TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A two-part trial to evaluate the safety, tolerability, clinical effect and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis

Compound Number: GSK2981278

Development Phase: IIa

Effective Date: 13-Dec-2016

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2016N275350_00	2016-SEP-12	Original
2016N275350_01	2016-DEC-13	Amendment No. 1
1. Psoriasis Symptom Diary revised to the original published version 2. Clarification of intent for urine sample analysis, minor text changes to Part A and B Time and Events tables to ensure consistency, and more comprehensive information on the allergic reaction risk		

SPONSOR SIGNATORY

PPD

12/13 -2016

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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.

Regulatory Agency Identifying Number(s): EudraCT number 2016-002671-10

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 203820

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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Rationale

In the first clinical trial of GSK2981278, once daily treatment of GSK2981278 ointment (at 0.03%, 0.1%, 0.8%, and 4%) on small test fields (1.13 cm^2) of stable plaque(s) over 19 days appeared to be well tolerated but did not show reduction in psoriatic infiltrate thickness. It is unclear whether the apparent lack of effect on infiltrate thickness in the first-time-in-human (FTIH) study was due to the very small surface area treated, the relatively short duration of exposure, or both. Therefore the present study will evaluate the safety, tolerability, clinical effect, and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis by treating all plaques on the body wholly for 8 weeks. The results of this study will provide preliminary information on the safety, tolerability, and effect of the GSK2981278 ointment on plaque psoriasis at the highest safe and feasible concentration to guide subsequent development strategy.

Objective(s)/Endpoint(s)

Part A	
Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of topically applied GSK2981278 in subjects with plaque psoriasis	• Incidence and nature of adverse events (AEs) and serious adverse events (SAEs) • Application site tolerability assessment score • Change in clinical laboratory parameters, vital signs, and electrocardiogram (ECG) from baseline
• To evaluate the systemic exposure of GSK2981278 following topical application in subjects with plaque psoriasis	• Plasma concentrations of GSK2981278
Secondary	
• To evaluate the clinical effect following topical application of GSK2981278 in subjects with plaque psoriasis	• Mean percent change in Target Plaque Severity Score (TPSS) from baseline to Week 8 • Mean percent change in Physician's Global Assessment (PGA) score from baseline to Week 8 • Mean percent change in Psoriasis Area and Severity Index (PASI) from baseline to Week 8
Exploratory	
• To evaluate the effect of GSK2981278 ointment on relevant gene expression	• Fold change in messenger ribonucleic acid (mRNA) biomarkers from baseline to Week 8 in skin biopsy samples
• To investigate the delivery profile of GSK2981278 into the psoriatic skin following repeat topical applications	• Quantification of GSK2981278 in the skin biopsy using Matrix Assisted Laser Desorption Ionization (MALDI) imaging mass spectrometry or High-performance liquid chromatography-mass spectrometry (HPLC-MS) at Week 8
• To evaluate the effect of GSK2981278 ointment on subject-reported outcomes	• Mean percent change in Psoriasis Symptom Diary score from baseline to each study visit
• To evaluate the potential metabolites of GSK2981278 in plasma, urine, and skin from biopsies in pooled subject samples, as data allow	• Identification of any compound-derived metabolite(s) from plasma and urine and if possible estimation of relative amounts of drug related material • Quantification of GSK2981278-derived metabolite(s) in the skin biopsy using MALDI imaging mass spectrometry or HPLC-MS at Week 8

Part B	
Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of topically applied GSK2981278 and its vehicle in subjects with plaque psoriasis	• Incidence and nature of AEs and SAEs • Application site tolerability assessment score • Change in clinical laboratory parameters, vital signs, and ECG from baseline
• To evaluate the clinical effect of topically applied GSK2981278 relative to vehicle control in subjects with plaque psoriasis	• Mean percent change in TPSS from baseline to Week 8 • Mean percent change in PGA score from baseline to Week 8 • Mean percent change in PASI from baseline to Week 8
Exploratory	
• To explore exposure-response relationship of sparse systemic exposures with the clinical endpoints (by performing population Pharmacokinetic (PK)/Pharmacodynamic (PD) analysis, if required), as data allows	• Plasma concentrations of GSK2981278 and clinical endpoints assessed to determine the clinical effect (e.g. TPSS, PGA, and PASI)
• To evaluate the effect of GSK2981278 ointment on subject-reported outcomes	• Mean percent change in Psoriasis Symptom Diary score from baseline to each study visit

Overall Design

This is a single-center, 2-part Phase I/IIa study to evaluate the safety, tolerability, clinical effect and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis. Drug delivery into the skin and changes in the relevant biomarkers will be explored using skin punch biopsies as well.

- **Part A**: open label, single arm study
- **Part B**: double-blind, randomized, 2-arm, parallel-group, vehicle-controlled study

After completion of Week 4 assessments and Week 8 assessments in Part A, the Sponsor will review the safety, tolerability, PK and clinical effect data. If data demonstrates a mean percent reduction of 40% or greater in TPSS and systemic exposure levels below the no observed adverse effect level (NOAEL) determined in the pre-clinical toxicity studies without significant safety or tolerability issues at either time point, the study will proceed to Part B.

Treatment Arms and Duration

Each part of this study will consist of 3 periods: the screening period of up to 4 weeks, the treatment period of 8 weeks, and the follow-up period of 2 weeks. Study visits will occur at Screening; Baseline; Weeks 1, 4, and 8 during the treatment period; and Week 10 for follow-up, which will be 2 weeks after the last application of study treatment. Additional visits may occur, as needed, for early withdrawal or to follow-up on any skin

reactions or ongoing AEs. A subject's total duration of study participation will be approximately 14 weeks.

In **Part A**, subjects will receive topical application of GSK2981278 4% ointment to all affected areas of the body twice daily for 8 weeks.

In **Part B**, subjects will receive topical application of either GKS2981278 4% ointment or the vehicle ointment, according to the randomization, to all affected areas of the body twice daily for 8 weeks.

The concentration of GSK2981278 may be lowered to 2% or 0.8% in Part A and/or Part B based on the newly available safety and tolerability data.

Type and Number of Subjects

In **Part A**, eight adult subjects with chronic stable plaque psoriasis will be enrolled. If subjects prematurely discontinue the study treatment, additional replacement subjects may be recruited at the discretion of the Sponsor in consultation with the investigator.

In **Part B**, approximately 18 adult subjects with chronic stable plaque psoriasis will be randomized with an allocation ratio of 2:1 to GSK2981278 4% ointment or vehicle ointment to have at least 15 evaluable subjects who comply closely with the protocol (e.g. have sufficient exposure and critical assessments completed). Subjects who were enrolled in Part A will not be eligible to participate in Part B.

If the concentration of GSK2981278 is lowered in either part of the study, additional subjects may be enrolled to have the minimum evaluable subjects in that part treated with the lower concentration of study treatment.

Analysis

No formal hypothesis tests are planned. Descriptive statistics will be used to assess the key objectives of this study.

2. INTRODUCTION

GSK2981278 is an inverse agonist of retinoic acid receptor-related orphan receptor gamma (RORγ) that is being developed for topical treatment of plaque psoriasis.

2.1. Study Rationale

In the first clinical trial of GSK2981278, once daily treatment of GSK2981278 ointment (at 0.03%, 0.1%, 0.8%, and 4%) on small test fields (1.13 cm^2) of stable plaque(s) over 19 days appeared to be well tolerated but did not show reduction in psoriatic infiltrate thickness. It is unclear whether the apparent lack of effect on infiltrate thickness in the FTIH study was due to the very small surface area treated, the relatively short duration of exposure, or both. Therefore the present study will evaluate the safety, tolerability, clinical effect, and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis by treating all plaques on the body wholly for 8 weeks. The results of this study will provide preliminary information on the safety, tolerability, and effect of the GSK2981278 ointment on plaque psoriasis at the highest safe and feasible concentration to guide subsequent development strategy.

2.2. Brief Background

Psoriasis is a chronic inflammatory skin disorder affecting 0.7 to 2.9% of the population in Europe and the United States [Parisi, 2013]. Plaque type psoriasis is characterized by raised, well-demarcated, erythematous oval plaques with adherent silvery scales [Nestle, 2009] and affects approximately 85 to 90% of all psoriasis patients [Griffiths, 2007]. There is substantial impairment of physical and psychological quality of life associated with the disease [DeKorte, 2004].

The primary goal of treatment for psoriasis is to improve the signs and symptoms as there is no curative treatment. Approximately 80% of psoriasis patients have mild to moderate disease, which is typically managed with topical agents. In patients with more severe disease, topical agents are often used adjunctively with either phototherapy or systemic medications. Topical corticosteroids are the mainstay of topical therapy and provide relatively high efficacy. However, local safety issues such as skin atrophy, telangiectasia, and striae distensae as well as systemic safety concerns such as hypothalamic-pituitary-adrenal (HPA) axis suppression limit their long-term use and use in sensitive areas [Menter, 2009]. Other topical agents such as vitamin D analogues and topical retinoids are available to complement the corticosteroid therapy. There is a need for an effective novel topical agent without the safety concerns associated with corticosteroids.

Although the pathophysiology of psoriasis is not fully understood, current evidence suggests that a combination of genetic, immunologic and environmental factors contributes to the disease. Growing understanding of the involvement of the immune system in the psoriasis pathophysiology indicates that Type 17 helper T-cell (Th 17) cells and their signature proinflammatory cytokine Interleukin-17 (IL-17) plays a critical role [Malakouti, 2015]. IL-17A is known to drive inflammatory pathways inherent in psoriasis pathogenesis by stimulating keratinocyte expression of multiple chemokines and increasing the expression of antimicrobial peptides and contributing to epidermal

hyperproliferation and skin barrier disruption. Increased numbers of IL-17 positive T cells and higher IL-17A messenger Ribonucleic acid (RNA) expression in psoriatic lesions compared with normal skin have been reported as well [Lynde, 2014]. In addition, the involvement of IL-17 cytokines was recently validated with monoclonal antibody (mAb) treatment. Three biologic therapies that inhibit the IL-17 cytokines have been shown to control the signs and symptoms of plaque-type psoriasis. Phase III study results have shown that a greater proportion of patients administered these agents have a higher PASI75 and PASI100 response compared to patients administered existing biologics that have different mechanisms of action (e.g., Tumor necrosis alfa (TNF-α) inhibitors and T-cell inhibitors) [Langley, 2014; Sandoval, 2015; Lebwohl, 2015; Gordon, 2015].

RORγt, a truncated isoform of RORγ, is a transcription factor involved in Th17 cell differentiation and Th17 cytokine expression. It is expressed in a few distinct types of immune cells and is described as the master regulator of Th17 cytokine expression [Ivanov, 2006].

RORγ is widely expressed throughout the body and has identical ligand-binding domains as RORγt [He , 1998]. Compounds targeting RORγ are expected to modulate the activity of RORγt as well. Therefore, local delivery of the selective RORγ inverse agonist GSK2981278 to lesional skin of psoriasis patients via topical application is expected to block the transcriptional activity of RORγt leading to the local suppression of cytokine expression from skin-resident T cells and ultimately to improvement in psoriasis, with no or minimal systemic effects.

Pre-clinical data show that GSK2981278 significantly inhibits production of the Th17 signature cytokines in multiple in vitro and human tissue-based assays, including human peripheral T cells and ex vivo human skin [GlaxoSmithKline Document Number 2016N286376_00 GSK2981278 Investigator's Brochure (IB)].

3. OBJECTIVE(S) AND ENDPOINT(S)

Part A	
Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of topically applied GSK2981278 in subjects with plaque psoriasis	• Incidence and nature of adverse events (AEs) and serious adverse events (SAEs) • Application site tolerability assessment score • Change in clinical laboratory parameters, vital signs, and electrocardiogram (ECG) from baseline
• To evaluate the systemic exposure of GSK2981278 following topical application in subjects with plaque psoriasis	• Plasma concentrations of GSK2981278
Secondary	
• To evaluate the clinical effect following topical application of GSK2981278 in subjects with plaque psoriasis	• Mean percent change in Target Plaque Severity Score (TPSS) from baseline to Week 8 • Mean percent change in Physician's Global Assessment (PGA) score from baseline to Week 8 • Mean percent change in Psoriasis Area and Severity Index (PASI) from baseline to Week 8
Exploratory	
• To evaluate the effect of GSK2981278 ointment on relevant gene expression	• Fold change in messenger ribonucleic acid (mRNA) biomarkers from baseline to Week 8 in skin biopsy samples
• To investigate the delivery profile of GSK2981278 into the psoriatic skin following repeat topical applications	• Quantification of GSK2981278 in the skin biopsy using Matrix Assisted Laser Desorption Ionization (MALDI) imaging mass spectrometry or High-performance liquid chromatography mass spectrometry (HPLC-MS) at Week 8
• To evaluate the effect of GSK2981278 ointment on subject-reported outcomes	• Mean percent change in Psoriasis Symptom Diary score from baseline to each study visit
• To evaluate potential metabolites of GSK2981278 in plasma, urine, and skin from biopsies in pooled subject samples, as data allow	• Identification of any compound-derived metabolite(s) from plasma and urine and if possible estimation of relative amounts of drug related material • Identification of GSK2981278-derived metabolite(s) in the skin biopsy using MALDI imaging mass spectrometry or HPLC-MS at Week 8

Part B	
Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of topically applied GSK2981278 and its vehicle in subjects with plaque psoriasis	• Incidence and nature of AEs and SAEs • Application site tolerability assessment score • Change in clinical laboratory parameters, vital signs, and ECG from baseline
• To evaluate the clinical effect of topically applied GSK2981278 relative to vehicle control in subjects with plaque psoriasis	• Mean percent change in TPSS from baseline to Week 8 • Mean percent change in PGA score from baseline to Week 8 • Mean percent change in PASI from baseline to Week 8
Exploratory	
• To explore exposure-response relationship of sparse systemic exposures with the clinical endpoints (by performing population PK/PD analysis, if required), as data allows	• Plasma concentrations of GSK2981278 and clinical endpoints assessed to determine the clinical effect (e.g. TPSS, PGA, and PASI)
• To evaluate the effect of GSK2981278 ointment on subject-reported outcomes	• Mean percent change in Psoriasis Symptom Diary score from baseline to each study visit

4. STUDY DESIGN

4.1. Overall Design

This is a single-center, 2-part Phase I/IIa study to evaluate the safety, tolerability, clinical effect and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis. Drug delivery into the skin and changes in the relevant biomarkers will be explored using skin punch biopsies as well.

- **Part A**: open label, single arm study
- **Part B**: double-blind, randomized, 2-arm, parallel-group, vehicle-controlled study

After completion of Week 4 assessments and Week 8 assessments in Part A, the Sponsor will review the safety, tolerability, PK and clinical effect data. If data demonstrates a mean percent reduction of 40% or greater in TPSS from baseline and systemic exposure levels below the NOAEL determined in the pre-clinical toxicity studies without significant safety or tolerability issues at either time point, the study will proceed to Part B.

4.2. Treatment Arms and Duration

This study will consist of 3 periods: the screening period of up to 4 weeks, the treatment period of 8 weeks, and the follow-up period of 2 weeks. Study visits will occur at

Screening; Baseline; Weeks 1, 4, and 8 during the treatment period; and Week 10 for follow-up, which will be 2 weeks after the last application of study treatment. Additional visits may occur, as needed, for early withdrawal or to follow-up on any skin reactions or ongoing AEs. A subject's total duration of study participation will be approximately 14 weeks.

In **Part A**, subjects will receive topical application of GSK2981278 4% ointment to all affected areas of the body twice daily for 8 weeks.

In **Part B**, subjects will receive topical application of either GKS2981278 4% ointment or the vehicle ointment, according to the randomization, to all affected areas of the body twice daily for 8 weeks.

The concentration of GSK2981278 may be lowered to 2% or 0.8% in Part A and/or Part B based on the newly available safety and tolerability data. Refer to Section 6.4 for planned dose adjustments.

4.3. Type and Number of Subjects

In **Part A**, eight adult subjects with chronic stable plaque psoriasis will be enrolled. If subjects prematurely discontinue the study treatment, additional replacement subjects may be recruited at the discretion of the Sponsor in consultation with the investigator.

In **Part B**, approximately 18 adult subjects with chronic stable plaque psoriasis will be randomized with an allocation ratio of 2:1 to GSK2981278 4% ointment or vehicle ointment to have at least 15 evaluable subjects who comply closely with the protocol (e.g. have sufficient exposure and critical assessments completed). Subjects who were enrolled in Part A will not be eligible to participate in Part B.

If the concentration of GSK2981278 is lowered in either part of the study, additional subjects may be enrolled to have the minimum evaluable subjects in that part treated with the lower concentration of study treatment.

4.4. Design Justification

Single-arm, open-label Part A will allow focused evaluation of safety, tolerability, clinical effect, and systemic exposure potential and the exploration of drug delivery to the skin and changes in relevant gene expressions following topically applied GSK2981278 ointment in a small number of subjects without exposing additional subjects to unnecessary burdensome assessments.

Treatment duration of 8 weeks is considered sufficiently long to look for the signal of drug effect and determine whether GSK2981278 may be a viable candidate for development as a topical treatment for plaque psoriasis.

The number of subjects proposed in this study is expected to provide reasonable information on the clinical effect, gene expression changes, and drug delivery into the psoriatic skin.

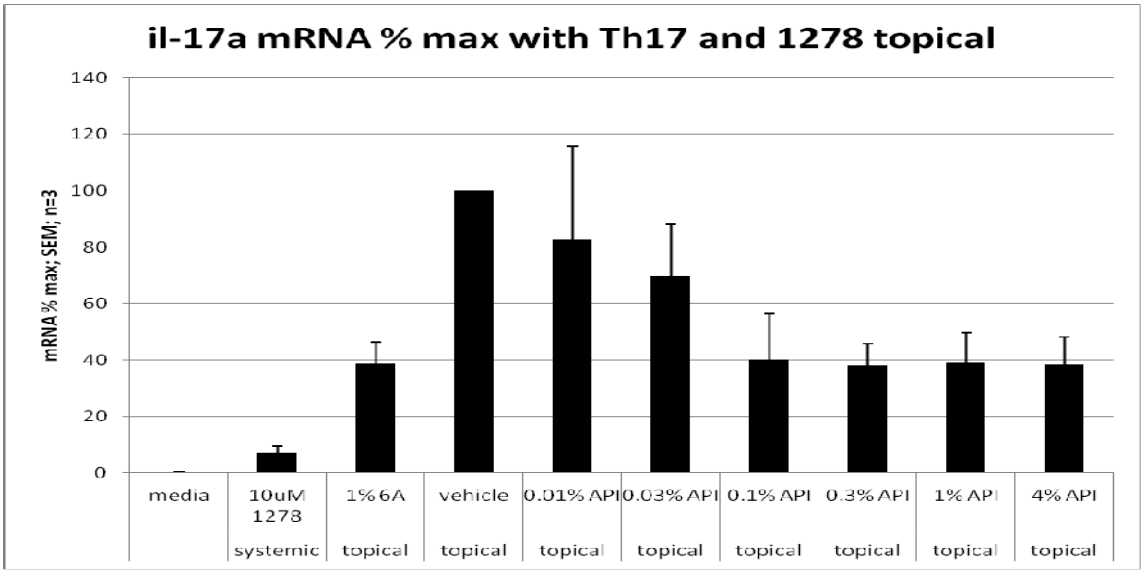
If data from Part A demonstrate sufficient signal of drug effect to meet the pre-defined criteria to proceed to Part B, any clinical effect observed in Part A will be further evaluated in a randomized, double-blind, vehicle-controlled fashion in Part B. Inclusion of the vehicle group will inform the treatment effect relative to the vehicle effect.

4.5. Dose Justification

In this study, the clinical effect of GSK2981278 will be evaluated in patients with psoriasis at a 4% w/w dose applied topically to up to 15% of total body surface area for 8 weeks as an ointment. Data from ex vivo target engagement studies, the first study in humans, and repeat dose toxicity studies in rat (oral) and minipig (oral and dermal) were considered for the selection of the concentration of GSK2981278 ointment in this study.

In ex vivo human skin following single dermal application of GSK2981278 with the current clinical formulation at concentrations ranging from 0.01 to 4%, a potent dose-dependent inhibition of Th17 signature cytokines mRNA levels was observed with effect reaching plateau after 0.1% concentration (Figure 1). Based on this data, concentrations ranging from 0.03% to 4% are being considered in the early phase clinical trials. In this study, using a single concentration of GSK2981278 ointment, the highest concentration 4% is selected to maximize the probability of observing the clinical effect of GSK2981278 in patients with psoriasis.

Figure 1 Percent maximum expression of IL-17A transcripts in ex-vivo human skin



In the first clinical study (201465), once daily treatment of GSK2981278 at 0.03%, 0.1%, 0.8% and 4% w/w each applied to a small area of a psoriatic plaque (1.13 cm^2) over 19 days was well tolerated in patients with psoriasis although reduction in the inflammatory infiltrate thickness measured by ultrasound was not observed for any of the tested concentrations.

GSK2981278 has been evaluated in repeat dose toxicity studies following oral administration for up to 13 weeks in rats and minipigs; following dermal administration for up to 13 weeks in minipigs.

No dose-limiting toxicities were observed in any of the nonclinical toxicity studies, hence the NOAELs for systemic effect were established at the highest tested dose levels.

The NOAEL established for systemic effects in the oral 13 week rat study was 200 mg/kg/day. The end of study area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) values at 200 mg/kg/day in rats were 302 ng.h/mL (males) and 4650 ng.h/mL (females) and 79.5 ng/mL (males) and 3390 ng/mL (females), respectively.

The NOAEL established for systemic toxicity in the dermal 13 week minipig study using the current clinical formulation was 140 mg/kg/day (7%; twice daily (BID); 10% body surface area). The end of study AUC and C_{max} values at 140 mg/kg/day were 325 ng.h/mL and 52.4 ng/mL (gender average mean), respectively.

The predicted human AUC at steady state is 58.5 ng.h/mL and C_{max} is 2.4 ng/mL (4% GSK2981278 [maximum concentration] applied twice daily to 15% body surface area [BSA]). Multiples of predicted mean human exposure for AUC and C_{max} at the NOAEL for systemic findings in the rat (oral) and in the minipig (dermal) are shown in Table 1.

Table 1 Predicted mean human exposures with 90% prediction intervals (PIs) for GSK2981278 ointment at 4% (w/w) and calculated mean safety covers with 90% PIs.

BSA Treated (%[cm^2][a])	Mean Predicted Human Exposure[b] at steady state (PI)		Mean Safety Cover-Fold Difference (PI)					
			13 Week Rat (Oral – Males)		13 Week Rat (Oral – Females)		13 Week Minipig (Dermal – Gender Averaged)	
	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	C_{max}	AUC_{0-24h}	C_{max}	AUC_{0-24h}	C_{max}	AUC_{0-24h}
15 [2595]	2.4 (2.0 – 2.9)	58.5 (47-70.5)	33 (27 – 41)	5 (4 – 6)	1413 (1153 – 1730)	79(66 – 99)	21 (17 – 26)	6 (4 – 7)
5 [865)	0.8 (0.7 – 1.0)	19.5 (15.7 – 23.5)	98 (81 – 122)	15 (13 – 19)	4170 (3460 – 5189)	238(198 – 297)	64 (51 – 77)	17 (13 - 20)

Key:
a=equivalent area of skin in cm^2 for a standard BSA of 1.73 m^2
b=calculated using BSA in cm^2 for BSA of 1.73m^2

The planned twice daily application of GSK2981278 ointment at 4% w/w concentration to up to 15% of total BSA in this study provides a safety cover of ≥5 fold for AUC and ≥21 fold for C_{max} for systemic effect.

In a 13-week dermal minipig study, test article-related adverse dermal irritation was observed. Dermal irritation included slight to marked erythema and eschar in most animals at all dose levels and ulceration, tissue damage, exfoliation and desquamation in less than 5 animals. A NOAEL was not established for this effect. However, there was no clear dose-response in the incidence and/or severity of clinical and microscopic skin findings, and irritation was reversible with treatment discontinuation. These findings were not observed with the same formulation in a 4 week dermal study in minipigs. No skin irritation findings have been observed in mice, rats or rabbits. In addition, the formulation with GSK2981278 was not a contact sensitizer in the mouse local lymph node assay, was not classified as an eye irritant in the bovine corneal opacity and permeability assay at concentrations up to 7%, and has no potential for phototoxicity in nonclinical models

The dermal minipig high dose concentration at 4% of GSK2981278 was equivalent to 960 µg/cm^2. When the minipig dose levels are compared with the clinical dose levels at a concentration 4% of GSK2981278, equivalent to 63 µg/cm^2, there is a 15 fold difference, indicating patients participating in this study will receive a 15 fold lower dose on a µg/cm^2 basis than minipigs received in the 13 week study due to the difference in the volume applied. In addition, even when compared with the lowest dose concentration tested in minipigs, 1%, the clinical dose at 4% concentration is almost 4 fold lower on a µg/cm^2 basis.

Patient's skin will be monitored for any signs of irritation using the application site tolerability scale at Days 1, 15, 29, and 57 in addition to regular AE/SAE monitoring, and with phone contact with patients at Days 8 and 43. In the event of skin irritation, study treatment will be discontinued according to the stopping criteria (Section 5.4.3).

Findings from preclinical in vivo pharmacology and toxicology studies with GSK2981278 have provided reasonable assurance that there are no undue or unforeseen risks for the administration of GSK2981278 to humans at up to 4% concentration twice a day to up to 15% BSA in this study (GlaxoSmithKline Document Number 2016N286376_00 GSK2981278 Investigator's Brochure).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2981278 can be found in the Investigator's Brochure (IB). 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) [GSK2981278]		
Skin irritation or allergic reaction to GSK2981278 or to components of its vehicle.	GSK2981278 was not a contact sensitizer in the mouse local lymph node assay and was not classified as an eye irritant in the bovine corneal opacity and permeability assay at concentrations up to 7%. GSK2981278 is a sulphonamide, chemically distinct from the antibiotic sulphonamides that are one of the most common causes of drug reactions. GSK2981278 does not contain the arylamine group that is known to be associated with allergies and hypersensitivity as the antibiotic sulphonamides do. Evidence suggests no cross-reactivity between arylamine sulphonamides and non-arylamine sulphonamides [Brackett, 2007; Strom, 2003]. In a 13-week dermal minipig study test article-related adverse dermal irritation was observed in a non-dose responsive manner and included marked erythema and eschar with occasionally ulceration, tissue damage, exfoliation and desquamation. A NOAEL was not established for this effect, although a systemic NOAEL was achieved at 7% concentration BID. There was no clear dose-response in the incidence and/or severity of clinical and microscopic skin findings, and irritation was reversible with treatment discontinuation. These findings were not observed with the same formulation	Potential subjects with a known or suspected intolerance to the components of GSK2981278 vehicle will be excluded. Subjects will be informed of the sulphonamide nature of the compound via informed consent. Subjects will not be excluded from the trial solely based on a history of sulphonamide allergy. The skin will be evaluated for any signs of allergic reaction or excessive irritation in addition to a regular AE/SAE monitoring. If a subject experiences application site reaction, the study treatment may be discontinued temporarily or permanently (see Section 5.4.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	in a 4 week dermal study in minipigs. No skin irritation findings have been observed in mice, rats or rabbits. In the one and only clinical study conducted to date with GSK2981278, study 201465, the physical examination of the skin did not show any findings in any of the 15 subjects treated with GSK2981278 in small areas (1.13 cm^2) of the plaque over 19 days.	
Systemic reactions including but not limited to end organ toxicity.	No adverse GSK2981278-related systemic findings have been observed up to 13 weeks duration in an oral rat study, 13 week oral minipig study, or 13 week dermal minipig study at doses up to 200 mg/kg/day, 30 mg/kg/day, or 140 mg/kg/day, respectively. GSK2981278 did not produce acute cardiovascular effects in minipigs or respiratory or neurobehavioural effects in rats in safety pharmacology studies at doses up to 30 and 200 mg/kg, respectively. GSK2981278 inhibited hERG tail current recorded from HEK 293 cells stably transfected with hERG cDNA, with an IC25 of 2.2 μM (1.02 μg/mL) or 100000 times greater than the predicted human free Cmax. One AE of nasopharyngitis, considered unrelated to study treatment, was reported and no SAEs were reported in study 201465. No remarkable changes in laboratory tests, ECGs or vital signs were reported in this study.	Standard laboratory tests, ECGs and physical examinations will be performed and vital signs will be reviewed Subjects will be monitored for the occurrence of AEs/SAEs throughout the study.
Reproductive and developmental toxicity	GSK2981278 administered to pregnant rats orally up to	Only females of non-reproductive potential will

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	200 mg/kg/day or dermal administration in a preliminary dose-range finding rabbit study up to 7% concentration resulted in no maternal or developmental toxicity. No effects on testes were reported in repeat dose toxicity studies.	be enrolled in this study. In addition, male subjects with female partners of child bearing potential will be required to use a male condom unless vasectomy was done and azoospermia was documented.
Study Procedures		
Worsening of psoriasis symptoms	Subjects discontinuing their current psoriasis treatment may experience a worsening of their psoriasis during the washout period before beginning treatment in this study. A worsening of psoriasis may also occur during the active treatment period. Patients did not discontinue the study 201465 due to worsening of psoriasis symptoms.	The informed consent for this study will state the risk of worsening of the symptoms of psoriasis. Subjects who either choose to withdraw or are withdrawn from the study treatment because they meet withdrawal/stopping criteria will be able to use alternate treatments for their psoriasis.
Punch biopsy	Local bleeding and bruising, pain, infection, allergic reaction (e.g. to a disinfectant or an anaesthetic agent) or damage to the structures beneath the skin (such as an artery or nerve) may occur. Scarring may occur at the biopsy site.	Staff performing the procedures will be adequately trained and subjects will be informed about potential risks. Local anaesthesia will be used prior to obtaining biopsies. Proper wound care (e.g. application of pressure, bandage, etc.) will be provided as needed and subjects will be checked for wound healing at the follow-up visit. Pain medication (e.g. ibuprofen) will be allowed.

4.6.2. Benefit Assessment

Subjects participating in this study may experience improvements, whether it is due to GSK2981278 or the vehicle, in their psoriasis lesions during the course of the study. Subjects may also benefit from the overall health assessment conducted while participating in this study. Subjects participating in the study will also contribute to the process of developing a novel agent for the topical treatment of plaque psoriasis.

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 GSK2981278 ointment are justified by the anticipated benefits that may eventually be afforded to subjects with plaque psoriasis.

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.

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.

The selection of subjects is in accordance with the requirements of §§ 40 and 41 of the German drug law (AMG) as well as the recommendations of the currently valid revision of the Helsinki Declaration and the International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH)-Good Clinical Practice (GCP) guideline.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. 18 years of age and above, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects with clinical diagnosis of stable plaque psoriasis for ≥6 months, as confirmed by the investigator. 3. Body surface area involvement ≥5% and ≤15%, excluding face and intertriginous areas, at Screening and Baseline (Appendix 2). The area of psoriasis involvement may include up to 2% of total BSA on the scalp with only sparse terminal hair and/or vellus hair.

4. A PGA score of ≥2 at Baseline (Appendix 3)
5. One target plaque located on the trunk or proximal parts of extremities (excluding scalp, knees, and elbows) that is at least 9 cm^2 in size at Screening and Baseline with a Target Plaque Severity Score (TPSS) ≥5 and induration subscore ≥2. (Appendix 4)

SEX

6. Male

   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 2 weeks after the last dose of study medication.

   a. 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.

   b. Male condom

   The allowed method of contraception is 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.

7. Female of non-reproductive potential (FNRP)

   A FNRP is eligible to participate in this study if she meets at least one of the following conditions:

   a. Females with one of the following procedures documented and no plans to utilize assisted reproductive techniques (e.g., in vitro fertilization or donor embryo transfer):
      - Bilateral tubal ligation or salpingectomy
      - Hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
      - Hysterectomy
      - Bilateral Oophorectomy (surgical menopause)

   b. Post-menopausal women (including all women over 60 years of age, see below),

   <u>Post-Menopause criteria</u>

   - Females 60 years of age or older
   - A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years, in the absence of hormone replacement therapy (HRT) or medical suppression of the menstrual cycle (e.g., leuprolide treatment).
     - In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's post-menopausal reference range is confirmatory (these

levels need to be adjusted for specific laboratories/assays) [Kronenberg, 2008; Strauss, 2004]. • Females under 60 years of age, who are on HRT and wish to continue, and whose menopausal status is in doubt, should not be enrolled in this study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can enrol into the study and resume use of HRT.

INFORMED CONSENT
8. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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. Psoriasis other than plaque variant (i.e. acute psoriasis guttate, psoriasis punctata, psoriasis erythroderma or pustular psoriasis).
2. Current evidence of another ongoing or any acute cutaneous infection, history of repeated or chronic significant skin infections (unless irrelevant in the opinion of the investigator, i.e. onychomycosis, labial herpes or other minor diagnosis).
3. Clinically-relevant skin disease or other skin pathologies, that may, in the opinion of the investigator, contraindicate participation or interfere with skin evaluations.
4. Alanine aminotransferase (ALT) >2xULN and bilirubin >1.5x upper limit of normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
6. QTcB >450 msec or QTcB >480 msec in subjects with Bundle Branch Block. The QTcB should be based on single QTcB values of ECG obtained over a brief recording period. If QTcB is outside the threshold value, triplicate ECGs may be performed with the QTcB values averaged.
7. Any condition that, in the judgement of the investigator, would put the subject at unacceptable risk for the participation in the trial.
8. History of malignancy within 5 years prior to dosing, except adequately treated non-invasive cancer of the skin (basal or squamous cell).

CONCOMITANT MEDICATIONS
9. Use of prohibited concomitant medications or products within the defined periods before the Day 1 visit and during the trial (Table 2).

CONTRAINDICATIONS
10. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
11. Symptoms of a clinically significant illness that may, in the opinion of the investigator, influence the outcome of the trial in the 4 weeks before baseline visit and during the trial.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
12. 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.
13. A positive pre-study drug/alcohol screen.
14. A positive test for human immunodeficiency virus (HIV) antibody.
15. **For Part B only**-the subject has participated in Part A of this study.
16. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 4 weeks, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
17. Prolonged exposure to natural or artificial sources of ultraviolet (UV) radiation (e.g., exposure to sunlight other than that associated with usual daily activities, use of tanning booth, etc.) within 2 weeks prior to the Day 1 visit or intention to have such exposure during the study, thought by the investigator likely to modify the subject's psoriasis.
18. In the opinion of the investigator or physician performing the initial examination the subject should not participate in the clinical trial, e.g. due to probable noncompliance, inability to understand the trial and give adequately informed consent, or inability to complete the Psoriasis Symptom Diary (Appendix 5).
19. Close affiliation with the investigator (e.g. a close relative) or persons working at bioskin GmbH or subject is an employee of sponsor.
20. Subject is institutionalized because of legal or regulatory order.

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 (Section 7.5.1.5).

Subjects who initially do not meet eligibility criteria (e.g., due to use of prohibited concomitant medications requiring a longer washout than the specified screening period) may be re-screened for the same Part of the study once if their potential eligibility status has changed. Eligible subjects may then be enrolled in the study.

A subject who previously failed screening for Part A may be re-screened for Part B if the investigator considers that the subject's potential eligibility status has changed.

5.4. Withdrawal/Stopping Criteria

Study treatment will be stopped and the subject will complete the Day 57 assessments and subsequently enter the follow-up period if any of the following stopping criteria are met:

- Subject experiences an AE that is severe enough in nature to warrant treatment discontinuation in the opinion of the investigator.
- Subject presents with a worsening of psoriasis that requires treatment with a prohibited concomitant medication in the opinion of the investigator (Table 2).
- Additional for **Part B**: The subject's randomized treatment assignment is unblinded by the investigator.

Reasons for withdrawal from the study may include but are not limited to the following:

- Withdrawal of consent. If specified by the subject, the investigator should document the reason for withdrawal of consent.
- Noncompliance with study procedures
- Lost to follow-up
- Termination of study by sponsor
- Protocol deviation
- Investigator discretion

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".

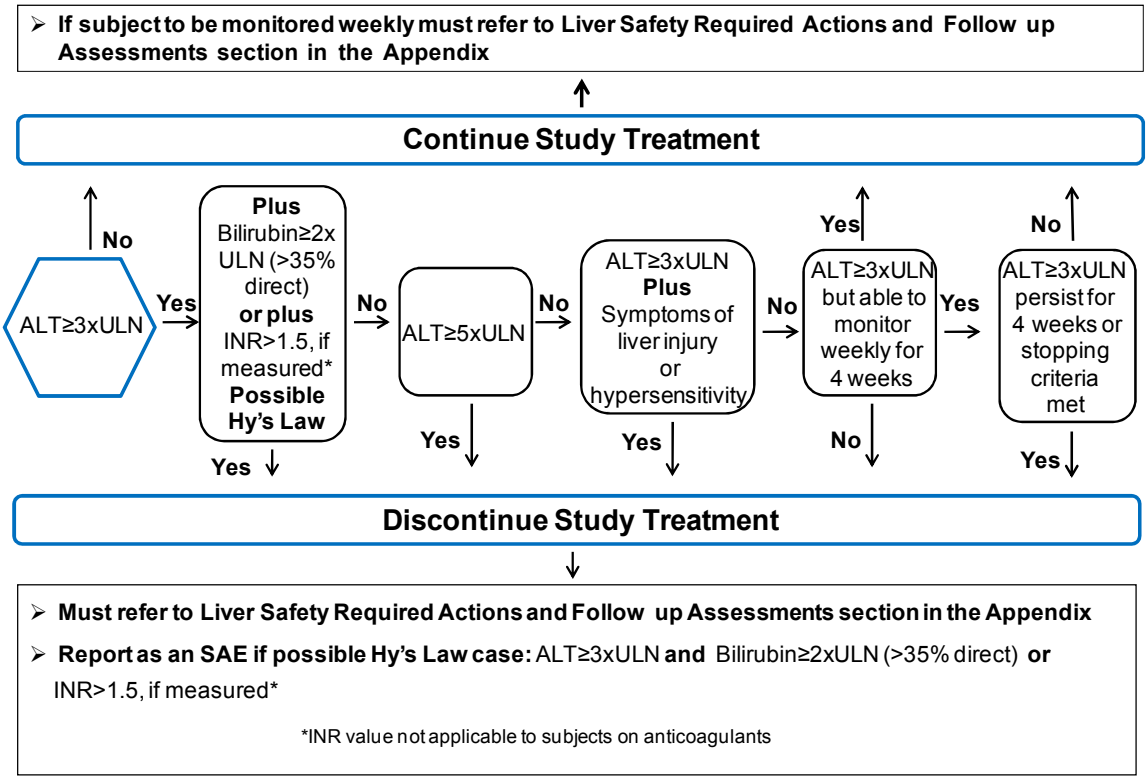
A subject may withdraw from study treatment or the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. If the subject has not withdrawn consent to participate in the study, then the Week 8 assessments should be performed at the time a subject is prematurely withdrawn from the treatment.

If a subject prematurely withdraws prior to enrollment in **Part A** or randomization in **Part B**, this subject will be classed as a screen failure and will not be counted towards the planned enrollment target. The primary reason for withdrawal from the study must be recorded in the eCRF.

5.4.1. 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

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow-up Assessments Section can be found in Appendix 6.

5.4.1.1. 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.

5.4.2. QTc Stopping Criteria

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. QTcB will be utilized for this study.

The QTcB should be based on single QTcB values electrocardiograms. If QTcB is outside of the threshold value of the stopping criteria shown below, triplicate ECGs will be performed over a brief (e.g., 5-10 minute) recording period with the QTcB values averaged.

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

- QTcB > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTcB > 60 msec

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

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

5.4.3. Topical Application Site Tolerability Stopping Criteria

If a subject experiences application site reaction of grade 3 (severe) or 4 (very severe) on the topical application site tolerability scale, study treatment will be discontinued permanently (Table 5).

If a subject experiences application site reaction of grade 2 (moderate) on the topical application site tolerability scale with cracking, study treatment WILL be temporarily discontinued and the subject will be put on a dosing holiday until the irritation resolves. If a subject experiences application site reaction of grade 2 (moderate) without cracking, investigator MAY temporarily discontinue study treatment and put the subject on a dosing holiday in consultation with the subject and medical monitor until the irritation resolves. No rescue medication will be allowed during a dosing holiday. Investigator in consultation with the Medical Monitor may allow the use of emollients during the dosing holiday. The dosing holiday will be limited to once in each subject over the course of the study and the duration will not exceed 1 week. After the dosing holiday, the subject may be retreated with the study treatment if the irritation resolves.

At the time of permanent (grade 3 or 4) or temporary (grade 2) treatment discontinuation due to the application site intolerability and at the time of treatment restart (if applicable, after a dosing holiday), photographic documentation of a representative area of irritation (preferably the target lesion or the vicinity, if affected) will be taken.

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:	GSK2981278	Vehicle
Dosage form:	Ointment	Ointment
Unit dose strength(s)/Dosage level(s):	4% (w/w) 2% (w/w) 0.8% (w/w)	0% (w/w)
Route of Administration	Topical	Topical
Dosing instructions:	Apply a thin layer to all affected areas as determined at baseline twice daily (morning and evening) for 8 weeks.	Apply a thin layer to all affected areas as determined at baseline twice daily (morning and evening) for 8 weeks.
Physical description:	White to off-white ointment	White to off-white ointment

6.2. Treatment Assignment

In **Part A**, all subjects will receive 4% ointment of GSK2981278.

In **Part B**, subjects will be assigned to 4% ointment of GSK2981278 or the vehicle ointment in accordance with the randomization schedule generated by GlaxoSmithKline (GSK), prior to the start of the study, using validated internal software.

The concentration of GSK2981278 may be lowered to 2% or 0.8% in Part A and/or Part B based on the newly available safety and tolerability data. See Section 6.4 for planned dose adjustments.

Once a randomization number has been assigned to a subject, it must not be re-assigned to a different subject.

6.3. Treatment Administration

At the baseline visit, subjects will be instructed on proper application of study treatment. The first application will be at the study center under the supervision of study staff. Subjects will self-administer study treatment where possible, ensuring that they cover all psoriasis lesions identified to be treated at baseline (except on the scalp covered with dense terminal hair: sparse terminal hair and/or vellus hair on the scalp are acceptable) and approximately 0.5 cm beyond the borders with a thin layer of GSK2981278 ointment or vehicle ointment, twice daily (morning and evening). In areas where self-

administration of study treatment is not possible, study treatment may be applied by another person (e.g. site staff during clinic visits, family member or friend outside the clinic). The skin should be clean and dry before applying study treatment. Subjects will continue to treat all original areas of involvement, even in the event of lesions clearing, and to any new areas at the first sign of flaring until the Week 8 visit. Subjects will be asked to contact the site if any new lesions are noticed. Subjects must wash hands after application, unless treating lesions on the hand(s).

If study treatment is applied to the subject by another person, that person must wear protected gloves (e.g. vinyl) and thoroughly wash his/her hands after application.

In the area of the skin where a punch biopsy has been taken and the surrounding areas of the skin approximately 1 cm from the edge of the bandage in all direction, study treatment will not be applied until the investigator confirms that the wound has healed and the bandage is removed.

Subjects should be requested not to take a shower within 15 minutes before or 2 hours after treatment application.

6.4. Planned Dose Adjustments

The concentration of GSK2981278 ointment will be lowered if the tested concentration shows tolerability issues as indicated below;

- In **Part A**, if 2 of the first 4 subjects who receive study treatment discontinue the study treatment permanently due to application site reaction, the remaining subjects in Part A will receive GSK2981278 2% ointment. If GSK2981278 2% ointment is used in Part A, Part B will be conducted using the 2% concentration rather than the 4%.
- In **Part B**, if 2 of the first 4 subjects who receive study treatment discontinue the study treatment permanently due to application site reaction, the remaining subjects will receive the next lower concentration GSK2981278 ointment (i.e. if 4% discontinued, 2%; if 2% discontinued, 0.8%)

The concentration of GSK2981278 ointment for an individual subject will not be changed during the study treatment.

Consideration will be also given to decreasing the concentration of the GSK2981278 ointment for the remaining subjects in the study in the following circumstances:

- Adverse events other than the application site reactions, which are of moderate or severe intensity and are consistent across subjects in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with study treatment, are observed in more than 2 of the subjects
- The same SAE occurs in more than one subject, reasonably attributable in the opinion of the investigator to administration of the study treatment
- In these two circumstances, but not limited to them, dosing will be temporarily halted and no further subjects will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor,

relevant GSK personnel, and with the Ethics Committee will then take place prior to any resumption of dosing.

6.5. Blinding

Part A will be an open-label study.

Part B will be a double-blind study and the following will apply:

- Only the unblinded pharmacist/staff responsible for handling and dispensing of the study treatment will have direct access to the subject's individual study treatment.
- The investigator or treating physician may gain access to 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.
- 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 case report form (CRF)
- A subject will be withdrawn from the study 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.

6.6. Packaging and Labeling

GSK2981278 ointment and vehicle ointment will be packaged in 30-gram tubes.

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

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff, as delegated by the principal investigator, 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 Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- 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.

6.8. Compliance with Study Treatment Administration

Detailed instructions concerning protocol requirements and application of the study treatment will be provided to the subject at baseline. Subjects will be instructed to record the time of the study treatment application or reason for missed application for each planned study treatment administration. At each post baseline study visit, subjects will be asked to provide information from the study diary to study personnel regarding their compliance with study product use. Subjects should bring their tube(s) of study treatment with them to each visit for study personnel to weigh and document the amount used.

When subjects are dosed at the site, they will self-apply study treatment under the direction and supervision of the investigator or designee. In areas where self-administration of study treatment is not possible, study treatment may be applied by the site staff (Section 6.3). 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. The weight of the tube of ointment will be collected before and after the study treatment application at the site.

6.9. Treatment of Study Treatment Overdose

For this study, an overdose may consist of accidental or intentional ingestion of the study ointment or excessive application onto the skin (e.g., exposure to larger BSA, using a greater quantity, or applying more frequently than instructed).

There is no specific antidote for overdose of GSK2981278 and GSK does not recommend specific treatment. Refer to Section 6 of GlaxoSmithKline Document Number 2016N286376_00 GSK2981278 Investigator's Brochure for information on overdose.

In the event of an overdose the investigator or treating physician should contact the medical monitor to discuss the event and proceed with the following as appropriate for the circumstances:

1. In the event of excessive topical application, instruct the subject to wash GSK2981278 ointment off the skin and monitor for application-site AEs.
2. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
3. Closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least 7 days or until GSK2981278 can no longer be detected systemically (if plasma level was measured per Medical Monitor's request)
4. Provide appropriate supportive clinical care

Decisions regarding interruptions in application of study treatment will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject and documented in the CRF.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study since the indication being studied is not life threatening or seriously debilitating and/or 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.

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Dietary Restrictions

Subjects should refrain from consumption of red wine, oranges, tangerine, tangelo, grapefruit, pummelos, other exotic citrus fruits, grapefruit hybrids or juices containing these fruits from 7 days prior to the first application of study treatment until after the final application.

6.11.2. Alcohol and Tobacco

- Subjects will be advised to limit alcohol consumption to 2 units/day during the treatment period. One unit is equivalent to 8g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 measure (25 mL) of spirits.
- Subjects who use tobacco products should not change their habits of using these products during the study treatment.

6.11.3. Activity

Subjects will abstain from very strenuous exercise (e.g. weight lifting exercise, marathon) for at least 1 week prior to each blood collection for clinical laboratory tests.

Subjects will abstain from sweat inducing physical exercise, bathing, swimming, or the use of a sauna before or after study treatment application to minimize any potential effect on study drug absorption (±2h).

Subjects should be requested not to take a shower within 15 minutes before or 2 hours after study treatment application.

Prolonged exposure to natural or artificial sources of UV radiation (e.g., exposure to sunlight other than that associated with usual daily activities, use of tanning booth, etc.), which is thought by the investigator to potentially impact the subject's psoriasis, is prohibited within 2 weeks prior to the baseline visit and throughout the study until the last follow-up visit.

6.12. Concomitant Medications and Non-Drug Therapies

All medications and nondrug therapies (including treatments listed in the exclusion criteria) received by the subject within 4 weeks (28 days) before the Screening visit and at any time throughout the study must be recorded in the source documents and eCRF with start and end dates, if end dates are available.

6.12.1. Permitted Medications and Non-Drug Therapies

Medications permitted during the study include contraceptives (for indications other than pregnancy prevention), antihistamines, selective leukotriene receptor antagonists (e.g., montelukast sodium, zafirlukast), mast cell stabilizers (e.g., cromolyn sodium or nedocromil sodium), acetaminophen/paracetamol, ibuprofen, vitamin and mineral supplements, medications for regulation of thyroid function, influenza vaccine, and medications for AEs, unless specifically prohibited.

Subjects may also use medications for chronic stable concomitant medical conditions (e.g, hypertension) that are not expected to affect the study assessments, provided the subject is on a stable dose that is not expected to change during the study.

Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.

Medicinal shampoos and other topical treatments for psoriasis lesions on the scalp that are not part of assessment in this trial are permitted during the study.

Sunscreen and regular moisturizers (site staff to verify that they are not emollients) may be used during the treatment period. However, on the areas to be treated with the study treatment, these products must be applied at least 15 minutes **after** the study treatment if applied. On the scheduled clinic visit days, subjects must not apply these products within 4 hours of a study visit.

6.12.2. Prohibited Medications and Non-Drug Therapies

Use of medications or treatments that would significantly influence or exaggerate responses to the test products or that would alter inflammatory or immune response to the products is prohibited. Prohibited concomitant medications, products, and procedures (Table 2) are not to have been used from the defined periods before the first study treatment applications at the Day 1 visit and throughout the study.

In the event a subject takes a prohibited medication, the investigator should consult with the Medical Monitor to determine if the subject should be withdrawn from the study.

Table 2 Prohibited Concomitant Medications, Products, and Procedures

Prohibited medications, products, and procedures:	**Prohibited period before Day 1**
Biologic agents: (e.g., alefacept 24 weeks; etanercept 12 weeks; ustekinumab 15 weeks)	5 half-lives
Oral retinoids (e.g., acitretin or isotretinoin)	12 weeks
Cyclosporin, interferon, methotrexate, fumaric acid or other systemic immunosuppressive or immunomodulating agents (e.g., mycophenolate or tacrolimus)	4 weeks
Other investigational products or procedures	4 weeks or 5 half-lives, whichever is longer
Systemic corticosteroids or adrenocorticotropic hormone (ACTH) analogs	4 weeks
Systemic anticoagulants (e.g. warfarin, heparin, low molecular weight heparin, etc.)	5 half-lives
Immunizations (influenza vaccine will be allowed)	2 weeks
Topical treatments: corticosteroids, immunomodulators, anthralin	2 weeks

Prohibited medications, products, and procedures:	**Prohibited period before Day 1**
(dithranol), Vitamin D derivatives, retinoids, coal tar (used on the body).	
Drugs known to possibly worsen psoriasis (unless on a stable dose for >12 weeks), such as, but not limited to: β-blockers (eg, propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin	2 weeks
Any other topical therapy (including emollients) on psoriasis lesions treated in this study **Note**: Emollients may be used if Investigator, in consultation with the Medical Monitor, allows the use during a dosing holiday due to application site reaction. (See Section 5.4.3)	1 day
Phototherapy including psoralen plus UVA (PUVA)	2 weeks

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, are essential and required for study conduct.

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 and Section 7.2)

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. 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 and pharmacokinetic 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.

- The Institutional review board (IRB)/ Independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table for Part A

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Screening and Safety assessments									
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Demography	X								
Medical history/family history (includes substance usage, CV medical history and family history of premature CV disease)	X								Substances: Drugs, alcohol and tobacco
Prior and Concomitant Medication review (including prior therapy for psoriasis)	X	X		X	X		X	X	
Fitzpatrick Skin Type Classification	X								
Brief physical exam (including height and weight)	X						X		Brief physical exam including weight only on Day 57
12-lead Electrocardiogram	X	X			X		X		Triplicate ONLY if first reading is outside the eligibility criteria threshold value or the stopping criteria threshold value.
Vital sign	X	X		X	X		X		Vital signs include heart rate, blood pressure and oral temperature. Ideally, heart rate and blood pressure will be obtained after the subject has been resting in a seated or supine position for at least 5 minutes.

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
HIV, Hep B and Hep C screen	X								If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Urine pregnancy test (FNRP)	X								
Laboratory assessments (include liver chemistries) and urinalysis	X	X		X	X		X		Urinalysis: On Days 1, 29, and 57, urine PK sample can be used.
AE/SAE review		X	X	X	X	X	X	X	Visits at Day 8 and Day 43 do not need to be office visits. This information may be collected via a phone call with the subject. On these days subject will be asked about application site tolerability also.
Application site tolerability		X		X	X		X		See Section 7.5.7.
Enrollment to study									
Identify and mark target lesion for TPSS		X							
Identify and mark area for biopsy collection		X							
Dispense tubes of study treatment		X		X	X				
Study treatment application		←----------					----------→		On clinic visit days, the morning application will be done in the clinic
Review compliance diary			X	X	X	X	X		Subjects will use a diary to record daily applications of study treatment and reasons for any missed applications On Day 8 and Day 43, subjects will be asked about compliance via phone.
Collect and weigh tubes of study treatment		X		X	X		X		
Efficacy assessments									

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Psoriasis Symptom Diary	X	X		X	X		X		To be completed by subject before any other assessments at a clinic visit
Target Plaque Severity Score (TPSS)	X	X		X	X		X		
Physician Global Assessment (PGA)	X	X		X	X		X		
Psoriasis Area Severity Index (PASI)		X		X	X		X		
%BSA affected	X	X		X	X		X		
%BSA treated		X		X	X		X		
Pharmacokinetics									
Plasma sample for GSK2981278		X		X	X		X		Day 1, Day 29, and Day 57: pre-dose, and 1h, 2h, 4h, 6h, 8h, and 10h post morning dose Day 15: pre-dose and 2h post morning dose
Plasma sample for metabolite(s)		X					X		Pre-dose, and 1h, 2h, 4h, 6h, 8h, and 10h post morning dose.
Urine sample for metabolite(s)		X					X		Pre-dose urine on Day 1, 0-10h pool Two aliquots to be made for metabolite analysis and urinalysis. See Section 7.6.2
Other assessments									
Skin punch biopsy		X					X		4 mm biopsy before study treatment application. 2 at Baseline (1 from non-lesional skin;1 from lesional skin-both for gene expression analyses) 2 at Day 57 (1 from lesions skin for gene expression analyses;1 from lesional skin for drug level)

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Biopsy wound assessment				X				X	
Photograph of target lesion		X					X		

7.2. Time and Events table for Part B

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (± 2 days)	**Day 15 (± 2 days)**	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Screening and Safety assessments									
Informed consent	X								
Inclusion and exclusion criteria	X	X							Will be assessed prior to randomization
Demography	X								
Medical history/family history (includes substance usage, CV medical history and family history of premature CV disease)	X								Substances: Drugs, alcohol and tobacco
Prior and Concomitant Medication review (including prior therapy for psoriasis)	X	X		X	X		X	X	
Fitzpatrick Skin Type Classification	X								
Brief physical exam (including height and weight)	X						X		Brief physical exam including weight on D57
12-lead Electrocardiogram	X	X			X		X		
Vital sign	X	X		X	X		X		Vital signs include heart rate, blood pressure and oral temperature. Ideally, heart rate and blood pressure will be obtained after the subject has been resting in a seated or supine position for at least 5 minutes.
HIV, Hep B and Hep C screen	X								If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (± 2 days)	**Day 15 (± 2 days)**	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Urine pregnancy test (FNRP)	X								
Laboratory assessments (include liver chemistries) and urinalysis	X	X		X	X		X		
Genetic sample		X							Informed consent for optional,genetic research must be obtained before collecting a sample. Pre-dose & post-randomisation
AE/SAE review		X	X	X	X	X	X	X	Visits at Day 8 and Day 43 do not need to be office visits. This information may be collected via a phone call with the subject. On these days subject will also be asked about application site tolerability.
Application site tolerability		X		X	X		X		See Section 7.5.7.
Enrollment to study									
Identify and mark target lesion for TPSS		X							
Randomisation		X							
Dispense tubes of study treatment		X		X	X				
Study treatment application		←----------					----------→		On clinic visit days, the morning application will be done in the clinic
Review compliance diary			X	X	X	X	X		Subjects will use a diary to record daily applications of study treatment and reasons for any missed applications. On Day 8 and Day 43, subjects will be asked about compliance via phone or text message.
Collect and weigh tubes of study treatment		X		X	X		X		

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (± 2 days)	**Day 15 (± 2 days)**	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Efficacy assessments									
Psoriasis Symptom Diary	X	X		X	X		X		To be completed by subject before any other assessments at a clinic visit
Target Plaque Severity Score (TPSS)	X	X		X	X		X		
Physician Global Assessment (PGA)	X	X		X	X		X		
Psoriasis Area Severity Index (PASI)		X		X	X		X		
%BSA affected	X	X		X	X		X		
%BSA treated		X		X	X		X		
Pharmacokinetics									
Plasma sample for GSK2981278		X		X	X		X		Day 1: between 3 and 12h post morning dose Day 15: pre-dose Days 29 and 57: within 12 h of morning dose
Other assessments									
Photograph of target lesion		X					X		

7.3. Screening and Critical Baseline Assessments

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

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

The subject's Fitzpatrick skin type (Table 3) will be documented.

Table 3 Fitzpatrick Skin Type Classification

Type	Constitutive Skin Color (Unexposed) and Typical Characteristics	Response to Ultraviolet Light Exposure
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red, blond, or brown hair; hazel or green eyes	Usually burns, tans with difficulty
III	White; any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	White or light brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Brown; mid-eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Source: Based on the characteristics originally described in Fitzpatrick, 1988

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

Screening procedures should not commence until after all relevant study approvals have been obtained and until after the informed consent has been signed. The investigator must maintain a subject screening log to document identification of subjects who signed the informed consent document.

Psoriasis Symptom Diary should be completed by subjects before any other assessment at a clinic visit, in the order specified (Appendix 5).

Photographic documentation of the target lesion will be collected at baseline and Day 57. Information on the photographic procedure is available in the SRM.

7.4. Efficacy

All efficacy assessments should be performed by the same investigator or designated evaluator for an individual subject. In the event the same evaluator is not available for the duration of the study, another investigator or designated evaluator with comparable training will perform the assessments.

7.4.1. Target Plaque Severity Score (TPSS)

A target lesion of at least 9 cm^2 with a TPSS ≥5 and an induration subscore ≥2 will be selected at baseline. The severity of erythema, scaling, and induration (plaque thickness) will be assessed by the investigator on a 5-point scale ranging from 0=none to 4=very marked (Appendix 4). A total score will be calculated by adding the individual scores (13-point scale; maximum score 12). TPSS is the primary measure of clinical effect for this study.

7.4.2. Physician Global Assessment (PGA)

The PGA is a clinical tool for assessing the current state/severity of a subject's psoriasis (Appendix 3). It is a static 5-point morphological assessment of overall disease severity, as determined by the investigator, using the clinical characteristics of erythema, plaque thickness, and scaling as guidelines. At each specified time point, the PGA is made without reference to previous scores. Variations of the PGA are frequently used in clinical studies because it is a simple assessment that is more similar to the assessments actually used in clinical practice [Feldman, 2005]. PGA will be assessed on the entire treated area (i.e. including the scalp lesion, if applicable).

7.4.3. Psoriasis Area and 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 scale, as well as the extent of BSA affected with psoriasis [Feldman, 2005] [Appendix 7]. The 3 clinical signs are each graded on a 5-point scale (0 to 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 individual scores are multiplied by a weighted factor for each body region; the sum of these scores gives the overall PASI score. Higher scores indicate more severe disease. PASI is a static assessment made without reference to previous scores.

7.4.4. Body surface Area (BSA)

The extent of BSA affected by psoriasis is a general indicator of disease severity and will be measured throughout the study. The extent of BSA to which study treatment is applied will also be recorded. It is suggested, for the purpose of approximate clinical estimation, the total palmar surface area of the palm plus five digits be assumed to be approximately equivalent to 1% BSA. See Appendix 2.

7.5. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1 and Section 7.2). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Safety will be assessed by the monitoring and recording of all AEs and SAEs; evaluation of application site tolerability; monitoring of hematology, clinical chemistry, urinalysis and vital signs; and the performance of ECGs and physical examinations.

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

The definitions of an AE or SAE can be found in Appendix 8

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

7.5.1.1. 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 until the follow-up contact (Section 7.5.1.3), at the timepoints specified in the Time and Events Table (Section 7.1 and Section 7.2).
- 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 8.
- 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 8

7.5.1.2. 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?”

7.5.1.3. 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 8.

7.5.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 8 and all deaths, whether or not they are considered SAEs, specific Cardiovascular 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.

This information should be recorded in the specific Cardiovascular or Death section of the CRF within 1 week of when the AE/SAE(s) or Death is first reported.

7.5.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee 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.

7.5.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 2 weeks post-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 9.

7.5.3. Physical Exams

- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and a measurement of weight. Height will be also measured and recorded at Screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.5.4. Electrocardiogram (ECG)

Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. QTcB will be utilized for this study. If QTcB is outside the threshold value of the eligibility criteria or stopping criteria, triplicate ECGs will be performed over a brief (e.g. 5 to 10 minutes) recording period with the QTcB values averaged. Refer to Section 5.4.2 for QTc stopping criteria.

7.5.5. Vital Signs

- Vital signs will be measured in seated or supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.
- Three readings of blood pressure and pulse rate will be taken
  - First reading should be rejected
  - Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.5.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4, 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 SRM OR 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 SRM 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 local laboratory, apart from liver events monitoring which will be performed by the central laboratory. The results of each test must be entered or electronically transferred into the eCRF.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate amino-transferase (AST) (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
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 (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (at Screening for women of non-child bearing potential)			

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 5.4.1 and Appendix 6.

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.

7.5.7. Application Site Tolerability

The investigator or designated evaluator will assess application site tolerability focusing on the treated non-lesional skin surrounding the plaques at each visit using the 5-point tolerability assessment scale presented in Table 5. Refer to Section 5.4.3 for topical application site tolerability stopping criteria.

Table 5 Topical Application Site Tolerability Assessment Scale

Grade	Severity	Description
0	None	No evidence of local intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking
3	Severe-To be reported as an AE	Erythema, edema glazing with fissures, few vesicles or papules: Remove and discontinue study treatment
4	Very Severe-To be reported as an AE	Strong reaction spreading beyond the treated area, bullous reaction, erosion: Remove and discontinue study treatment

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for PK analysis of GSK2981278 and related metabolite(s) will be collected at the time points indicated in Section 7.1 and Section 7.2, 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.

Blood samples will be collected into 2 EDTA tubes, each containing 3 mL of blood: one for GSK2981278 and another for related metabolite(s).

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

7.6.2. Urine Sample Collection

Urine samples for analysis of GSK2981278 and related metabolite(s) will be collected at the timepoints listed in Section 7.1, Time and Events Table. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Total urine voided will be collected over the period of collection as specified in Section 7.1.

Details of PK urine sample collection, processing, storage and shipping procedures are provided in the SRM.

7.6.3. Skin Sample Collection

Skin samples for evaluation of drug delivery will be collected at Day 57 by taking a 4 mm punch biopsy from the area of psoriatic plaque identified for skin biopsies at baseline.

Details of PK skin sample processing, storage and shipping procedures are provided in the SRM.

Additional skin samples will be collected for gene expression analyses. See Section 7.7.1 for details.

7.6.4. Sample Analysis

Plasma analysis will be performed under the control of PTS-IVIVT-BIB/TPR, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2981278 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).

Plasma will also be analyzed for other compound-related metabolites and the results reported under a separate PTS-PDS-ASD, GlaxoSmithKline protocol. Raw data will be archived at the GlaxoSmithKline.

Analysis of urine sample analysis will be performed under the control of PTS-PDS-ASD, GlaxoSmithKline. Urine will be analyzed for GSK2981278 and other compound-related metabolites and the results will be reported under a separate PTS-PDS-ASD, GlaxoSmithKline protocol. Raw data will be archived at GlaxoSmithKline.

Skin biopsy samples analysis will be performed under the control of PTS-IVIVT-Bioimaging, GlaxoSmithKline. Skin biopsy samples may be analyzed for concentrations of GSK2981278 and compound-related metabolites using MALDI imaging or HPLC-MS and the results will be reported under a separate PTS-IVIVT-Bioimaging, GSK protocol. Raw data will be archived at GSK.

7.7. Biomarker(s)/Pharmacodynamic Markers

7.7.1. Novel Biomarkers

Skin samples for biomarker analyses will be collected at Baseline and Day 57.

With the subject's consent, a total of 3 4-mm punch skin biopsies will be taken from each subject for biomarker analyses in Part A of this study: 1 from non-lesional skin at baseline, 1 from lesional skin at baseline and 1 at Day 57 from the treated skin of the same plaque where the baseline biopsy was taken. Skin sample(s) may be used for the purposes of measuring novel biomarkers to identify factors that may influence psoriasis as well as the biological and clinical responses to GSK2981278.

Samples will be collected at the timepoints indicated in Section 7.1.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with psoriasis and/or the action of GSK2981278 may be identified by application of:

- RNA transcriptome analysis of skin samples.
- Measurement of the levels of mRNA in skin samples.

Details of skin sample storage are provided in the SRM.

7.7.1.1. RNA Transcriptome Research

Transcriptome studies will be conducted using microarray, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each skin sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to psoriasis or the action of GSK2981278.

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

7.7.1.2. RNA Expression Research of a Subset of RNA Species

RNA expression studies will be conducted using quantitative RT-PCR technologies. The RNAs assayed will be those expected to be modulated by GSK2981278. These biomarkers include IL-17A, IL-17F, DEFB4A, IL-19, IL-36, CCL20, S100A7a, IL-8, IL-22, RORC and Krt6A. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to psoriasis or the action of GSK2981278.

7.8. Genetics

Information regarding genetic research is included in Appendix 10

7.9. Value Evidence and Outcomes

7.9.1. Psoriasis Symptom Diary

The Psoriasis Symptom Diary was developed to assess daily self-reports of psoriasis symptoms and the functional impact related to the underlying pathophysiology of the disease [Strober, 2013]. Questions about how severe and how bothersome various signs and symptoms are to the subject are answered using an 11-point numerical rating scale (Appendix 5). In this study, subjects will be asked to complete the Psoriasis Symptom Diary questionnaire at the clinic during the scheduled visits.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK/bioskin defined eCRFs, 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.
- eCRFs (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

Refer to the reporting and analysis plan (RAP)/statistical analysis plan (SAP) for additional details regarding data analyses. Reporting will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards.

9.1. Hypotheses

No formal hypothesis tests are planned. Descriptive statistics will be used to assess the key objectives of this study: evaluation of safety, tolerability, systemic exposure and clinical effect of topically applied GSK2981278 ointment in subjects with plaque psoriasis.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size is based on feasibility and the estimated number of subjects expected to provide reasonable information on the key objectives of the study.

For **Part A**:

Summary statistics, such as mean % of reduction in TPSS, mean % reduction in PGA and mean % of reduction in PASI will be estimated. With 8 evaluable subjects, precisions on these estimates are assessed as below.

Endpoint	Assumptions	Sample Size	95%CI estimate
Mean % reduction in TPSS	50% reduction with 20% standard deviation will be observed	N=8	33.3% - 66.7%
Mean % reduction in PGA	50% reduction with 30% standard deviation will be observed	N=8	24.9%-75.1%
Mean % reduction in PASI	50% reduction with 25% standard deviation will be observed	N=8	29.1% -70.9%

For **Part B**:

With 15 subjects (10 in GSK2981278 arm and 5 in the Vehicle arm), the power to detect difference between GSK2981278 arm and the vehicle arm in terms of TPSS reduction, and PASI reduction are assessed below:

Endpoint	Assumptions	Sample Size (API:Vehicle)	Power to reject* H_0: API=Vehicle (Alpha=5%)
Mean % reduction in TPSS	50% reduction in GSK arm and 20% reduction in Vehicle with 20% standard deviation will be observed	N=10:5	71.7%
Mean % reduction in PASI	50% reduction in GSK arm and 10% in Vehicle with 20% standard deviation will be observed	N=10:5	92.1%

*2-sample t test
API- Active Pharmaceutical Ingredient

9.2.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment is planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Per Protocol (PP) analysis set will include all randomized subjects who comply closely with the protocol (e.g. have sufficient exposure). PP analysis set details will be defined in the RAP/SAP. The PP analysis set will be the primary set for efficacy analyses.

Safety analysis set will include all subjects exposed to at least 1 application of study product. The safety analysis set will be the primary set for safety analyses.

Pharmacokinetic (PK) analysis set will include subjects with at least one sample collected and analyzed for plasma drug concentration. The PK analysis set will be the primary set for PK analyses.

9.3.2. Interim Analysis

No interim analysis is planned.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Safety and tolerability analyses:

Extent of exposure will be summarized. A by-subject listing of data on subject exposure to study drug will be produced. AEs will be tabulated according to the current version of MedDRA. Frequencies and percentages will be presented overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related AEs, AEs leading to discontinuation of study product applications, and SAEs will be completed. AE onset, severity, relationship to study product, action taken, and outcome will be listed by subject.

Each quantitative laboratory test will be summarized at every scheduled time point. The number of subjects with abnormal values based on values relative to the laboratory normal ranges will be summarized for each assessed time point. A listing of laboratory data for subjects with values out of the laboratory normal range will be provided.

Vital sign value and change from baseline at Week 8 for each vital sign parameter will be summarized using descriptive statistics. A listing of vital signs and a listing of change from baseline for vital signs will be provided.

ECG value and change from baseline at every scheduled time point for each ECG parameter will be summarized using descriptive statistics. The ECG will be evaluated by the investigator as “Normal”, “Abnormal, not clinically significant”, and “Abnormal, clinically significant”. A summary of ECG findings will be provided. Also, a listing of ECG values and a listing of ECG findings will be generated.

If applicable, liver event data will be listed.

Systemic exposure/Pharmacokinetic Analyses (Part A):

Plasma concentrations of GSK2981278 will be determined. For **Part A**, if the concentration data permits, the following PK parameters will be calculated: AUC(0-t), AUC(0-τ), Cmax, tmax, and half-life (t1/2), steady state assessments such as Cτ and R0.

Clinical effect analyses (Part B):

Mean percentage change in TPSS, PGA and PASI scores from baseline to each study visit will be summarized based on the per protocol analysis set.

The data may also be summarized using the following measures as needed:

- proportion of subjects who achieve a PGA score of 0 or 1 and a minimum 2-grade improvement from baseline to each study visit
- proportion of subjects with ≥50% improvement in PASI from baseline to each study visit
- change in PASI from baseline to each study visit

In addition, statistical comparisons may be made as necessary between GSK arm and the Vehicle arm for mean percentage change from baseline to Week 8 in terms of TPSS, PGA and PASI score.

9.4.2. Secondary Analyses

Secondary analyses will be the clinical effect analyses for **Part A**. Clinical effect data will be summarized using both the Observed Cases (OC) approach and the last observation carried forward (LOCF) approach if there are missing values.

Mean percentage change in TPSS, PGA and PASI scores from baseline to each study visit will be summarized based on the per protocol analysis set.

The data may also be summarized using the following measures as needed:

- proportion of subjects who achieve a PGA score of 0 or 1 and a minimum 2-grade improvement from baseline to each study visit
- proportion of subjects with ≥75% improvement in PASI from baseline to each study visit
- proportion of subjects with ≥50% improvement in PASI from baseline to each study visit
- change in PASI from baseline to each study visit

9.4.3. Other Analyses

Additional analyses may be performed as described in the RAP/SAP.

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

Prior to initiation of a site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH GCP and applicable country-specific regulatory requirements.

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 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
- 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 Part B 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

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He YW, Deftos ML, Ojala EW, Bevan MJ. RORγt, a novel isoform of an orphan receptor, negatively regulates Fas ligand expression and IL-2 production in T cells. *Immunity*1998;9(6):797-806.

Ivanov II. The orphan nuclear receptor RORγt directs the differentiation program of proinflammatory IL-17^{+} T helper cell. *Cell* 2006;126(6):1121-1133.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
cm^2	Centimeter squared
C_{max}	Maximum plasma concentration
CRF	Case report form
CV	Cardiovascular
ECGs	Electrocardiograms
eCRF	Electronic case report form
FNRP	Females of non-reproductive potential
FRP	Females of reproductive potential
FTIH	First time in humans
GCP	Good clinical practice
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
HPA	Hypothalamic-Pituitary-Adrenal
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	Independent ethics committee
IFN-γ	Interferon-gamma
INR	International normalized ratio
IRB	Institutional review board
kg	kilogram
m^2	meter squared
mAb	Monoclonal antibody
MALDI	Matrix Assisted Laser Desorption Ionization
Max	Maximum
MCH	Mean corpuscular hemoglobin

MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram
Min	minimum
mL	milliliter
mRNA	Messenger ribonucleic acid
msec	millisecond
ng	nanogram
NOAEL	No observed adverse effect level
PASI	Psoriasis area and severity index
PD	Pharmacodynamic
PGA	Physician's global assessment of improvement
PI	Prediction interval
PK	Pharmacokinetic
PP	Per protocol
PTS	Platform technology and science
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
RAP	Reporting and analysis plan
RBC	Red blood cell
RORγ	Retinoic acid receptor-related orphan receptor gamma
SAE	Serious adverse event
SAP	Statistical analysis plan
SRM	Study reference manual
Th-17	Type 17 helper T-cell
TPSS	Target plaque severity score
μg	microgram
ULN	Upper limit of normal
μM	micromolar
UV	Ultraviolet
WBC	White blood cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Body Surface Area

Assessment of body surface area with Psoriasis will be performed separately for four body surface regions: the head (h), the upper extremities (u), the trunk (t), and the lower extremities (l), corresponding to 10, 20, 30, and 40% of the total body area, respectively.

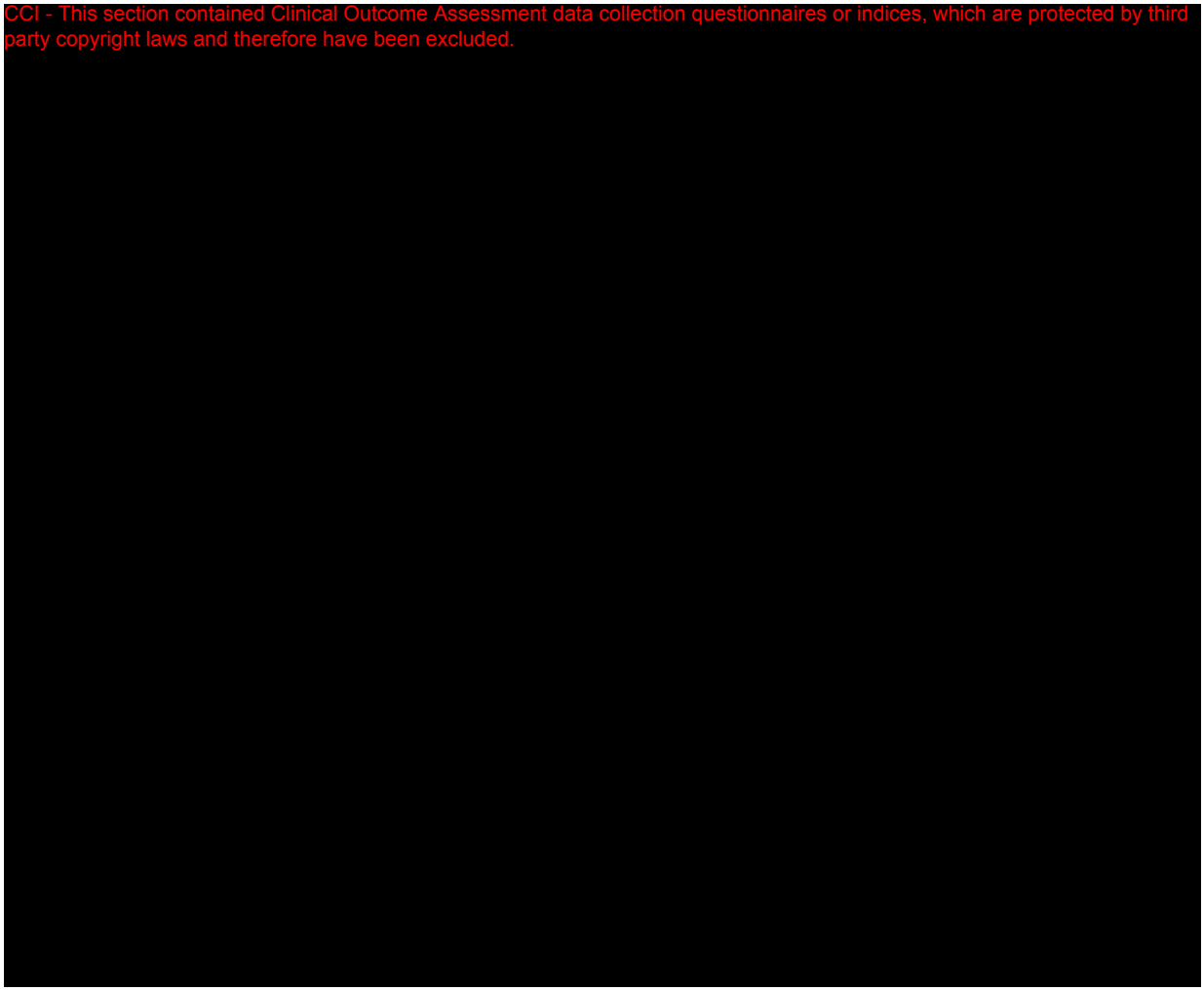
Body Region	Surface Area of Body Region
head (h)	10%
upper extremities (u)	20%
trunk (t)	30%
lower extremities (l)	40%

12.2.1. Reference

Finlay A.Y., Current Severe Psoriasis and the Rule of Tens. British J. of Dermatology. 2005;152:861-867.

12.3. Appendix 3: Physician Global Assessment (PGA)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



12.4. Appendix 4: Target Plaque Severity Score (TPSS)

Score	Scaling	Erythema	Induration
0 None	No evidence of scaling	No evidence of erythema; hyperpigmentation may be present	No elevation over normal skin
1 Slight	Occasional fine scale over less than 5% of the lesion	Faint erythema	Possible but difficult to ascertain whether there is a slight elevation above normal skin
2 Moderate	Fine scales predominate	Light red coloration	Slight but definite elevation, typically edges are indistinct or sloped
3 Marked	Coarse scales predominate	Moderate red coloration	Moderate elevation with rough or sloped edges
4 Very marked	Very thick tenacious scale predominates	Dusky to deep red coloration	Very marked elevation typically with hard sharp edges

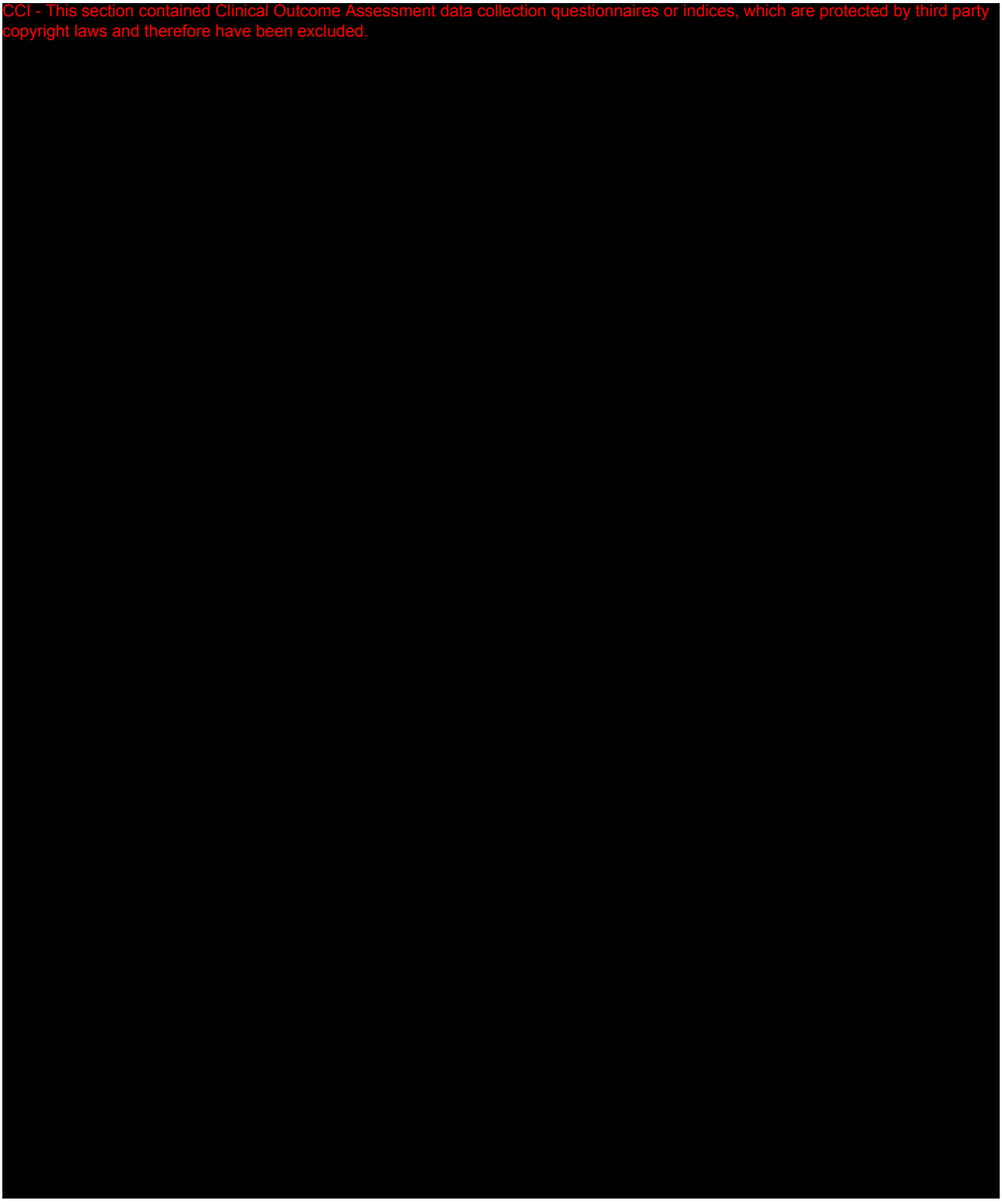
12.4.1. References

Menter A, Papp KA, Tna H, Tyring S, Wolk R, Buonanno M. Efficacy of tofacitinib, an oral janus kinase inhibitor, on clinical signs of moderate-to-severe plaque psoriasis in different body regions. J Drugs Dermatol 2014;13(3):252-256.

Ports WC, Khan S, Lan S, Lamba M, Bolduc C, Bissonnette R, Papp K. A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitiib in the treatment of chronic plaque psoriasis. Br J Dermatol 2013;169:137-145.

12.5. Appendix 5: Psoriasis Symptom Diary

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



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

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

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

Required Actions and Follow-up Assessments following ANY Liver Stopping Event	
Actions	**Follow-Up Assessments**
• **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 treatment and may continue subject in the study for any protocol specified follow-up assessments	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within 12 hours 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 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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
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	**<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]). Liver imaging (ultrasound, magnetic resonance, or computerized 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. 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.

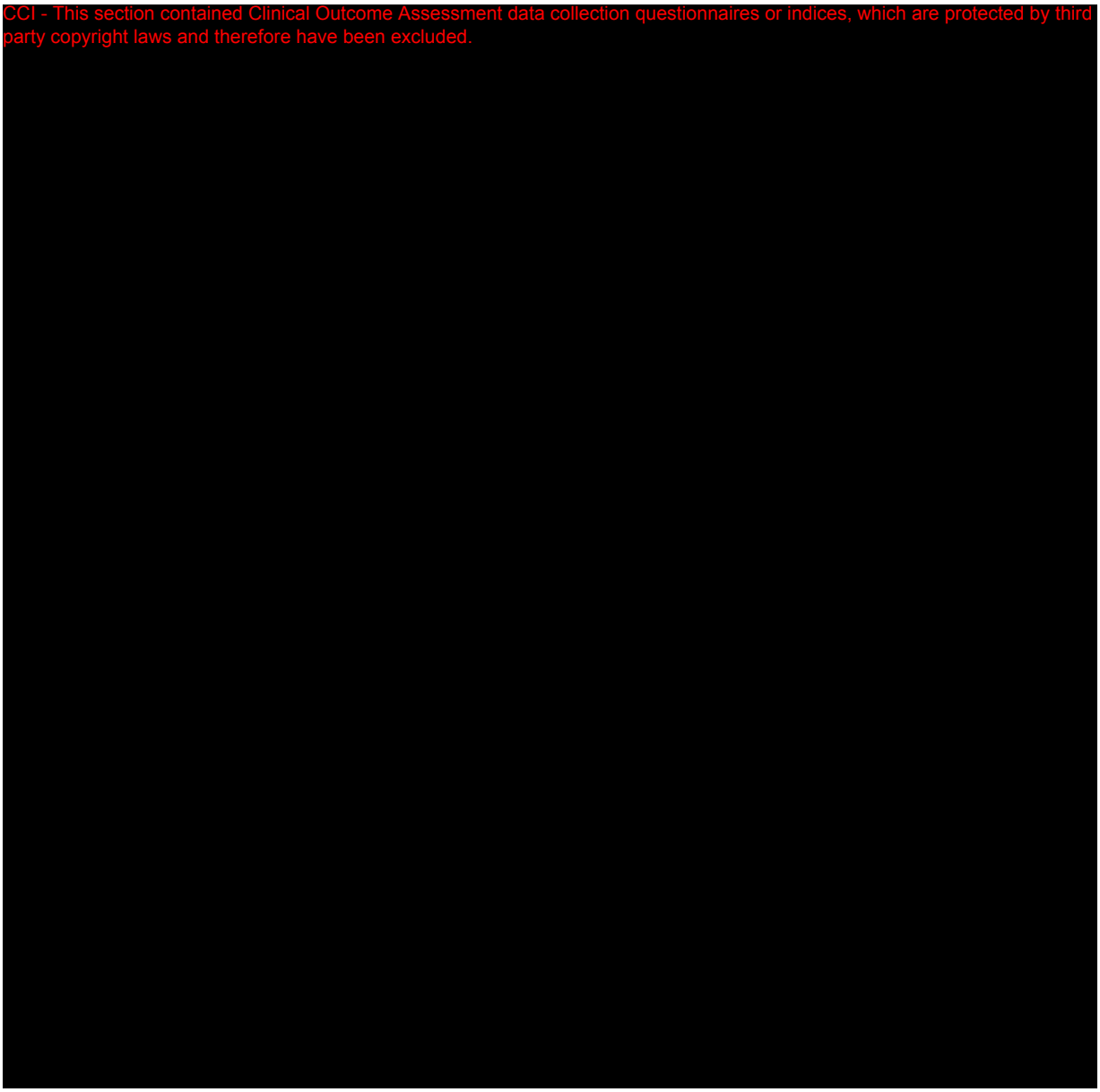
Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

12.6.1. Reference

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.

12.7. Appendix 7: Psoriasis Area and Severity Index (PASI)



12.8. Appendix 8: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.8.1. 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

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.

12.8.2. 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 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.

12.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.8.4. 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 Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes 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

12.8.5. 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.

12.8.6. 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 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.

12.9. Appendix 9: 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 8. 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 discontinue study medication or 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.

12.10. Appendix 10 - 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 GSK2981278 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).

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.

12.10.1. References

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. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.11. Appendix 11-Protocol Changes

Protocol Amendment 1: 13 December 2016
Applicable to all subjects.

Section	Original Text	Changes	Rationale
Medical Monitor/Sponsor Information Page	PPD PPD 1250 South Collegeville Rd, Collegeville, PA 19426 ~~(UP4300)~~	PPD PPD 1250 South Collegeville Rd, Collegeville, PA 19426 (**UP1410**), **USA**	Updated primary medical monitor's fax number and address
1 and 3	Identification of any compound-derived metabolite(s) from plasma and urine ~~To evaluate the urinary elimination of GSK2981278 after topical application in subjects with plaque psoriasis/Urine concentration of GSK2981278~~	Identification of any compound-derived metabolite(s) from plasma and urine **and if possible estimation of relative amounts of drug related material** Removed the exploratory urinary elimination evaluation objective and corresponding endpoint from Part A Objective(s) and Endpoint(s)	Clarification that urine sample is collected for analysis of metabolites and GSK2981278 for structure elucidation and not for absolute measurement of GSK2981278 in urine
7.1	Pharmacokinetics Urine sample 0-10h pool ~~Three~~ aliquots to be made for ~~parent drug analysis,~~ metabolite analysis and urinalysis. See Section 7.6.2. N/A	Pharmacokinetic Urine sample **for metabolite analysis** **Pre-dose urine on Day 1**, 0-10h pool **Two** aliquots to be made for metabolite analysis and urinalysis. See Section 7.6.2 Removed urine PK sample collection at Day 29	
7.6.2	Urine samples for ~~PK~~ analysis of GSK2981278 and related metabolite(s)	Urine samples for analysis of GSK2981278 and related metabolite(s)	
4.1	... reduction of 40% or greater in TPSS and ...	... reduction of 40% or greater in TPSS **from baseline** and ...	Clarification

Section	Original Text	Changes	Rationale
4.6.1	N/A	Added additional information related to the risk of 'Skin irritation or allergic reaction to GSK2981278 or to components of its vehicle': Line 6-line 13 added to Summary of Data/Rational for Risk and line 5-line 9 to Mitigation Strategy.	More complete risk assessment of GSK2981278
7.1	Screening Day ~~-27 to 0~~	Screening Day **-28 to -1**	Consistency with Part B Time and Events Table
7.2	N/A	Added vital signs assessment at the Screening Visit	Aligned with other safety assessments (ECG, labs, etc.)
7.2	N/A	Added "**(including prior therapy for psoriasis)**" to Prior and Concomitant Medication Review description	Consistency with Time and Events Table Part A description
7.5.5	...in supine ~~or semi-supine~~ position...	...in **seated** or supine position...	Consistency with description in Time and Events Table
7.7.1	~~All samples will be retained for a maximum of 15 years after the last subject completes the trial.~~	Added "**Details of skin sample storage are provided in the SRM.**"	Correction and more appropriate placing of information
7.9.1 12.5 Appendix 5	~~In addition to the 16 questions in the published instrument, 6 questions have been added to assess the severity and bother of skin flaking, dryness and bleeding.~~ N/A	Reference to 6 additional questions in Psoriasis Symptom Diary removed Removed questions 17-22 from the Psoriasis Symptom Diary	Novartis did not approve modified PSD
9.2.1	~~Fisher's Exact Test~~	**2-sample t test**	Correction
Throughout the protocol			Correction of typographical errors