therefore, it is predicted that a dose of GSK2982772 60 mg BID may be clinically efficacious in subjects with active PsO~~.

~~It is anticipated that a human dose of 60 mg BID will produce AUC(0-24) and Cmax values of approximately 9 ug.h/mL and 1 ug/mL, respectively, which are approximately 1/6th and 1/12th of the gender-averaged AUC (48.4 ug.h/mL) and Cmax (12.3 ug/mL) achieved in the 13-week monkey study at the NOAEL dose of 30 mg/kg/day.~~

The safety of increasing the dose frequency to 60 mg TID is justified based on nonclinical safety findings to date with GSK2982772. It is anticipated that a human dose of 60 mg TID (180 mg/day) will produce $AUC_{(0-24)}$ and C_{max} values of approximately 9.9 ug.h/mL and 0.8 ug/mL, respectively, which are approximately 1/5th and 1/15th of the gender-averaged AUC (48.4 ug.h/mL) and C_{max} (12.3 ug/mL) achieved in the 13 week monkey study at the no adverse effect level (NOAEL) dose of 30 mg/kg/day. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01].

Up to 03 Apr 2017, a total of approximately 93 subjects across 4 clinical studies have been randomised to receive GSK2982772. In Study 200975, GSK2982772 administered up to 120 mg BID for 14 days and was well tolerated and no safety concerns were identified. A total of 9 subjects had received 120 mg BID in that study. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_01]. In this current study, 203167, approximately 22 of 33 subjects have been randomised to GSK2982772 60 mg BID. In other Phase 2a studies in Rheumatoid Arthritis [(RA); Study 203168] and Ulcerative Colitis [(UC); Study 202152], a total of 4 subjects have been randomised to GSK2982772 60 mg BID. GSK2982772 was well tolerated and no drug-related SAEs have been reported. There was a death of a 19 year old male subject in this current study due to an accidental overdose with 3,4-methylenedioxy-methamphetamine (MDMA) that was not considered drug related by the Principal Investigator (PI).

The proposed 60 mg TID dose regimen is predicted to have mean C_{max} (0.80 µg/mL) and $AUC_{(0-24)}$ (9.9 µg.hr/mL) that are approximately 10% and 50% higher, respectively than for 60 mg BID (0.70 µg/mL and 6.6 µg.hr/mL). This exposure is well within the observed C_{max} and $AUC_{(0-24)}$ values at 120 mg BID in Study 200975.

Section 5.1 Inclusion Criteria

For both cohorts, a subject will be eligible for inclusion in this study only if all of the following criteria apply:

Section 5.2 Exclusion Criteria

For both cohorts, a subject will not be eligible for inclusion in this study only if all of the following criteria apply:

20. The subject has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer 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. **Subjects who were randomized into Cohort 1 are not eligible to be re-randomized into Cohort 2**.

21. Haemoglobin <11 g/dL; haematocrit <30%, white blood cell count ≤3000/mm3 (≤3.0 x 10^9/L); ~~or ≥14,000/mm3 (≥14 x 109/L);~~ platelet count ≤ 100,000/µL (≤100 x 10^9/L); absolute neutrophil count ≤**1.5** ~~3~~ x 10^9/L ~~lymphocyte count <1 x 109/L~~ at the screening visit.

Section 5.3 Screening / Baseline / Run-in Failures

Subjects who do not qualify to participate in the study due to a screening laboratory value or ECG abnormality can repeat the test once within the original screening time window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

Subjects can be re-screened only on approval of the GSK Medical Monitor and only once. Re-screening is allowed when a subject failed inclusion/exclusion criteria or some other screening condition initially, but the Investigator believes there is a reasonable probability that the subject would be eligible if re-screened.

Section 5.4.1 Individual Safety Stopping Rules

Study medication will be discontinued in the event of any of the following:

- If a subject experiences a serious or severe clinically significant AE that in the clinical judgement of the investigator, after consultation with the medical monitor, there is a reasonable possibility that the AE is related to investigational product.
- The subject becomes pregnant.
- The subject initiates treatment with any prohibited medication for the treatment of PsO as listed in Section 6.11.2.
- The subject develops a serious opportunistic or atypical infection.

- If the liver chemistry stopping criteria (Section 5.4.3), QTc stopping criteria (Section 5.4.4), or haematologic stopping criteria (Section 5.4.5) are met.

- **The subject experiences any signs of suicidal ideation or behaviour (Section 7.3.7).**

Section 5.4.5 Haematologic Stopping Criteria

Study treatment will be stopped for a subject if any of the following haematological stopping criteria is met:

- Haemoglobin <9 g/dL or an absolute decrease of ≥3 g/dL from baseline (pre-dose Day 1)
- ~~Neutrophils <1 x 10^9/L~~
- ~~Lymphocytes <0.5 × 10^9/L~~
- Platelets <50 × 10^9/L

Section 6.1 Investigation Product and Other Study Treatment

	Study Treatment	
Product name:	GSK2982772	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg	NA
Route of Administration	For oral use only	For oral use only
Dosing instructions **for Cohort 1:**	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed	Take TWO tablets in the MORNING and TWO tablets in the EVENING as directed
Dosing instructions for Cohort 2:	**Take TWO tablets THREE times daily as directed by your physician**	**Take TWO tablets THREE times daily as directed by your physician**
Physical description	White to almost white, round, film coated tablet	White to almost white, round film coated tablet
Source of procurement	Study medication is supplied by GlaxoSmithKline	Placebo is supplied by GlaxoSmithKline

Section 6.2 Treatment Assignment

In Cohort 1, subjects will take study medication every day, twice a day, approximately 12 hours apart. Subjects will be randomised to receive either GSK2982772 or placebo in a 2:1 ratio. **In Cohort 2, subjects will take study medication every day, three times a day, with approximately 8 hours between each dose. Subjects will be randomised to receive either GSK2982772 or placebo in a 3:1 ratio.**

Section 6.4 Blinding

This will be a double blind (sponsor unblind) study and the following will apply.

Sponsor unblinded refers only to the Data Review Committee (DRC) consisting of the GSK ~~study physician~~ **Project Physician Lead (PPL),** the study statistician, the study pharmacokineticist, Pattern Recognition Receptor (PRR) Discovery Performance Unit (DPU) Head, the Early Development Leader (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis.

Section 6.8 Treatment of Study Treatment Overdose

For this study, any dose of GSK2982772 >120 mg daily will be considered an overdose **in Cohort 1 and any dose of GSK2982772 >180 mg daily will be considered an overdose in Cohort 2**. GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat any overdose as and when they are made aware of this.

Section 7.1 Time and Events Table

Procedures	Screening	Treatment Period													Early Withdrawal [14]	Follow Up	Notes
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43 (week 6)	Day 50	Day 57	Day 64	Day 71	Day 78	Day 85 (week 12)			Visit windows Screening: up to 30d before Day 1. Treatment Period (except Day 1 & 85): ± 3d. Day 1 NA; Day 85 ± 2d. Early Withdrawal: NA Follow Up: 28d after last dose ± 3d
Screening Procedures	Screening procedures in addition to those listed below are (outpatient visit): informed consent; inclusion/ exclusion criteria; demography; medical history (includes past and current conditions, medication history, and family history of premature CV disease); HIV, Hep B and Hep C screen; serum pregnancy test (WCBP only).																
Site Visit	X	X	X	X		X		X		X		X		X	X	X	1. Full physical exam: height/weight at Screening, height not required at later timepoints. 2. Vitals: BP, HR, RR, temperature. ECG triplicate at Screening only. 3. Urinalysis not required on Days 29, 57 and 71. 4. If urine test is positive, confirmatory serum test must be performed. 5. Pre-dose 6. **In Cohort 1,** subjects must take study medication twice a day approx. 12h apart**. In Cohort 2, subjects must take study medication three times a day approx. 8h apart**. Exact time of dosing to be recorded in diary cards. On Days 43 and 85, subjects must not take medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Day 43 only. On Day 85, subjects no longer dosed. 7. Diary card checked by site staff and new diary card dispensed at every study visit.
Phone call					X		X		X		X		X				
Safety Assessments																	
Full physical exam[1]	X													X	X	X	
Brief physical exam		X[5]		X		X		X[5]		X		X					
12-lead ECG, vital signs[2]	X	X[5]	X	X		X		X[5]		X		X		X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[5]						X[5]						X	X		
Hematology, chemistry, urinalysis	X	X[5]	X	X		X[3]		X[5]		X[3]		X[3]		X	X	X	
FSH & estradiol (if applicable)	X																
Serum pregnancy (WCBP)	X																
Urine pregnancy test (WCBP only)[4]		X[5]	X	X		X		X[5]		X		X		X	X	X	
Study Treatment																	
Randomisation		X															
Study medication ~~(twice daily)~~[6]		X	X----------											----------X			
Dispensing of study medication		X				X				X							
Dispensing of diary cards[7]		X	X	X		X		X		X		X					

Procedures	Screening	Treatment Period													Early Withdrawal [14]	Follow Up	Notes
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43 (week 6)	Day 50	Day 57	Day 64	Day 71	Day 78	Day 85 (week 12)			Visit windows Screening: up to 30d before Day 1. Treatment Period (except Day 1 & 85): ± 3d. Day 1 NA; Day 85 ± 2d. Early Withdrawal: NA Follow Up: 28d after last dose ± 3d
PROs/ Disease Assessments																	8. Blood samples for inflammatory biomarkers and mRNA taken pre-dose on Day 1, Day 43 and Day 85. 9. PK blood samples taken pre-dose on Day 43. Post-dose serial PK samples taken on Day 1 and Day 43 at 1, 2, 4, and 6 hours post-dose. 10. Pre-dose Day 1 one biopsy taken from non-lesional skin and two biopsies taken from biopsy target lesion. 11. On Day 43, two biopsies taken from the same target lesion that was selected at Day 1. Punch biopsies on Day 43 are to be taken pre-dose. 12. Biopsy only required at Early Withdrawal visit if completed at least 14 days of treatment and prior to Day 43. 13. PGx sample collected at Day 1, after randomization and separate informed consent. If sample not collected at Day 1, can be collected at any time post-randomization. 14. If subject withdraws early, every effort will be made for the subject to complete an Early Withdrawal visit prior to Follow Up.
Psoriatic Body Surface Area	X	X[5]												X	X		
PASI, PGA, PLSS, Itch	X	X[5]		X		X		X[5]		X		X		X	X		
DLQI	X	X[5]						X[5]						X	X		
Photograph of lesions		X[5]						X[5]						X	X		
Other Assessments and Procedures																	
Blood sample for inflammatory biomarkers[8]		X[5]						X[5]						X	X		
Blood sample for mRNA analysis[8]		X[5]						X[5]						X	X		
Blood sample for Target Engagement		X[5]						X[5]						X	X		
PK blood samples[9]		X						X[5]						X	X		
Skin punch biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement		X[5,10]						X[11]							X[12]		
Pharmacogenetic sample (PGx)		X[13]															
Con med review & AE/SAE reporting		X----------X															

Section 7.3.7 Suicidal Risk Monitoring

Subjects being treated with GSK2982772 should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. ~~Consideration should be given to discontinuing GSK2982772 in subjects who experience signs of suicidal ideation or behaviour.~~ **All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication**.

Section 9.1 Hypotheses

The primary objective of the study is to investigate the safety and tolerability of GSK2982772 **60 mg BID and 60 mg TID** following 12 weeks of treatment. No formal statistical hypotheses will be conducted to assess this objective.

Section 9.2.1 Sample Size Assumptions

The study is not powered to detect pre-defined differences. **In Cohort 1**, approximately 30 subjects and up to a maximum of 36, will be randomised into the study to either GSK2982772 or placebo in a 2:1 ratio to ensure that approximately 24 evaluable subjects complete the study.

In Cohort 2, approximately 24 subjects and up to a maximum of 32, will be randomised into the study to either GSK2982772 or placebo in a 3:1 ratio to ensure that approximately 20 evaluable subjects complete the study.

A subject is considered evaluable if they have completed at least one post-treatment biopsy.

The primary objective of the study is safety and tolerability, where there will be 20 subjects randomised to GSK2982772 **60 mg BID and 18 subjects randomised to GSK2982772 60 mg TID**. Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1, 1) prior, and if we were to observe one safety event in 20 then the posterior distribution would be Beta (2, 20), as outlined below in Figure 4.

Thus, we can be 95% certain that the true probability of the safety event lies between 0.01 and 0.24. **Similarly, if we were to observe one safety event in 18 then the posterior distribution would be Beta (2, 18), thus we can be 95% certain that the true probability of the safety event lies between 0.01 and 0.26**.

For supportive information the properties of the secondary endpoint PLSS have also been considered. Assuming a standard deviation of 25%, it is estimated that the lower and upper bounds of the 95% confidence interval for the difference between GSK2982772 **60 mg BID** (n=20) and placebo (n=10) in percentage change in index lesion PLSS will be within approximately ~~20.3~~ **17.1**% of the point estimate, **and that the lower and upper bounds of the 95% confidence interval for the difference between GSK2982772 60 mg TID (n=18) and placebo (n=6) in percentage change in index lesion PLSS will be within approximately 17.5% of the point estimate.**

Section 9.2.2 Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint to investigate the different safety event rates. If the number of subjects who complete the 12 weeks is lower than ~~20 in the GSK2982772 group~~ **anticipated**, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in Table 4.

Figure deleted:

Figure 5 Sample Size Sensitivity for Percentage Change in PLSS

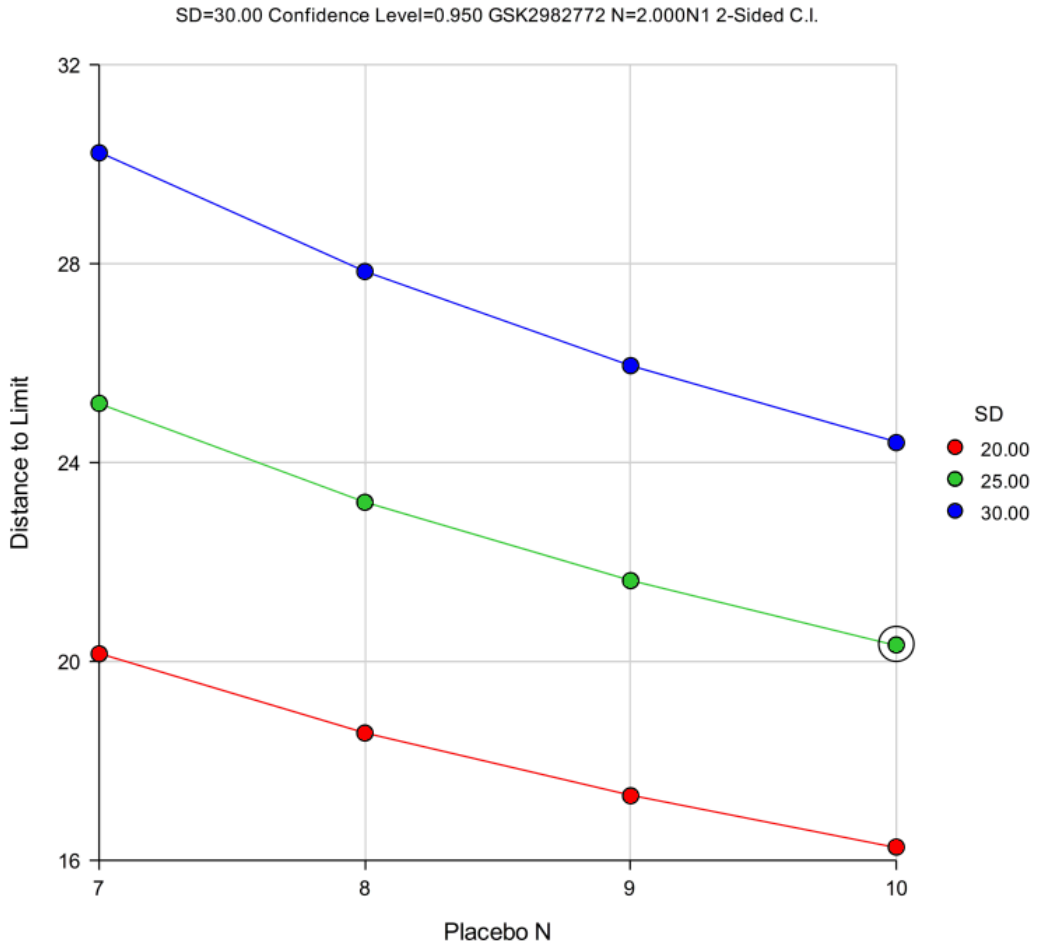
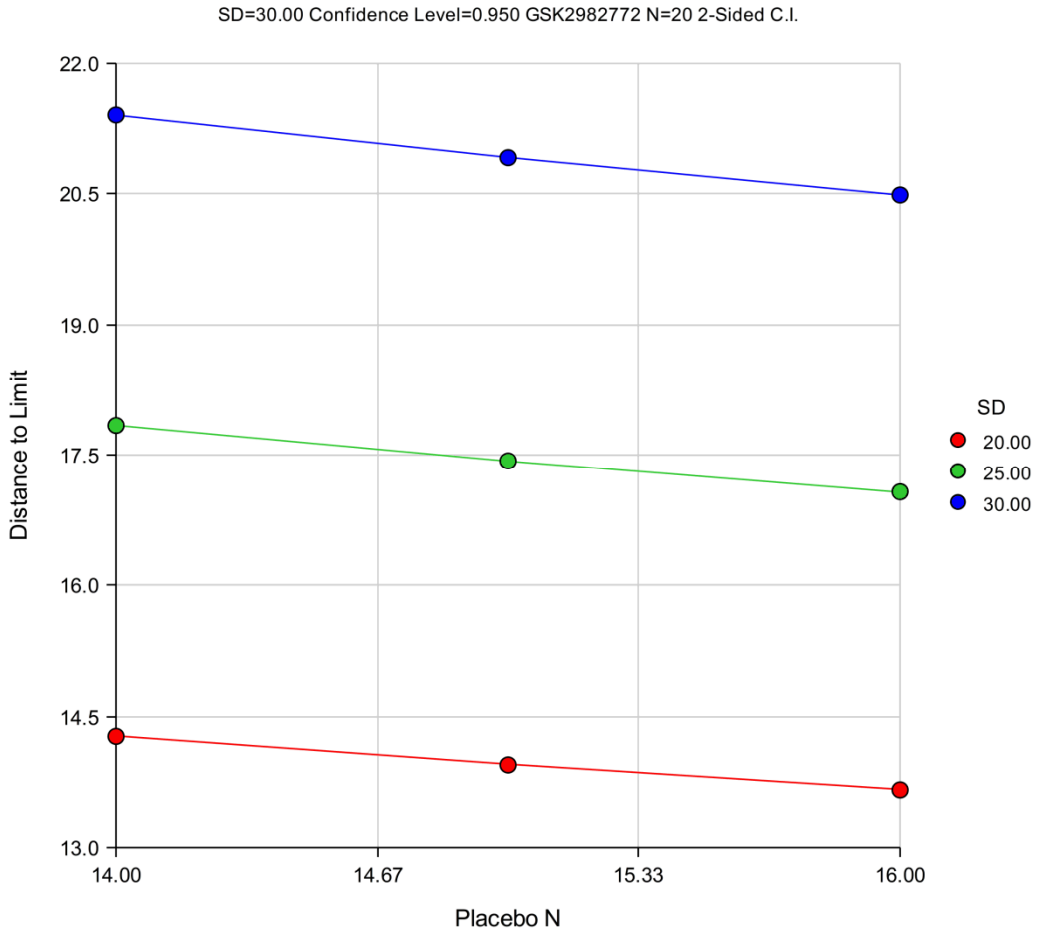


Figure added:

Figure 5 Sample Size Sensitivity for Percentage Change in PLSS



Section 9.3.2 Interim Analysis

In both cohorts, once an appropriate number of subjects randomised to GSK2982772 have completed Day 43 (Week 6), the PLSS data will be reviewed in an unblinded manner by a Data Review Committee (DRC) consisting of the GSK ~~study physician~~ **Project Physician Lead (PPL),** the study statistician, the study pharmacokineticist, the PRR DPU Head, the Early Development Lead (EDL), the Safety Review Team (SRT) leader, or their designees on an ongoing basis. A physician external to the GSK2982772 project team may also be involved in the data review. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. No other member of the GSK core study team will be unblinded to this data. The primary purpose of these reviews will be to monitor PLSS changes for internal decision making purposes. A data review charter will identify the specific GSK individuals involved, outline in detail the activities of this review and how the integrity of the study will be maintained.

A formal interim analysis will be conducted after the completion of Cohort 1 and will only include those subjects randomised to a BID dosing regimen. The purpose of the interim analysis is primarily to provide the project team and key GSK stakeholders with an early indication of the safety and efficacy from the trial, and to facilitate decision making regarding the subsequent clinical development of GSK2982772.

Section 9.3.4 Secondary Analyses

Comparisons between treatment groups on any changes observed will be conducted for the secondary endpoints if deemed appropriate, e.g. changes in the mean target engagement, changes in inflammatory markers and percentage change in index lesion PLSS be statistically analyzed using a MMRM (repeated measures mixed effects model) comparing **each** GSK2982772 **arm** with placebo at each time point. If sufficient numbers of subjects are enrolled with a BSA >5% then the proportion of subjects achieving PASI 50/75/90 at Day 85 (12 Weeks), will be statistically analysed using a Generalised Estimating Equations (GEE) model comparing **each** GSK2982772 **arm** with placebo at each time point if appropriate. Similar analyses will be conducted for other secondary endpoints if deemed appropriate.

GSK2982772 plasma concentrations will be summarised descriptively by Day and nominal time point **by dosing regimen**.

Section 12.1. Appendix 1 – Abbreviations and Trademarks

MDMA	**3,4-methylenedioxy-methamphetamine**
PI	**Principal Investigator**
PPL	**Project Physician Lead**
TID	**Three times daily**