A Phase I Trial to Evaluate Safety and Efficacy of Topically Applied GSK2981278 Ointment in a Psoriasis Plaque Test.
SPONSOR SIGNATORY

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<tr>
<th>Role</th>
<th>Name</th>
<th>Day Time Phone Number and email address</th>
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<td>Primary Medical Monitor</td>
<td>PPD</td>
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<td>bioskin GmbH, Burchardstrasse 17, 20095 Hamburg, Germany</td>
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<td>SAE contact information</td>
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</tbody>
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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 2015-002614-72.
INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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.

<table>
<thead>
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<th>Investigator Name:</th>
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<td>Investigator Address:</td>
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<td>Investigator Phone Number:</td>
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<td>Investigator Signature</td>
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1. PROTOCOL SYNOPSIS FOR STUDY 201465

Rationale

This is the first study to administer GSK2981278 to patients with psoriasis. This proof-of-concept study will evaluate the safety, tolerability and initial efficacy of a range of concentrations of GSK2981278 ointment with repeated topical applications in adult subjects with psoriasis. Results of this study will provide the first clinical information on the drug’s safety and efficacy in psoriasis and inform the selection of concentration of GSK2981278 ointment to be evaluated in subsequent clinical studies.

Objective(s)/Endpoint(s)

<table>
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<th>Objectives</th>
<th>Endpoints</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>• To evaluate the safety and tolerability of topically applied GSK2981278 in subjects with plaque psoriasis.</td>
<td>• Incidence and nature of adverse events (AE).</td>
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<td></td>
<td>• Change from baseline in clinical laboratory parameters, vital signs, electrocardiogram (ECG).</td>
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<td>• The reduction in infiltrate thickness of the psoriatic plaque(s) from baseline using 22-MHz sonography measurement.</td>
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<tr>
<td>• To evaluate the efficacy of topical formulation strengths of GSK2981278 ointment in patients with psoriasis.</td>
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<tr>
<td><strong>Secondary</strong></td>
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<tr>
<td>• To evaluate the improvement of psoriatic lesions following application of GSK2981278 ointment.</td>
<td>• Clinical assessment score using a 5-point scale.</td>
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<tr>
<td><strong>Exploratory</strong></td>
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<tr>
<td>• To evaluate the pharmacodynamic (PD) effects of topical GSK2981278 in psoriasis plaques.</td>
<td>• messenger ribonucleic acid (mRNA) biomarkers in skin biopsy samples.</td>
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Overall Design

• This is a Phase 1, single-center, randomized, vehicle- and positive-controlled, subject- and evaluator- blind proof-of-concept trial in subjects with chronic plaque type psoriasis.
All subjects will receive all treatments on stable plaque(s) on the upper extremities, thighs and/or trunk for intra-individual comparison with random assignment of the treatments to the test fields within the identified plaque(s).

A blinded evaluator (an investigator or designee) will perform the measurements and assessments whereas an unblinded study staff member (not an evaluator) will perform biopsy collection.

### Treatment Arms and Duration

Screening will occur within 14 days preceding the Day 1 visit. Study visits will occur from Day 1 through Day 19 for applications of study treatments and evaluations of dermal reactions. A total of 16 applications will be made over 19 days. Day 19 will be the end of study visit for those subjects who do not consent to biopsy. A follow-up visit will occur at Day 27 (±2) for those subjects consenting to biopsies. The total duration of study participation for those subjects who do not consent to biopsy will be approximately 33 days. The total duration of study participation for those subjects consenting to biopsies will be approximately 41 days.

All subjects will have a set of 6 randomized test fields on identified stable plaque(s) on the upper extremities, thighs, and/or trunk, to be treated once-daily (except Days 7 and 14) over 19 days under semi-occlusive conditions (covered by an adhesive non-woven fabric) with the following study products:

- GSK2981278 0.03% ointment
- GSK2981278 0.1% ointment
- GSK2981278 0.8% ointment
- GSK2981278 4% ointment
- Vehicle to match GSK2981278 ointment (without active ingredient)
- Betamethasone valerate 0.1% cream (positive control)

The same study products will be applied in all subjects. There will be no subdivision into separate dosing groups.

### Type and Number of Subjects

This study will be conducted in male subjects and female subjects of non-reproductive potential (FNRP) with chronic stable plaque type psoriasis.

Approximately 15 subjects will be randomized such that at least 13 evaluable subjects complete the study. Skin biopsies will be collected from at least 8 consenting subjects for PD biomarker evaluation. Additional subjects may need to be randomized in order to achieve 8 consenting subjects for biopsies.

### Analysis

The primary efficacy endpoint is the area under the time curve (AUC) of change in infiltrate thickness using the linear trapezoidal rule over the period starting with Day 1 up
to Day 19. Missing data will be handled by the last observation carried forward (LOCF) approach. The AUC will be analyzed using a mixed-model repeated-measures (MMRM) analysis including treatment. The treatment will be treated as repeated measures within the same subject. Pair-wise treatment comparisons will be performed. The primary comparison is between each active dose and the vehicle ointment.

In addition, for each post-baseline assessed time point, the reduction in infiltrate thickness of the psoriatic plaque(s) from baseline will be summarized using both the Observed Cases (OC) approach and the LOCF approach. Pair-wise treatment comparisons will be performed.

Clinical efficacy assessment using a 5-point scale will be evaluated for each post-baseline assessed time point. The ordinal clinical score and the cumulative total score will be presented by descriptive statistics. Additionally, frequency counts will be provided for the clinical scores.

Safety analyses include a summary of extent to exposure, summaries of AEs, laboratory data, vital signs data, and ECG data. Safety data will be listed as well.

Gene expression of biomarkers from skin punch biopsy sample(s) will be analyzed.
2. INTRODUCTION

GSK2981278 is a highly potent and selective inverse agonist of retinoic acid receptor-related orphan receptor gamma (RORγ) that is under development for topical treatment of plaque type psoriasis suitable for topical therapy.

2.1. Study Rationale

This is the first study to administer GSK2981278 to patients with psoriasis. This proof-of-concept study will evaluate the safety, tolerability and initial efficacy of a range of concentrations of GSK2981278 ointment with repeated topical applications in adult subjects with psoriasis. Results of this study will provide first clinical information on the drug’s safety and efficacy in psoriasis and inform the selection of concentration of GSK2981278 ointment to be evaluated in subsequent clinical studies.

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 [De Korte, 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 T-helper 17 (Th17) 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 contribute to epidermal hyperproliferation and skin barrier disruption. Increased numbers of IL-17 positive T cells and higher IL-17A messenger ribonucleic acid (mRNA) 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 3 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., Tumour necrosis factor (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 (LBD) as RORγt [He, 1998]. Compounds targeting RORγ is expected to modulate the activity of RORγt as well. Therefore, local delivery of selective RORγ inverse agonist GSK2981278 to lesional skin of psoriasis 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 2015N240000_00; GSK2981278 Investigator’s Brochure (IB)].

3. OBJECTIVE(S) AND ENDPOINT(S)

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</table>
Objectives | Endpoints
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**Exploratory**

- To evaluate the pharmacodynamic (PD) effects of topical GSK2981278 in psoriasis plaques.
- mRNA biomarkers in skin biopsy samples.

### 4. STUDY DESIGN

#### 4.1. Overall Design

<table>
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<tr>
<th>Sign Visit</th>
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<th>Biopsies</th>
<th>Follow-up Visit*</th>
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<tr>
<td>Screening Visit</td>
<td>Days -14 to -1</td>
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<td>Day 27</td>
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<td>ICF</td>
<td></td>
<td></td>
<td>Day 18</td>
<td></td>
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<tr>
<td>Dosing begins</td>
<td>Day 19</td>
<td>Day 1</td>
<td>Day 19</td>
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*Follow-up visit (Day 27) is only for subjects consenting to biopsy. All other subjects complete the study at Day 19.*

This is a Phase 1, single-center, randomized, vehicle- and positive- controlled, subject- and evaluator- blind proof-of-concept trial in subjects with chronic plaque type psoriasis. All subjects will receive all treatments on stable plaque(s) on the upper extremities, thighs and/or trunk for intra-individual comparison with random assignment of the treatments to the test fields within the identified plaque(s). A blinded evaluator (an investigator or designee) will perform the measurements and assessments whereas an unblinded study staff member (not an evaluator) will perform biopsy collection.

#### 4.2. Treatment Arms and Duration

Screening will occur within 14 days preceding the Day 1 visit. Study visits will occur from Day 1 through Day 19 for applications of study treatments and evaluations of dermal reactions. A total of 16 applications will be made over 19 days. Refer to Section 6.3.1 for discontinuation and withdraw criteria. Day 19 will be the end of study visit for
those subjects who do not consent to biopsy. A follow-up visit will occur at Day 27 (±2) for those subjects consenting to biopsies. The total duration of study participation for those subjects who do not consent to biopsy will be approximately 33 days. The total duration of study participation for those subjects consenting to biopsies will be approximately 41 days.

All subjects will have a set of 6 randomized test fields on identified stable plaque(s) on the upper extremities, thighs, and/or trunk, to be treated once-daily (except Days 7 and 14) over 19 days under semi-occlusive conditions (covered by a be covered an adhesive non-woven fabric) with the following study products:

- GSK2981278 0.03% ointment
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- GSK2981278 0.8% ointment
- GSK2981278 4% ointment
- Vehicle to match GSK2981278 ointment (without active ingredient)
- Betamethasone valerate 0.1% cream (positive control)

The same study products will be applied in all subjects. There will be no subdivision into separate dosing groups. Refer to Section 6.2 and Section 6.3 for information regarding assignment of treatment and manner of treatment.

4.3. Type and Number of Subjects

This study will be conducted in male subjects and female subjects of non-reproductive potential (FNRP) with chronic stable plaque type psoriasis.

Approximately 15 subjects will be randomized such that at least 13 evaluable subjects complete the study. Skin biopsies will be collected from at least 8 consenting subjects for PD biomarker evaluation. Additional subjects may need to be randomized in order to achieve 8 consenting subjects for biopsies.

If subjects prematurely discontinue the study, additional replacement subjects may be randomised at the discretion of the sponsor in consultation with the investigator. Subjects who discontinue for safety reasons will not be replaced.

4.4. Design Justification

The objective of this trial is to explore the safety, tolerability and efficacy of GSK2981278 ointment after repeated topical applications in small test fields within plaque(s) in psoriatic subjects. The psoriasis plaque test (PPT) is a standardized model allowing for intra-individual comparison of the safety and efficacy of multiple drugs and/or formulations in subjects with stable plaque psoriasis. PPT is often used as an initial proof-of-concept trial in the early development of topical drugs and can use occlusive, semi- or non-occlusive applications.
In the original test design described by Dumas and Scholtz [Dumas, 1972], the efficacy of corticosteroids for treatment of plaque-type psoriasis was evaluated clinically following standardized occlusive application over several days. Meanwhile biophysical measurement methods have been used in the PPT to objectively measure the inflammatory alterations accompanying psoriasis, greatly improving the sensitivity of the test [Bangha, 1996; Fluhr, 2009]. The clinical relevance of this study design has been established based on the experience translating the efficacy results to later phase trials [Bangha, 1996].

This study includes semi-occlusive applications to allow for testing conditions reflective of a clinical application regimen. In this trial the study products will be administered once daily (except Days 7 and 14) in a semi-occluded application manner, over a period of 19 days. Areas to be treated are selected at the Day 1 visit based on uniformity of the sonographic measurements within the lesion(s). The vehicle is included in one test field in order to provide vehicle-related safety and efficacy information. As a positive control a marketed drug (betamethasone valerate 0.1% cream) is included in an additional test field. Approximately 24 ± 2 hours after application, the test sites will be evaluated by sonographic measurement and with clinical scoring on days 4, 8, 15, and 19. A new set of dressings will be applied to the same randomized test sites after evaluation. The final evaluations will be performed on Day 19, at approximately 24 ± 2 hours after final drug application on Day 18. Conditions under which application of a study product may be discontinued are described in Section 6.3.1. Based on predicted low systemic drug levels in this study and the fact that multiple concentrations of GSK2981278 will be applied to each subject simultaneously, pharmacokinetic (PK) assessments would provide at best only qualitative information. Therefore, PK information will not be collected in this study.

A 19 day treatment duration was selected based on historical PPT design data coupled with the feasibility of daily clinic visits and the goal to reduce patient burden. The treatment duration of 19 days under semi-occlusive conditions should allow sufficient time for drug penetration and activity. Furthermore, this duration may capture separation of response to the range of GSK2981278 doses, therefore more clearly identifying a dose-response relationship. Sonographic measurements and clinical scoring will allow for evaluation of improvement in psoriatic plaques over 19 days. Changes in gene expression of biomarkers are expected to be observed within the timeframe set up for this study based on gene expression changes observed at 14 days post-treatment with a systemic IL-17a mAb [Russell, 2014].

Since the most important guide to potential clinical efficacy in psoriasis in this study design is the extent to which the inflammatory infiltrate in the psoriatic plaque resolves, high-frequency 22-MHz skin ultrasound for the evaluation of the thickness of the inflammatory infiltration will be used as the primary efficacy assessment method. The inflammatory infiltrate is seen as a clearly definable Echo Lucent Band (ELB) below the entrance echo [Fluhr, 2009]. Thus, the objective sonographic measurement of the thickness of the ELB at 22-MHz is a relevant outcome. At baseline (before beginning of treatment) the clinical condition in the test fields of individual subjects has to be comparable.
A total of four 3mm punch biopsies will be collected at the end of the study from a subset of consenting subjects. One biopsy will be collected from a non-lesional area, one from a lesional untreated area, another from the vehicle-treated test field, and one biopsy from the 4% GSK2981278-treated test field. At the time of the first biopsy collection the unblinded Investigator will assess all available tolerability and safety data from the test field treated with 4% GSK2981278. If data from the 4% GSK2981278-treated test field reveals safety concerns, the Investigator may decide to collect the biopsy from a test field treated with a lower concentration of GSK2981278. The sponsor should be notified of this decision. Exploratory pharmacodynamic assessment of skin biopsies will be evaluated using gene expression analysis of relevant biomarkers reported to be modulated by GSK2981278 including, but not limited to, IL-17A, IL-17F, DEFB4A, IL-19, IL-36, CCL20, S100A7a, IL-8, and Krt6A. The analysis of these PD biomarkers will allow for investigation of target engagement of GSK2981278 in the study.

4.5. Dose Justification

In this study, the anti-psoriatic activity of GSK2891278 will be evaluated in a psoriasis plaque test (microplaque assay). In order to evaluate the dose-response, 4 different concentrations of GSK2981278, 0.03%, 0.1%, 0.8% and 4% will be applied. Each subject will receive all 4 concentrations of GSK2981278 ointment, along with a positive control, and vehicle ointment once daily (except Days 7 and 14) for 19 days.

Data from ex vivo target engagement studies and repeat dose toxicity studies in rat and minipig were used to select the doses of GSK2891278 ointment for this study. In ex vivo human skin following single topical application of GSK2981278 in the proposed clinical formulation at concentrations ranging from 0.01 to 4%, a potent dose-dependent inhibition of Th17 signature cytokines mRNA levels were observed with effect reaching plateau after 0.1% concentration (Figure 1). Based on this data, concentration ranging from 0.03% to 4% will be considered in the early phase clinical trials. Four concentrations of relatively even spread across the dose response curve in this range are selected for the PPT study due to the limit on the number of test fields.
GSK2981278 has been evaluated in repeat dose toxicity studies following dermal administration for up to 7 days in rats and rabbits and 28 days in minipigs; following oral administration for up to 28 days in rats, 7 days in rabbits, and 28 days in minipigs; and following subcutaneous administration for up to 7 days in rabbits.

The no adverse effect levels (NOAELs) established for systemic effects in the oral 28 day rat and dermal 28 day minipig toxicity studies were 200 mg/kg/day and 400/300 mg/kg/day male/female, respectively. The end of study area under the curve (AUC) and maximum concentration ($C_{\text{max}}$) values at 200 mg/kg/day in rats were 437 ng.h/mL (males) and 4700 ng.h/mL (females) and 106 ng/mL (males) and 3030 ng/mL (females), respectively. In minipigs, the end of study AUC and $C_{\text{max}}$ values at 400/300 mg/kg/day were 1054 ng.h/mL and 350 ng/mL (gender average mean), respectively.

The exposures at the proposed doses were predicted using the mean predicted volume of distribution of 175.9 L and mean expected clearance of 52.5 L/hr. A conservative prediction of systemic exposure to GSK2981278 following topical application of 0.03 to 4% concentrations to 1.13 cm$^2$ area each as proposed in this study suggests that the safety margin against the NOAEL identified are >1000 fold for both AUCss and Cmaxss and supports evaluation of GSK2981278 ointment.

Table 1 represents the predicted exposure and safety covers for clinical evaluation of GSK2891278 [FDA, 2005; CHMP, 2007]. Findings from in vivo pharmacology and toxicology studies with GSK2891278 have provided reasonable assurance that there are no undue or unforeseen risks for the first administration of GSK2891278 to humans at the dose levels proposed in this study.
Table 1  
Dose range and exposure predictions of GSK2891278 at steady state following 15cm$^2$ area of application

<table>
<thead>
<tr>
<th>Dose (Formulation strength)</th>
<th>Flux (dermis) (ng/hr/cm$^2$) Mean (90%CI)</th>
<th>Cmax Predicted Css (pg/mL) Mean (90%CI)</th>
<th>Safety Cover Cmax (males) = 106 ng/mL Predicted AUCss (pg*hr/mL) Mean (90%CI)</th>
<th>Safety Cover AUC(males) = 437 ng*hr/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03%</td>
<td>4.82 (1.3-11.2)</td>
<td>1.38 (0.38-3.21)</td>
<td>76986</td>
<td>33.04 (9.05-77.06)</td>
</tr>
<tr>
<td>0.1%</td>
<td>11.41 (4.7-24.4)</td>
<td>3.26 (1.34-6.96)</td>
<td>32528</td>
<td>78.21 (32.13-167.12)</td>
</tr>
<tr>
<td>0.8%</td>
<td>34.81 (23.0-54.3)</td>
<td>9.95 (6.58-15.51)</td>
<td>10658</td>
<td>238.70 (157.83-372.25)</td>
</tr>
<tr>
<td>4%</td>
<td>49.25 (40.1-59.5)</td>
<td>14.07 (11.45-17.01)</td>
<td>7533</td>
<td>337.70 (274.73-408.30)</td>
</tr>
</tbody>
</table>

In this study the planned total surface area (four active concentrations at four test field) will be ~5cm$^2$. Average concentration based on four active strength used (0.03, 0.1, 0.8 and 4%) is ~1.2%. Application of ~1.2% concentration over ~5cm$^2$ area provides a safety cover of >4500 fold for AUC and >20000 fold for Cmax at steady state.

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

<table>
<thead>
<tr>
<th>Potential Risk of Clinical Significance</th>
<th>Summary of Data/Rationale for Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin irritation or allergic reaction to GSK2981278 or to components of its vehicle.</td>
<td>GSK2981278 was not a contact sensitizer in the mouse local lymph node assay, and it was not an eye irritant in the bovine corneal opacity and permeability assay. 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].</td>
<td>The skin will be evaluated for signs of skin reaction and allergic reaction. Subjects will be informed of the sulphonamide nature of the compound via informed consent and be monitored daily, except on Days 7 and 14, for signs of allergic reactions during the treatment period. Subjects will not be excluded from the trial solely based on a history of sulphonamide allergy. Subjects with a known or suspected intolerance to the components of GSK2981278 vehicle will be excluded. If needed, study treatment may be held and an appropriate topical or systemic treatment may be provided.</td>
</tr>
<tr>
<td>Systemic reactions including but not limited to end organ toxicity.</td>
<td>The principal test article-related findings observed in repeat dose dermal and oral toxicity studies with GSK2981278 occurred in skin and thymus, with findings in the</td>
<td>Relevant first time in human (FTIH) laboratory tests as well as periodic ECGs and baseline and end of study vital signs will be reviewed.</td>
</tr>
<tr>
<td>Potential Risk of Clinical Significance</td>
<td>Summary of Data/Rationale for Risk</td>
<td>Mitigation Strategy</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------------------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
| heart that were considered to be of uncertain relationship to treatment.  
GSK2981278 did not produce test-article related 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 IC\textsubscript{25} of 2.2 µM (1.02 µg/mL).  
The risk for any end-organ toxicity is considered low due to the limited predicted systemic exposure and large safety margins for this study. | Serious Adverse Events (SAEs)/AEs will be collected and reviewed.  
If needed, study treatment may be held and an appropriate treatment may be provided. | |
| Reproductive and developmental toxicity | Embryofetal development and female fertility studies have not been conducted with GSK2981278. Data from the literature suggest that the intended drug-target interaction, reduction in Th17 cells, could potentially impact implantation and maintenance of normal pregnancy. However, GSK2981278 at doses up to 200 mg/kg/day for 28 days did not have an effect on activation of Th17 and regulatory T cells in female rats and multiples of human exposure | Only females of non-reproductive potential will be enrolled in the FTIH study.  
In addition, male subjects will be required to use condoms unless they have had a prior vasectomy. |
<table>
<thead>
<tr>
<th>Potential Risk of Clinical Significance</th>
<th>Summary of Data/Rationale for Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening of psoriasis symptoms</td>
<td>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.</td>
<td>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 may be able to use alternate treatments for their psoriasis.</td>
</tr>
<tr>
<td>Punch biopsy</td>
<td>Local bleeding and bruising, pain, infection, or allergic reaction (e.g. to an anaesthetic agent) may occur. Scarring may occur at the biopsy site.</td>
<td>Staff performing the procedures will be adequately trained and subjects will be informed about potential risks. Local anesthesia will be used prior to obtaining biopsies. Proper wound care (e.g. application of pressure, antibiotic ointment, dressing) will be provided as needed and subjects will be checked for wound healing at the follow-up visit. Pain medication (i.e., acetaminophen or paracetamol) will be allowed.</td>
</tr>
</tbody>
</table>
4.6.2. Benefit Assessment

Subjects may benefit from the overall health assessment conducted while participating in this study. Subjects participating in the study will contribute to the process of developing a novel anti-inflammatory agent for the topical treatment of plaque psoriasis.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the risk minimization measures for subjects participating in this study, the potential risks identified in association with exposure to GSK2981278 are justified by the anticipated benefits that may eventually be afforded to subjects with chronic 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.

The subjects will be selected according to defined inclusion and exclusion criteria. 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 ICH-GCP guideline.

5.1. Inclusion Criteria

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

<table>
<thead>
<tr>
<th>AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 18 years of age and above, at the time of signing the informed consent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Subjects with stable plaque psoriasis for ( \geq 6 ) months, as confirmed by the subject.</td>
</tr>
<tr>
<td>3. Up to three plaque area(s) sufficient for six test fields. The target lesion(s) should be on the trunk, upper extremities or thighs (excluding hands and skin folds); psoriatic lesion(s) on the knees or elbows are not to be used as a target lesion. It is recommended, but not required, that all selected plaques are symmetrical in location, size and clinical characteristics.</td>
</tr>
<tr>
<td>4. Plaques to be treated should have a comparable thickness of the ELB (as a surrogate for the psoriatic infiltrate thickness) of at least 200( \mu )m on Day 1.</td>
</tr>
</tbody>
</table>
5. **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 after the last dose of study medication.

a. Vasectomy with documentation of azoospermia.

b. Male condom

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

6. **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),

**Post-Menopause criteria**

- 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, are required to use a highly effective method to avoid pregnancy, as outlined in the protocol (Appendix 4). Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. 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 resume use of HRT during the study without use of a highly effective method to avoid pregnancy.

### INFORMED CONSENT

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

### 5.2. Exclusion Criteria

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. 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%).

2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

3. QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block. The QTc is the QT interval corrected for heart rate according to Bazett’s formula (QTcB), and/or machine-read. The QTc should be based on single QTc values of ECG obtained over a brief recording period.

4. Any condition that, in the judgement of the investigator, would put the subject at unacceptable risk for the participation in the trial.

5. 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).

6. Clinically-relevant skin disease, other skin pathologies, or a history of skin cancer, that may, in the opinion of the investigator, contraindicate participation or interfere with test field evaluations.

7. History of malignancy within 5 years prior to dosing, except adequately treated non-invasive cancer of the skin (basal or squamous cell).

8. Psoriasis other than plaque variants.
CONCOMITANT MEDICATIONS

9. Use of prohibited concomitant medications or products within the defined washout periods before the Day 1 visit and during the trial (see Section 6.11.2).

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. Contraindications according to summary of product characteristics of the active positive control.

12. 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

13. 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.


15. A positive test for human immunodeficiency virus (HIV) antibody.

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: 30 days, 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 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 or inability to understand the trial and give adequately informed consent.

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 any SAEs.

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

5.4. Withdrawal/Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. The reason for a subject’s premature discontinuation from the study must be fully documented in the source documents and the electronic case report form (eCRF).

Subjects who withdraw early from the study should complete the Day 19 visit assessments (refer to Section 7.1) except for biopsy collection.

Criteria for study treatment withdrawal or discontinuation of an individual subject from the clinical study may include:

- Sponsor terminates the study.
- Subject lost to follow-up.
- Subject withdraws consent.
- Protocol deviation.
- Investigator discretion.
- Subject experiences a(n) SAE/AE that is considered to be related to study drug or study procedures and is severe enough in nature to warrant treatment discontinuation.
- Refer to Section 6.3.1 for additional criteria for discontinuing study treatments.

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”.

5.4.1. Liver Chemistry Stopping Criteria

Study treatment will be discontinued for a subject if liver chemistry stopping criteria are met; *NB – this protocol will not use the increased monitoring criteria listed below. Therefore, if the subject meets liver stopping criteria outlined below, study treatment will be discontinued:

**Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm**

- **If subject to be monitored weekly must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**

  ![Liver Chemistry Stopping Criteria Diagram](image)

  - **Continue Study Treatment**
    - ALT ≥ 3xULN
    - No
    - Yes
      - Plus Bilirubin ≥ 2x ULN (>35% direct) or plus INR > 1.5, if measured*
        - Possible Hy’s Law
    - No
    - Yes
      - ALT ≥ 5xULN
      - No
        - Symptoms of liver injury or hypersensitivity
        - No
          - ALT ≥ 3xULN
          - Persist for 4 weeks or stopping criteria met
        - Yes
          - ALT ≥ 3xULN
          - Persist for 4 weeks or stopping criteria met
      - Yes
        - ALT ≥ 3xULN
        - Yes
          - Continue Study Treatment
        - No
          - Discontinue Study Treatment

- **Discontinue Study Treatment**
  - **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
  - **Report as an SAE if possible Hy’s Law case: ALT ≥ 3xULN and Bilirubin ≥ 2x ULN (>35% direct) or INR > 1.5, if measured**

  *INR value not applicable to subjects on anticoagulants

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

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 all subjects to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.

- For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
- Once the QT correction formula has been chosen for a subject’s eligibility, the same formula must continue to be used for that subject for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.

The QTc should be based on single QTc values of an electrocardiogram obtained over a brief (e.g., 5-10 minute) recording period.

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

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

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

<table>
<thead>
<tr>
<th>Baseline QTc with Bundle Branch Block</th>
<th>Discontinuation QTc with Bundle Branch Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 450 msec</td>
<td>&gt; 500 msec</td>
</tr>
<tr>
<td>450 – 480 msec</td>
<td>≥ 530 msec</td>
</tr>
</tbody>
</table>

5.5. Subject and Study Completion

For subjects consenting to biopsies, a completed subject is one who has completed all phases of the study including the Day 27 (± 2) follow-up visit. For subjects not consenting or withdrawing consent to biopsies, a completed subject is one who has completed all study visits, including the Day 19 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.

<table>
<thead>
<tr>
<th>Study Treatment</th>
<th>Product name: GSK2981278</th>
<th>Vehicle</th>
<th>Betamethasone valerate 0.1% (positive control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation description:</strong></td>
<td>GSK2981278 Ointment is supplied as a white to off-white ointment containing GSK2981278A drug substance at 0.03% w/w, 0.1% w/w, 0.8% w/w, and 4% w/w for topical administration.</td>
<td>GSK2981278 Vehicle is supplied as a white to off-white ointment for topical administration.</td>
<td>Betnesol™-V containing 0.1% betamethasone valerate is supplied as a cream for topical administration.</td>
</tr>
<tr>
<td><strong>Dosage form:</strong></td>
<td>Ointment</td>
<td>Ointment</td>
<td>Cream</td>
</tr>
<tr>
<td><strong>Unit dose strength(s)/Dosage level(s):</strong></td>
<td>0.03%</td>
<td>0%</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Topical</td>
<td>Topical</td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Dosing instructions:</strong></td>
<td>Apply approximately 200 µL to the assigned test field once daily.</td>
<td>Apply approximately 200 µL to the assigned test field once daily.</td>
<td>Apply approximately 200 µL to the assigned test field once daily.</td>
</tr>
<tr>
<td><strong>Physical description:</strong></td>
<td>The product is packaged into white aluminium tubes.</td>
<td>The product is packaged into white aluminium tubes.</td>
<td>The product is packaged into tubes.</td>
</tr>
</tbody>
</table>

#### 6.2. Assignment of Treatments to Test Sites and Randomization

Upon signature of informed consent each subject receives a screening number. Subjects meeting the eligibility criteria will receive their randomization number on Day 1. Once a randomization number has been assigned to a subject, it should not be reassigned to any other subject.
All subjects will receive the same treatments. There will be no subdivision into treatment groups. The 4 concentrations of GSK2981278 ointment (0.03%, 0.1%, 0.8%, and 4%) will be assigned the codes A, B, C, and D. The vehicle and positive control will be assigned the codes E and F, respectively.

The test fields will be numbered with 1, 2, 3, 4, 5, and 6 beginning with the uppermost or most proximal site on the left from the investigator's view. Fields along the same line will be numbered left to right.

For each subject a permutation of the treatment codes A to F will be randomly assigned. The treatment code listed first in the respective permutation will be assigned to test field 1, the second to test field 2, etc.

A randomization list will be generated by the CRO and kept in the trial master file in a sealed envelope.

6.3. Manner of Treatment

Individual treatment code templates reflecting the borders of the plaques and the location of the test fields will be prepared for each randomization number for use at the clinical site. The study nurse can use the template as a guide for study product application.

Approximately 200 μL of each of the six study treatments will be topically applied to test fields (approximately 1.1 cm²) under semi-occlusive conditions. Six test fields will be treated in all subjects. The distance between the test fields must be at least 1.5 cm. This distance is sufficient to exclude interactions between neighboring test fields. Altogether, 16 topical applications will be performed once daily (except Days 7 and 14) over a 19 day study period.

The study treatments will be applied in holes punched in a self-adhesive hydrocolloid dressing (Varihesive E (Convatec), Munich, Germany). The hydrocolloid dressing will be fixed on the skin with adhesive patches (Fixomull (BSN medical), Hamburg, Germany, or comparable) containing the same holes for the study treatments like the hydrocolloid dressing. The test fields will be covered semi-occlusively with an adhesive non-woven fabric (Fixomull (BSN medical), Hamburg, Germany).

All study products will be prepared, applied, and removed at the study center by a trained study nurse not involved in measurements and assessments. Details of the exact time of the applications and assessments (date, hour, minute) will be documented in the source documents and eCRF. Before each new application, remaining preparation residues will be removed with a soft tissue. The hydrocolloid dressing stays in place until the next sonography measurement, but will be replaced more frequently if necessary. On Days 4, 8, 15 and 19, approximately 24 ±2 hours after the last application, the blinded evaluator assesses the test fields for sonographic measurement and clinical scoring within 60 minutes of removal of hydrocolloid dressings. New semi-occlusive patches will be applied to the same test fields immediately after completion of the ultrasound and clinical scoring assessments (within 1 hour after removal).
In the event of scheduling conflicts, subjects may miss a maximum of 2 planned application visits; however, the missed visits may not be on consecutive days with no more than 48 hours between applications and all dressings should remain in place until the next visit (approximately 48 hours after the last application of study products). The subject is advised to return to the clinical center as soon as possible. Trial procedures performed will be such that any procedures that were to be performed on the missed day are performed at this visit. Unless criteria for discontinuing test field applications are met, no other modifications of the dosing regimen are allowed.

6.3.1. Criteria for discontinuing treatments

Conditions under which application of an individual study treatment may be discontinued in a subject:

Individual treatments will be discontinued in the event of the following dermal reactions limited to the respective test fields:

- severe blistering
- skin necrosis
- contact dermatitis
- allergic reaction
- marked skin discoloration
- severe or unexpected itching, burning, or pain

If this occurs, a photograph showing all of the test fields in the affected plaque(s) will be taken for sponsor review. An additional photograph will be taken of the affected test field(s) alone. Photographs will not be used for grading or analysis purposes.

General discontinuation of a specific treatment for the trial:

In case of severe reactions due to a specific treatment, the principal investigator, in consultation with the sponsor, may prematurely discontinue this treatment for the whole trial population. To keep the investigator observer-blind he/she will inform the study nurse responsible for the treatment application about the test field(s) he/she deems necessary to be discontinued. The study nurse will determine which treatment is assigned to this test field, the sponsor will be informed and the respective treatment will be discontinued in all subjects.
6.4. **Blinding**

This is a subject- and evaluator-blinded study; therefore, the designated evaluator performing the measurements and assessments will be unaware of the particular treatment assignment for the subjects. Investigator(s) responsible for biopsy collection will be unblinded. Study-center staff responsible for preparation and application of the study products will not be blinded to the test field allocations and will be instructed not to reveal the identity of the allocations to the blinded evaluator.

The randomization list with the treatment codes will be sealed in an envelope and kept in the trial master file in a secure manner at the study center.

The randomization code will only be broken after the clinical database is locked or in the case of an emergency or in the event of a serious medical condition, when knowledge of the study treatment allocation is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator. Since each subject will be exposed to all study products concurrently and there will be no subdivision into separate dosing groups, it is unlikely that unblinding the randomized test field allocations will provide any additional knowledge that would be essential. However, if the investigator determines that the occurrence of a test field-specific or other serious medical condition requires the information contained on the randomization list, the study-center staff responsible for preparation and application of the test chambers (who are unblinded to the randomization list) will determine which treatment is assigned to the test fields(s) of concern and inform the investigator. Should the investigator also be the designated evaluator, they are to remain blinded to the other test site allocations for the subject.

It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate sponsor study personnel to discuss options before unblinding the subject’s treatment assignment. If the Medical Monitor or appropriate sponsor study personnel are not contacted before the unblinding, the investigator must notify the sponsor as soon as possible after unblinding. The date and reason for the unblinding must be fully documented in the appropriate eCRF. For any AE or SAE associated with breaking the blind, the investigator’s assessment of relationship to investigational product should be performed prior to breaking the blind.

Subjects will be withdrawn from the study if the blinded evaluator becomes aware of the test field allocations (i.e., is unblinded). The primary reason for discontinuation (the event or condition that led to the unblinding) will be recorded in the eCRF.

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

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

6.6. Preparation/Handling/Storage/Accountability

Study product will be supplied in bulk tubes. The site staff will load study product from bulk supply into syringes for administration to subjects. The individual syringes containing study treatment will be weighed before and after each application to each subject. The weight of study treatment applied to each individual subject will be documented in the accountability records. Refer to the study reference manual (SRM) for additional information.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product administered to study subjects, and the amount received from and returned to Stiefel/GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

6.7. Compliance with Study Treatment Administration

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff. Syringes of study treatment will be weighed before and after administration to each test field for each subject by study personnel to document the amount used.

Subjects will be dosed at the site and will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose
administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.8. Treatment of Study Treatment Overdose

Study product will be prepared and applied at the study center by a trained study nurse; therefore, overdose is unlikely.

There is no known specific treatment for overdose of GSK2981278. Symptomatic, supportive treatment should be administered.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening and other treatment options are available.

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

6.10. Lifestyle and/or Dietary Restrictions

- Test fields must be kept dry. Subjects should not go swimming, sit in a hot tub or sauna, or take deep baths, but may take showers if the test field does not get wet.

- Dressings and plasters must not be removed by the subject. If a dressing and/or plaster falls off before the next visit, the subject should not put it back on. Subjects should return the dressing and/or plaster to the study center at the next visit and report the time (or approximate time if unsure) that the dressing/plaster fell off. Study staff will document this information in the source documents and eCRF.

- Test fields must not be exposed to sunlight or other sources of ultraviolet light throughout the study.

- Subjects should use the same personal care products and laundry detergent throughout the study.

6.10.1. Alcohol

Subjects should limit alcohol consumption during the study and should not exceed the following guidelines:

- an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
6.10.2. Activity

- Subjects should avoid vigorous exercise that results in excessive sweating.
- Swimming is prohibited.

6.11. 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.

6.11.1. Permitted Medications and Non-Drug Therapies

Medications permitted during the study include contraceptives (for indications other than pregnancy prevention), antihistamines, selective leukotriene receptor antagonists (eg, montelukast sodium, zafirlukast), mast cell stabilizers (eg, cromolyn sodium or nedocromil sodium), acetaminophen/paracetamol, 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 (eg, 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 and/or psoriatic plaques that are not part of assessment in this trial are permitted during the study.

Sunscreen may be used on nonlesional skin.

6.11.2. 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 washout periods before the first patch 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

<table>
<thead>
<tr>
<th>Prohibited medications, products, and procedures:</th>
<th>Washout period before Day 1</th>
</tr>
</thead>
</table>
| Biologic agents:  
eg, alefacept 24 weeks; etanercept 12 weeks; ustekinumab 15 weeks | 5 half-lives |
| Oral retinoids (eg, acitretin or isotretinoin) | 12 weeks |
| Cyclosporin, interferon, methotrexate, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus); psoralen plus UVA | 8 weeks |
| Other investigational products or procedures | Longer of 4 weeks or 5 half-lives |
| Systemic corticosteroids or adrenocorticotropic hormone (ACTH) analogs | 4 weeks |
| Immunizations (influenza vaccine will be allowed) | 2 weeks |
| Topical treatments: corticosteroids, immunomodulators, anthralin (dithranol), Vitamin D derivatives, retinoids, coal tar (used on the psoriatic lesions under evaluation in this study) | 2 weeks |
| Drugs known to possibly worsen psoriasis (unless on a stable dose for >12 weeks), such as: 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 | 1 day |
| UV-therapy | 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.

Subjects will have study visits once daily (except Days 7 and 14), at approximately the same time each day, for 19 consecutive days. Visit schedules should be timed such that test field evaluations are conducted approximately 24 ±2 hours after the study products were applied. This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

The following points must be noted:

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

Note: Blood will be collected as close as possible to planned sampling times. Actual times for each of the blood draws taken will be recorded.

- The timing and number of planned study assessments, including safety assessments may be altered during the course of the study based on newly available data 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 250 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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening [Day]</th>
<th>Treatment Period [Days]</th>
<th>Follow-up [Day]</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-14 to -1</td>
<td>1</td>
<td>2 to 6</td>
<td>7 8 9 to 13 14 15 16 to 18 19 27 (±2)</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Subjects who withdraw early from the study should complete the Day 19 visit assessments except for biopsy collection.</td>
</tr>
<tr>
<td>Demographics/medical history</td>
<td>X</td>
<td></td>
<td></td>
<td>Will be assessed prior to randomization.</td>
</tr>
<tr>
<td>Brief physical exam (including height and weight)</td>
<td>X</td>
<td></td>
<td></td>
<td>Fitzpatrick skin type (Section 7.2, Table 3) will be documented. Site to document any known drug allergies.</td>
</tr>
<tr>
<td>Physical examination of the skin</td>
<td>X</td>
<td></td>
<td></td>
<td>Any adverse changes to the skin will be recorded as an AE.</td>
</tr>
<tr>
<td>Descaling with salicylic acid</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descaling of test sites with detergent solution</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Will be completed prior to dosing.</td>
</tr>
<tr>
<td>HIV, Hep B, and Hep C screen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>On Day 15 ECG will be completed prior to dosing.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>To be performed before drug removal and within a time window of 2 hours prior to dosing</td>
</tr>
<tr>
<td>Vital sign</td>
<td>X</td>
<td></td>
<td></td>
<td>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 position for at least 5 minutes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>To be performed before drug removal and within a time window of 2 hours prior to dosing</td>
</tr>
<tr>
<td>Determination of test fields</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Screening [Day]</td>
<td>Treatment Period [Days]</td>
<td>Follow-up [Day]</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Subjects who withdraw early from the study should complete the Day 19 visit assessments except for biopsy collection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory assessments (include liver chemistries) and urinalysis</td>
<td>-14 to -7</td>
<td>1</td>
<td>2 to 6</td>
<td>7</td>
</tr>
<tr>
<td>*Including drug and alcohol screening (Screening visit only). Refer to Section 7.3.5 for laboratory and urinalysis assessment information. Assessment to occur before drug removal and within 2 hours prior to dosing on Days 8 and 15.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Syringes should be weighed before and after application of each study treatment for each subject. Study treatment will be re-applied after evaluation and within 1 hour after removal. Study treatment applied on days 6 and 13 remains on the skin until subject returns to the clinic on days 8 and 15 respectively.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE/SAE review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prior and concomitant medication review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Photographic documentation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Screening [Day]</td>
<td>Treatment Period [Days]</td>
<td>Follow-up [Day]</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>-14 to -7</td>
<td>1 2 to 6 7 8 9 to 13 14 15 16 to 18 19</td>
<td>27 (+2)</td>
<td>Subjects who withdraw early from the study should complete the Day 19 visit assessments except for biopsy collection.</td>
</tr>
<tr>
<td>Clinical assessments</td>
<td></td>
<td></td>
<td></td>
<td>At Day 1 the score will be documented as “0.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X*</td>
<td>X X X X</td>
<td>*Day 4 only.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assessment to occur within 60 minutes of study product removal.</td>
</tr>
<tr>
<td>HFUS (sonography)</td>
<td></td>
<td>X X*</td>
<td>X X X X</td>
<td>Day 1 is baseline HFUS and completed prior to dosing.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Day 4 only.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ultrasound to occur within 60 minutes of study product removal.</td>
</tr>
<tr>
<td>Skin biopsies</td>
<td></td>
<td></td>
<td>X</td>
<td>Four 3mm punch biopsies will be collected from each consenting subject.</td>
</tr>
<tr>
<td>Wound assessment</td>
<td></td>
<td></td>
<td>X</td>
<td>This assessment applies only to subjects consenting to biopsy collection.</td>
</tr>
</tbody>
</table>
7.2. Screening and Critical Baseline Assessments

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.

Subject screening should be conducted within 14 days prior to the Day 1 visit. Baseline tests and procedures must be performed before randomization and the first application of study products.

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

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

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

Refer to Section 7.3 for baseline safety assessments (physical exam, vital sign measurement, ECG and laboratory parameters).

Photographic documentation will be collected at the Day 1 and Day 19 visits before any procedures will be performed using a digital camera. This will include overview pictures of all test fields (the number of pictures depends on the number of plaques(s) used and location on the body). If a treatment-related AE occurs, additional photographic documentation of single test fields and of all test fields within the affected plaque(s) will be taken. Photographs will not be used for grading or analysis purposes. Refer to the SRM for additional information on the photographic procedure.
At the screening visit it will be determined whether pretreatment with 5 % salicylic acid in Vaseline is necessary. This is required since it is not possible to perform sonography on psoriasis plaques with extensive scaling. The maximum length of this pretreatment is five days. The last pre-treatment application with salicylic acid has to be performed two days before the first application of study treatment on Day 1. Washing of the test fields with a mild detergent solution may occur at Day 1 and at later timepoints in the study as outlined in Section 7.1.

HFUS (sonographic) measurements will be performed using a 22 MHz high frequency sonograph. Serial A-scans will be composed and presented on a monitor as a section of the skin. A lateral resolution of approximately 200 μm and an axial resolution of 80 μm are possible. Dependent on the echo patterns, components of the epidermis, dermis and subcutis are presented. Therefore exact measurement of skin thickness is possible. The inflammatory psoriatic infiltrate is seen as a clearly definable ELB below the entrance echo. The thickness of the echo lucent psoriatic band will be determined and documented. The thickness will be measured in μm. At the Day 1 visit, plaques to be treated should have a comparable thickness of the ELB (as a surrogate for the infiltrate thickness) of at least 200 μm.

7.3. Safety

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

Significant findings of physical examination of skin, vital signs, significant findings of ECG and safety laboratory parameters, and local and systemic adverse events will be recorded. Spontaneously noted complaints will be recorded with duration, intensity and probability of a correlation with the study treatments (see Section 7.3.1).

Hematology, clinical chemistry, urinalysis and additional safety laboratory parameters to be tested are listed in Section 7.3.5.

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

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

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

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
• 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.

• All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.

• 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 3.

7.3.1.2. Method of Detecting AEs and SAEs

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

• “How are you feeling?”

• “Have you had any (other) medical problems since your last visit/contact?”

• “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator or designee to GSK of SAEs and non-serious AEs 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, IRB/IEC and investigators.
Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

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

7.3.2. Physical Exams

A brief physical examination will be performed by a medically qualified study personnel at screening and include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Height and weight will also be measured and recorded.

Investigators or delegate should pay special attention to clinical signs related to previous serious illnesses.

7.3.3. Vital Signs

Vital signs will be measured in seated position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

Single readings of blood pressure and pulse rate will be taken and recorded in the eCRF.

Vital signs should be collected before drug removal and within a time window of 2 hours prior to dosing.

7.3.4. ECG

Single 12-lead ECGs will be obtained at each specified time point during the study using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals. The same QT correction formula (ie, QTcB) should be used for subject eligibility, withdrawal criteria, and data analysis. Refer to Section 5.4.2 for QTc withdrawal criteria and additional readings that may be necessary.

ECG should be performed before drug removal and within a time window of 2 hours prior to dosing. If a plaque is located in the ECG region the dressings, study treatment may be removed before ECG measurement. In this situation, the time window from drug removal to the new application may be 3 hours.

7.3.5. 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 eCRF.

Laboratory assessments should be performed before drug removal and within a time window of 2 hours prior to dosing. Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

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

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Protocol Required Safety Laboratory Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td>Parameters</td>
</tr>
<tr>
<td>Assessments</td>
<td></td>
</tr>
<tr>
<td>Haematology</td>
<td>Platelet Count</td>
</tr>
<tr>
<td></td>
<td>RBC Indices:</td>
</tr>
<tr>
<td></td>
<td>WBC count with Differential:</td>
</tr>
<tr>
<td></td>
<td>RBC Count</td>
</tr>
<tr>
<td></td>
<td>MCV</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin</td>
</tr>
<tr>
<td></td>
<td>MCH</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
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<tr>
<td></td>
<td>Hematocrit</td>
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<tr>
<td></td>
<td>Monocytes</td>
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<tr>
<td></td>
<td>Eosinophils</td>
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<tr>
<td></td>
<td>Basophils</td>
</tr>
<tr>
<td>Cliniic</td>
<td>BUN</td>
</tr>
<tr>
<td>Chemistry 1</td>
<td>Potassium</td>
</tr>
<tr>
<td></td>
<td>AST (SGOT)</td>
</tr>
<tr>
<td></td>
<td>Total and direct bilirubin</td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
</tr>
<tr>
<td></td>
<td>Sodium</td>
</tr>
<tr>
<td></td>
<td>ALT (SGPT)</td>
</tr>
<tr>
<td></td>
<td>Total Protein</td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatise</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
</tr>
<tr>
<td>Routine</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>pH, glucose, protein, blood and ketones by dipstick</td>
</tr>
<tr>
<td></td>
<td>Microscopic examination (if blood or protein is abnormal)</td>
</tr>
<tr>
<td>Other</td>
<td>HIV</td>
</tr>
<tr>
<td>Screening</td>
<td>Hepatitis B (HBsAg)</td>
</tr>
<tr>
<td>Tests</td>
<td>Hepatitis C (Hep C antibody)</td>
</tr>
<tr>
<td></td>
<td>Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)</td>
</tr>
</tbody>
</table>

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 2: Liver Safety Required Actions and Follow up Assessments.

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.

7.4. Efficacy

An objective parameter of efficacy is the evaluation of the infiltrate thickness by ultrasound measurement (refer to Section 7.2). The ultrasound measurements of the ELB representing the thickness of the psoriatic infiltrate as a surrogate allows for greatly improved discrimination and sensitivity compared to clinical assessment. This method has been clinically and scientifically accepted for many years (Bangha, 1996; Remitz, 1999; Gassmueller, 1993; Willers, 2002).

The efficacy variable is the change from baseline in psoriatic skin thickness on Day 4, 8, 15 and 19 as assessed by measurement of the thickness of the ELB of the psoriatic infiltrate using 22-MHz sonography.

The efficacy signal can also be based on the clinical assessment of improvement of the test site(s) using the following 5-point score:

-1 = worsened
0 = unchanged (no effect)
1 = slight improvement
2 = clear improvement but not completely healed
3 = completely healed

Clinical assessment will be done after removal of treatments but before any gentle descaling necessary prior to sonography measurements. The comparison of single test fields will be made to the untreated area of plaque(s) not covered by the hydrocolloid dressing and close to the respective test field. Clinically apparent differences in erythema and infiltration will contribute to this global assessment. At Day 1 the score will be documented as “0” (unchanged).

Ideally, the same investigator or designated evaluator should carry out all assessments for an individual subject. In the event the same evaluator is not available for the duration of the study, another blinded investigator or designated evaluator with comparable training will perform the assessments.

With reference to the EMA Guideline for assessment of short-term efficacy of topical treatments [CHMP, 2004] the response to treatment will be documented as the difference between baseline and post treatment score (Day 19) for the single treated test fields, and in addition assessments will be made on Days 4, 8, and 15.
7.5. Biomarker(s)/Pharmacodynamic Markers

7.5.1. Novel Biomarkers

With the subject’s consent, tissue sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence psoriasis, and/or medically related conditions, as well as the biological and clinical responses to GSK2981278.

Four 3 mm punch biopsies scheduled on the Day 19 visit will be performed after all the observer assessments are complete.

Biomarker analysis in skin biopsies will be conducted using gene expression analysis of relevant biomarkers reported to be modulated by GSK2981278. These biomarkers include, but are not limited to, IL-17A, IL-17F, DEFB4A, IL-19, IL-36, CCL20, S100A7a, IL-8, and Krt6A. The analysis of these PD biomarkers will allow for investigation of target engagement of GSK2891278 in the study.

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/bioskin 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 CRO standards.

9.1. Hypotheses

There is no formal statistical hypothesis testing for the study.

Descriptive statistics will be used to assess safety and tolerability objectives. An estimation approach will be used to address the efficacy and pharmacodynamic study
objectives, where point estimates and corresponding confidence intervals will be constructed.

To assess the safety and tolerability of GSK2981278 ointment, adverse events and changes in laboratory parameters, ECGs, and vital signs will be evaluated. Treatment comparisons with vehicle ointment and the positive control will be based on review of descriptive statistics.

Efficacy and PD endpoints will be compared between different doses of GSK2981278 ointment, and vehicle ointment, and the positive control. Point estimates and 95% confidence intervals will be presented for each of the differences.

9.2. Sample Size Considerations

The sample size is driven by feasibility and prior experience by bioskin (CRO) in conducting these studies (based on published data on clinical.gov and unpublished bioskin data).

Approximately 15 subjects will be randomized in order to achieve at least 13 evaluable subjects.

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.

PD analysis set will include subjects with at least one sample collected for PD assessments. The PD analysis set will be the primary set for PD analyses.

9.3.2. Interim Analysis

No interim analysis is planned.

9.4. Key Elements of Analysis Plan

9.4.1. Efficacy Analyses

9.4.1.1. Reduction in psoriatic infiltrate thickness

The primary efficacy endpoint is the area under the time curve (AUC) of change in infiltrate thickness using the linear trapezoidal rule over the period starting with Day 1 up to Day 19. Missing data will be handled by the last observation carried forward (LOCF) approach. The AUC will be analyzed using a mixed-model repeated-measures (MMRM) analysis including treatment. The treatment will be treated as repeated measures within.
the same subject. Pair-wise treatment comparisons (see Table 5) will be performed. The primary comparison is between each active dose and the vehicle ointment. The least-square mean for each treatment group, an estimate of the difference between treatments, corresponding 95% confidence interval (CI) and p-value will be presented.

In addition, for each post-baseline assessed time point, the reduction in infiltrate thickness of the psoriatic plaque(s) from baseline will be summarized using both the Observed Cases (OC) approach and the LOCF approach. Pair-wise treatment comparisons (see Table 5) will be performed using a MMRM analysis similar to that for the primary efficacy endpoint. The least-square mean for each treatment group, an estimate of the difference between treatments, corresponding 95% CI and p-value will be presented.

Table 5 Pair-wise Comparisons of Test and Control Products

<table>
<thead>
<tr>
<th>Study products:</th>
<th>GSK2981278 Ointment</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.03%</td>
<td>0.1%</td>
</tr>
<tr>
<td>GSK2981278 Ointment</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>0.03%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>0.1%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>0.8%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vehicle</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

9.4.1.2. Improvement in clinical assessment

Clinical efficacy assessment using a 5-point scale (see Section 7.4) will be evaluated for each post-baseline assessed time point. The ordinal clinical score and the cumulative total score will be presented by descriptive statistics. Missing data, when computing the cumulative score, will be handled by the LOCF approach. Additionally, frequency counts will be provided for the clinical scores.

9.4.2. Safety Analyses

Extent to 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 summarised 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 Day 19 for each vital sign parameter would be summarised 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 would be summarised 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 provided.

If applicable, liver event data will be listed.

9.4.3. Other Analyses

Gene expression of biomarkers (refer to Section 7.5.1) from skin punch biopsy sample(s) will be analyzed.

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 favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (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 Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Signed informed consent to be obtained for each subject before participation in the study (and for 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.
• 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 for studies conducted at a GSK Phase I unit 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 Publicly 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.

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


CHMP 2007. Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products; Committee For Medicinal Products For Human Use. EMEA/CHMP/SWP/28367/07.


Gordon K. Ixekizumab for Treatment of Moderate-to-Severe Plaque Psoriasis: 60-week Results from a Double-Blind Phase 3 Induction and Randomized Withdrawal Study (UNCOVER-1). AAD 2015 Late-breaking abstract F010.


Lebwohl, M. AMAGINE-2: A Randomized, Double-blind, Phase 3 Efficacy and Safety Study of Brodalumab Compared With Placebo and Ustekinumab in Moderate to Severe Plaque Psoriasis Patients. AAD 2015 Late-breaking abstract F010.


Willers CP, Frase T, Schmidt A. The USE-(Ultrasound-Erythema-)Index in antipsoriatic testing. 20th World Congress of Dermatology, 2002, Paris, France.
### 12. APPENDICES

#### 12.1. Appendix 1 – Abbreviations and Trademarks

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AMG</td>
<td>German drug law (Arzneimittelgesetz)</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>cm²</td>
<td>Centimeter squared</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum concentration</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract research organization</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>ELB</td>
<td>Echo lucent band</td>
</tr>
<tr>
<td>FRP</td>
<td>Female of reproductive potential</td>
</tr>
<tr>
<td>FNRP</td>
<td>Female of non-reproductive potential</td>
</tr>
<tr>
<td>FTiH</td>
<td>First time in humans</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GCSP</td>
<td>Global Clinical Safety and Pharmacovigilance</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HFUS</td>
<td>High frequency ultrasound</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International conference on harmonisation</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
</tr>
<tr>
<td>IL-17</td>
<td>Interleukin 17</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
</tr>
<tr>
<td>LBD</td>
<td>Ligand-binding domains</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
</tr>
<tr>
<td>mAb</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MMRM</td>
<td>Mixed-model repeated-measures</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MSDS</td>
<td>Material safety data sheet</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogram</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No observed adverse effect level</td>
</tr>
<tr>
<td>OC</td>
<td>Observed cases</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>pg</td>
<td>Picogram</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>PPT</td>
<td>Psoriasis plaque test</td>
</tr>
<tr>
<td>QTc</td>
<td>Corrected QT</td>
</tr>
<tr>
<td>QTcB</td>
<td>Corrected QT using Bazett’s formula</td>
</tr>
<tr>
<td>RAP</td>
<td>Reporting and analysis plan</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RORγ</td>
<td>Retinoic acid receptor-related orphan receptor gamma</td>
</tr>
<tr>
<td>SAEs</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SRM</td>
<td>Study reference manual</td>
</tr>
<tr>
<td>Th 17</td>
<td>T-helper 17</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor alpha</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
</tbody>
</table>

**Trademark Information**

<table>
<thead>
<tr>
<th>Trademarks of the GlaxoSmithKline group of companies</th>
<th>Trademarks not owned by the GlaxoSmithKline group of companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>BETNESOL</td>
<td>Fixomull</td>
</tr>
<tr>
<td></td>
<td>Varihesive</td>
</tr>
<tr>
<td></td>
<td>Vaseline</td>
</tr>
</tbody>
</table>
12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

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


Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<thead>
<tr>
<th>Liver Chemistry Stopping Criteria – Liver Stopping Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT-absolute</strong></td>
</tr>
<tr>
<td><strong>ALT Increase</strong></td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
</tr>
<tr>
<td><strong>INR</strong></td>
</tr>
<tr>
<td><strong>Cannot Monitor</strong></td>
</tr>
<tr>
<td><strong>Symptomatic</strong></td>
</tr>
</tbody>
</table>

**Required Actions and Follow up Assessments following ANY Liver Stopping Event**

<table>
<thead>
<tr>
<th>Actions</th>
<th>Follow Up Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediately</strong> discontinue study treatment</td>
<td>• Viral hepatitis serology¹</td>
</tr>
<tr>
<td>Report the event to GSK within 24 hours</td>
<td>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</td>
</tr>
<tr>
<td>Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE²</td>
<td>• Fractionate bilirubin, if total bilirubin ≥ 2xULN</td>
</tr>
<tr>
<td>Perform liver event follow up assessments</td>
<td>• Obtain complete blood count with differential to assess eosinophilia</td>
</tr>
<tr>
<td>Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)</td>
<td>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</td>
</tr>
<tr>
<td><strong>Do not restart/rechallenge</strong> subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted</td>
<td>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.</td>
</tr>
<tr>
<td>If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue subject in the study</td>
<td></td>
</tr>
</tbody>
</table>
for any protocol specified follow up assessments

**MONITORING:**

**For bilirubin or INR criteria:**

- 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

**For All other criteria:**

- 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
- Record alcohol use on the liver event alcohol intake case report form

**For bilirubin or INR criteria:**

- 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 computerised tomography) and/or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible ‘Hy’s Law’), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Definition:</th>
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<tr>
<td>• 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.</td>
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<tr>
<td>• 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.</td>
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<thead>
<tr>
<th>Events meeting AE definition include:</th>
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<tr>
<td>• 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.</td>
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<tr>
<td>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</td>
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<tr>
<td>• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.</td>
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<tr>
<td>• Signs, symptoms, or the clinical sequelae of a suspected interaction.</td>
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<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• &quot;Lack of efficacy&quot; or &quot;failure of expected pharmacological action&quot; 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.</td>
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<tr>
<th>Events NOT meeting definition of an AE include:</th>
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<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
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| • 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.

### 12.3.2. 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).

<table>
<thead>
<tr>
<th>Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:</th>
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<tbody>
<tr>
<td><strong>a. Results in death</strong></td>
</tr>
<tr>
<td><strong>b. Is life-threatening</strong></td>
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<tr>
<td><strong>NOTE:</strong> 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.</td>
</tr>
<tr>
<td><strong>c. Requires hospitalization or prolongation of existing hospitalization</strong></td>
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<td><strong>NOTE:</strong></td>
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<tr>
<td>- 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.</td>
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<tr>
<td>- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.</td>
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<tr>
<td><strong>d. Results in disability/incapacity</strong></td>
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<tr>
<td><strong>NOTE:</strong></td>
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<tr>
<td>- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</td>
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</table>
| - 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 and impaired liver function defined as:
   - ALT $\geq$ 3xULN and total bilirubin$^*$ $\geq$ 2xULN (>35% direct), or
   - ALT $\geq$ 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 $\geq$ 3xULN and total bilirubin $\geq$ 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.

12.3.3. 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.
12.3.4. 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 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.

12.3.5. Reporting of SAEs to GSK

<table>
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<tr>
<th>SAE reporting to GSK via electronic data collection tool</th>
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<tr>
<td>- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool.</td>
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<tr>
<td>- 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 or the SAE coordinator.</td>
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<tr>
<td>- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.</td>
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<tr>
<td>- 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.</td>
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<tr>
<td>- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data</td>
</tr>
<tr>
<td>- 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 or the SAE coordinator by telephone.</td>
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<tr>
<td>- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.</td>
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12.4. Appendix 4: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

A. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label

B. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

C. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]

D. Injectable progestogen [Hatcher, 2007a]

E. Contraceptive vaginal ring [Hatcher, 2007a]

F. Percutaneous contraceptive patches [Hatcher, 2007a]

G. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].

H. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007a]

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