TITLE PAGE

Division: Worldwide Development
Information Type: Clinical Protocol Amendment

| Title: | An Evaluator-Blinded Study to Evaluate the Cumulative Irritation Potential of Topically-Applied GSK2894512 Cream in Healthy Subjects |
| Study Identifier: | IPS117191 |
| Compound Number: | GSK2894512 |
| Development Phase: | I |
| Effective Date: | 13-DEC-2013 |
| Protocol Amendment Number: | 2 |

Subject: cumulative irritation, dermal safety, GSK2894512

Authors:

Revision Chronology:

2013N169902_00  2013-SEP-18  Original
2013N169902_01  2013-OCT-16  Amendment 1: Addition of ECGs, clinical laboratory assessments, and determination of plasma concentrations of GSK2894512.
2013N169902_02  2013-DEC-13  Amendment 2: Change in patch-testing conditions, concentration of positive control, and total number of subjects.

Copyright 2013 the GlaxoSmithKline group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited.
SPONSOR SIGNATORY

[Redacted] MD, PhD, MBA, FAAD

Executive Director, Medicines Development, Dermatology

December 13, 2013
Date
SPONSOR INFORMATION PAGE

Clinical Study Identifier: IPS117191

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
United Kingdom

Sponsor Contact Address:

Stiefel, a GSK company
20 TW Alexander Drive
PO Box 13398
Research Triangle Park, NC 27709
United States
Telephone: [redacted]

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information:

[redacted] MD, PhD, MBA, FAAD
Executive Director, Medicines Development, Dermatology

Sponsor Serious Adverse Events (SAE) Contact Information:

Fax: [redacted]
E-mail: [redacted]

Regulatory Agency Identifying Number(s): US IND 104601; EudraCT Number 2013-005156-15
INVESTIGATOR PROTOCOL AGREEMENT PAGE

For Study IPS117191:

- I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____________________________

Investigator Signature Date

__________________________________________  __________
## PROTOCOL SUMMARY

<table>
<thead>
<tr>
<th>Title</th>
<th>An Evaluator-Blinded Study to Evaluate the Cumulative Irritation Potential of Topically-Applied GSK2894512 Cream in Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>This study will assess the potential of topically-applied GSK2894512 cream at 3 concentrations (0.5%, 1%, and 2%) to induce skin irritation at the site of application in healthy subjects. Results from this study will be considered when selecting the concentration(s) of GSK2894512 to evaluate in the Phase II and Phase III clinical safety and efficacy studies.</td>
</tr>
<tr>
<td>Development Phase</td>
<td>I</td>
</tr>
</tbody>
</table>
| Objective(s) | **Primary:**
To evaluate the cumulative irritation potential of GSK2894512 cream.

**Secondary:**
- To evaluate the safety profile of topical application of GSK2894512 cream.
- To determine plasma concentrations of GSK2894512. |
| Study Design | This is a Phase I, multicenter, randomized, evaluator-blinded, controlled, 21-day cumulative irritation study to evaluate the potential of 3 concentrations of GSK2894512 (0.5%, 1%, and 2%) cream to induce skin irritation following repeated exposures under exaggerated conditions (ie, constant exposure under semi-occlusion) in healthy adult subjects. Study visits will occur daily from Baseline/Day 1 through the final study evaluation on Day 22. Including a 28-day screening period, the total duration of subject participation may be up to 50 days. |
| Test and Reference Product(s), Dose, and Mode of Administration | All subjects will have a set of 6 specialized patches applied to randomized test sites on their backs once daily. A total of 21 applications will be made over a period of 22 days. Patches will remain in place for approximately 23 hours, with new patches applied to the same test sites. Each set will consist of the following study products: GSK2894512 0.5% cream, GSK2894512 1% cream, GSK2894512 2% cream, the cream vehicle (without the active ingredient), a positive control (sodium lauryl sulfate 2% solution), and a negative control (petrolatum).

All patches will be prepared, applied, and removed at the study center. In the event of irritation with a score ≥3 on the dermal response grading scale or a letter score of F, G, or H for other effects, applications of that individual study product will be discontinued for that subject. Applications of the remaining study products will continue, unless discontinuation criteria are also met at those test sites. |
| Number of Subjects and Study Centers | Up to 46 subjects will be enrolled at 2 study centers (1 in the United States and 1 in Germany) in order to have at least 30 evaluable subjects patched under semi-occlusive conditions. |
**Key Inclusion and Exclusion Criteria**

**Refer to Protocol Section 4.2 and Section 4.3 for the complete list of inclusion and exclusion criteria**

**Key Inclusion Criteria:**
- Age 18 to 65 years, inclusive, at time of consent.
- In generally good overall health, with healthy skin in the potential test sites.
- Skin tone in the potential test sites such that erythema and other dermal reactions can be easily visualized (ie, Fitzpatrick skin types I, II, III, or IV).
- Female of nonchildbearing potential or male.

**Key Exclusion Criteria:**
- History of known or suspected intolerance to study products or supplies.
- Inability to evaluate the skin at and around the potential test sites on the back due to sunburns, unevenness in skin tone, tattoos, scars, excessive hair, freckles, birthmarks, moles, or other skin damage or abnormality.
- Clinically-relevant skin disease or clinically-relevant history of or currently suffering from any disease or condition that, in the opinion of the investigator, might affect the evaluation of the study product or placed the subject at undue risk.
- Used prohibited concomitant medications or products or participated in another clinical study within the defined washout periods.
- Abuse of alcohol or other drugs.
- Considered vulnerable.
- Employee or immediate family member of an employee who is involved in the study.
- Current or chronic history of liver disease, or known hepatic or biliary abnormalities. Alanine aminotransferase, alkaline phosphatase, or bilirubin >1.5x upper limit of normal.
- QTc ≥450msec or QTc ≥480msec for subjects with bundle branch block.

**Study Endpoints/Assessments:**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>No efficacy assessments are planned for this study.</th>
</tr>
</thead>
</table>
| Irritation             | A blinded evaluator will assess test sites for dermal irritation after each removal of the patches.  
                          | Primary Endpoints:  
                          | - Mean cumulative irritation scores  
                          | - Total cumulative irritation scores |
| Safety                 | Safety will be assessed by evaluating adverse events, vital signs, electrocardiograms, clinical laboratory test results, and reasons for withdrawal from the study. |
| Pharmacokinetic        | Plasma trough concentrations of GSK2894512. |
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROTOCOL SUMMARY</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>LIST OF ABBREVIATIONS</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>1. INTRODUCTION</strong></td>
<td>10</td>
</tr>
<tr>
<td>1.1. Background</td>
<td>10</td>
</tr>
<tr>
<td>1.2. Rationale</td>
<td>10</td>
</tr>
<tr>
<td>1.3. Benefit:Risk Assessment</td>
<td>10</td>
</tr>
<tr>
<td>1.3.1. Risk Assessment</td>
<td>10</td>
</tr>
<tr>
<td>1.3.2. Benefit Assessment</td>
<td>12</td>
</tr>
<tr>
<td>1.3.3. Overall Benefit:Risk Conclusion</td>
<td>12</td>
</tr>
<tr>
<td><strong>2. OBJECTIVES AND ENDPOINTS</strong></td>
<td>12</td>
</tr>
<tr>
<td>2.1. Objectives</td>
<td>12</td>
</tr>
<tr>
<td>2.2. Endpoints</td>
<td>13</td>
</tr>
<tr>
<td><strong>3. INVESTIGATIONAL PLAN</strong></td>
<td>13</td>
</tr>
<tr>
<td>3.1. Study Design</td>
<td>13</td>
</tr>
<tr>
<td>3.2. Discussion of Design</td>
<td>14</td>
</tr>
<tr>
<td>3.2.1. Design Rationale</td>
<td>14</td>
</tr>
<tr>
<td>3.2.2. Dose Rationale</td>
<td>15</td>
</tr>
<tr>
<td><strong>4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA</strong></td>
<td>15</td>
</tr>
<tr>
<td>4.1. Number of Subjects</td>
<td>15</td>
</tr>
<tr>
<td>4.2. Inclusion Criteria</td>
<td>16</td>
</tr>
<tr>
<td>4.3. Exclusion Criteria</td>
<td>16</td>
</tr>
<tr>
<td>4.4. Lifestyle Restrictions</td>
<td>17</td>
</tr>
<tr>
<td>4.5. Withdrawal Criteria</td>
<td>18</td>
</tr>
<tr>
<td>4.5.1. Subject Discontinuation</td>
<td>18</td>
</tr>
<tr>
<td>4.5.2. Termination of the Study</td>
<td>19</td>
</tr>
<tr>
<td>4.6. Screening/Run-in Failures</td>
<td>19</td>
</tr>
<tr>
<td><strong>5. STUDY TREATMENTS</strong></td>
<td>19</td>
</tr>
<tr>
<td>5.1. Investigational Product and Other Study Treatments</td>
<td>19</td>
</tr>
<tr>
<td>5.1.1. Application of Study Products</td>
<td>20</td>
</tr>
<tr>
<td>5.1.2. Criteria for Discontinuing Individual Study Products</td>
<td>21</td>
</tr>
<tr>
<td>5.2. Treatment Assignment</td>
<td>21</td>
</tr>
<tr>
<td>5.3. Blinding</td>
<td>22</td>
</tr>
<tr>
<td>5.4. Product Accountability</td>
<td>23</td>
</tr>
<tr>
<td>5.5. Compliance</td>
<td>23</td>
</tr>
<tr>
<td>5.6. Concomitant Medications and Nondrug Therapies</td>
<td>24</td>
</tr>
<tr>
<td>5.6.1. Permitted Medications and Nondrug Therapies</td>
<td>24</td>
</tr>
<tr>
<td>5.6.2. Prohibited Medications and Nondrug Therapies</td>
<td>24</td>
</tr>
<tr>
<td>5.7. Treatment of Study Treatment Overdose</td>
<td>25</td>
</tr>
<tr>
<td><strong>6. STUDY ASSESSMENTS AND PROCEDURES</strong></td>
<td>25</td>
</tr>
<tr>
<td>6.1. Screening and Baseline</td>
<td>25</td>
</tr>
<tr>
<td>6.2. Completion of Study</td>
<td>26</td>
</tr>
<tr>
<td>6.3. Efficacy</td>
<td>26</td>
</tr>
</tbody>
</table>
6.4. Assessment of Cumulative Irritation ............................................................ 26
6.5. Safety ......................................................................................................... 28
6.5.1. Electrocardiogram ........................................................................ 28
6.5.2. Clinical Laboratory Assessments .................................................... 28
6.5.3. Adverse Events .............................................................................. 29
   6.5.3.1. Definition of an AE .................................................................. 29
   6.5.3.2. Definition of a Serious Adverse Event ........................................ 30
6.5.4. Assessment of Intensity .................................................................... 31
6.5.5. Assessment of Causality ................................................................. 31
6.5.6. Laboratory and Other Safety Assessment Abnormalities
       Reported as AEs and SAEs ............................................................... 32
6.5.7. Time Period and Frequency of Detecting AEs and SAEs ............... 32
6.5.8. Method of Detecting AEs and SAEs ............................................. 32
6.5.9. Follow-up of AEs and SAEs ........................................................... 33
6.5.10. Prompt Reporting of Serious Adverse Events and Other
       Events to the Sponsor ...................................................................... 33
       6.5.10.1. Regulatory Reporting Requirements for SAEs ............ 33
6.6. Pharmacokinetics .................................................................................... 34

7. DATA MANAGEMENT .................................................................................. 34

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS .................... 34
  8.1. Hypotheses ........................................................................................... 34
  8.2. Study Design Considerations ............................................................. 34
     8.2.1. Sample Size ................................................................................ 34
  8.3. Data Analysis Considerations ............................................................. 35
     8.3.1. Analysis Data Sets ....................................................................... 35
     8.3.2. Treatment Comparisons .............................................................. 35
     8.3.3. Key Elements of Analysis Plan .................................................... 36
        8.3.3.1. Efficacy Analyses .................................................................. 36
        8.3.3.2. Safety Analyses ...................................................................... 37
        8.3.3.3. Pharmacokinetic Analyses .................................................... 37
     8.3.4. Interim Analysis ........................................................................... 37

9. STUDY CONDUCT CONSIDERATIONS ....................................................... 37
  9.1. Posting of Information on Publicly Available Clinical Trial Registers .... 37
  9.2. Regulatory and Ethical Considerations, Including the Informed
       Consent Process .................................................................................. 37
  9.3. Quality Control (Study Monitoring) .................................................... 38
  9.4. Quality Assurance ............................................................................... 38
  9.5. Study and Site Closure ........................................................................... 39
  9.6. Records Retention ............................................................................... 39
  9.7. Provision of Study Results to Investigators, Posting of Information
       on Publicly Available Clinical Trials Registers and Publication .......... 40

10. REFERENCES .............................................................................................. 41

11. APPENDICES ............................................................................................. 42
  11.1. Appendix 1: Predicted Exposure to GSK2894512 under Maximized
       Occlusive Testing Conditions ............................................................. 42
  11.2. Appendix 2: Liver Safety Process ..................................................... 45
  11.3. Appendix 3: Protocol Changes ......................................................... 48
LIST OF ABBREVIATIONS

AE adverse event
ALT alanine aminotransferase
AST aspartate aminotransferase
cm centimeter
CRF case report form
ECG electrocardiogram
g gram
GCP good clinical practice
GSK GlaxoSmithKline
IB investigator brochure
ICH International Conference on Harmonisation
IEC independent ethics committee
INR international normalized ratio
IRB institutional review board
MedDRA Medical Dictionary for Regulatory Activities
mg milligram
mL milliliter
mm millimeter
msec millisecond
NOAEL no observed adverse effects level
QTcF QT interval corrected for heart rate according to Fridericia’s formula
SAE serious adverse event
SLS sodium lauryl sulfate
SPM study procedures manual
μL microliter
ULN upper limit of normal

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></td>
<td>Eppendorf</td>
</tr>
<tr>
<td></td>
<td>Finn Chamber</td>
</tr>
<tr>
<td></td>
<td>SAS</td>
</tr>
</tbody>
</table>
1. **INTRODUCTION**

1.1. **Background**

GSK2894512 is a novel anti-inflammatory agent that is currently under development as a cream for the topical treatment of atopic dermatitis and chronic plaque psoriasis. The mechanism of action is related to inhibition of secretion of pro-inflammatory cytokines from activated T-cells, keratinocytes, and endothelial cells. Initial clinical studies of GSK2894512 cream (in a different vehicle) have shown efficacy in subjects with mild-to-severe atopic dermatitis and plaque psoriasis; the most frequently-reported adverse events (AEs) were application site reactions, including dermatitis, folliculitis, and skin discoloration (hyperpigmentation) [Bissonnette 2010; Bissonnette 2012a; Bissonnette 2012b].

1.2. **Rationale**

Substances that come into contact with human skin need to be evaluated for their potential to induce skin irritation and sensitization in a controlled clinical setting. Skin irritation is a nonimmunologic response that occurs when the skin is exposed to an irritating agent. The response may be immediate or may appear with continual exposure. Symptoms are generally described as irritant contact dermatitis, which presents as delineated erythema, with or without infiltration and epidermal defects, at the site of exposure and improves when exposure ceases. The cumulative irritation potential of GSK2894512 has not been evaluated in a standardized cumulative patch testing study, which is typically conducted to detect irritation under conditions of maximal stress. The exposure to study products under semi-occlusion continuously for 3 weeks in this study is greater than would be experienced under recommended normal-use conditions, thereby maximizing the probability of characterizing the irritancy profile of GSK2894512 cream.

This study is being conducted to assess the potential of topically-applied GSK2894512 cream at 3 concentrations (0.5%, 1%, and 2%) to induce skin irritation at the site of application in healthy subjects. Results from this study will be considered when selecting the concentration(s) of GSK2894512 to evaluate in the Phase II and Phase III clinical safety and efficacy studies.

1.3. **Benefit:Risk Assessment**

Findings from both clinical and nonclinical studies conducted with GSK2894512 are summarized in the Investigator’s Brochure. This section outlines the risk assessment and mitigation strategy for this protocol.

1.3.1. **Risk Assessment**

The clinical assessments of dermal reactions (ie, visual evaluation and scoring) are noninvasive procedures that pose minimal risk for the subjects. A summary of potential risks from study procedures and exposure to test articles is provided in Table 1.
# Table 1  Potential Risks and Mitigation Strategies

<table>
<thead>
<tr>
<th>Potential Risk of Clinical Significance</th>
<th>Data Available / Rationale for Risk</th>
<th>Impact on Eligibility Criteria and Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational Product: GSK2894512</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin irritation or allergic reaction to GSK2894512</td>
<td>Nonclinical dermal toxicity studies of up to 8% GSK2894512 for up to 13 weeks indicated local effects are primarily mild-to-moderate skin irritation that is reversible (see IB Section 4.5). GSK2894512 did not show evidence of sensitization. GSK2894512 or the components of its vehicle may induce skin irritation that could be amplified by the occlusive test conditions. Allergic or irritant reactions in the exposed areas may present as erythema, with itching, papules, and vesicles. In extreme cases with corresponding sensitization and disposition, more generalized dermal responses may occur. After cessation of exposure, such reactions generally subside either spontaneously or with a topical treatment.</td>
<td>Potential subjects with a known or suspected intolerance to GSK2894512 or the components of its vehicle will be excluded. The skin will be evaluated daily to observe any signs of allergic reaction or excessive irritation. In the event of an erythema score ≥3, the individual study product will be discontinued for that subject (see Section 5.1.2). If needed, appropriate topical or systemic treatment will be provided.</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td>In a nonclinical study in minipigs using intravenous administration, reversible decreases in arterial blood pressure and PR interval were observed; however, in dermal toxicity studies there were no effects on QT interval or heart rate. Considering the small quantity of study product to be applied, and the topical nature of delivery, systemic exposure to GSK2894512 and the risk of associated systemic reactions is expected to be low (see Appendix 1 and IB Section 5.2.2).</td>
<td>Subjects will be monitored for adverse events throughout the study. Vital signs will be taken at screening, baseline, and every other day during the study. An ECG will be performed and blood will be collected at screening, Day 11, and Day 22 to monitor cardiac safety, laboratory parameters, and plasma concentrations of GSK2894512.</td>
</tr>
<tr>
<td>Study Procedures</td>
<td>The patches and adhesive bandages (ie, tape/plasters) are typically well-tolerated. However, there is a risk of erythema and allergic reaction at the points of skin contact in predisposed individuals.</td>
<td>Potential subjects with a known or suspected intolerance to the patches or adhesives will be excluded. The skin will be evaluated daily to observe any signs of allergic reaction or excessive irritation related to the testing materials. The subject may be discontinued from the study at the discretion of the investigator (Section 4.5.1). If needed, appropriate topical or systemic treatment will be provided.</td>
</tr>
</tbody>
</table>
During the initial clinical studies of a different formulation of GSK2894512 in subjects with atopic dermatitis or psoriasis, the following skin-related AEs were reported by 1% to 6% of subjects overall (“often”) regardless of causality: skin hyperpigmentation, application site dermatitis, papular rash, pruritus, contact dermatitis, folliculitis, erythema, and skin burning sensation. Skin-related AEs reported by <1% of subjects overall (“occasionally”) included eczema, eczema asteatotic, skin site pain, swelling face, hyperkeratosis, paraesthesia, acne aggravated, and laceration of hand. Nasopharyngitis and headache were the most frequently-reported (>10% of subjects) nondermatological AEs overall.

The clinical protocol will be submitted to the responsible institutional review boards (IRB)/independent ethics committees (IEC) for approval and subjects will be fully informed of all potential risks of participation in the study.

1.3.2. Benefit Assessment

There is no direct individual benefit to subjects from participation 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 atopic dermatitis and plaque psoriasis.

1.3.3. Overall Benefit:Risk Conclusion

Taking into account the potential risks and benefits and the measures taken to minimize risk to subjects participating in this study, the performance of the study is considered ethically acceptable since the inherent risks identified for subjects in this study are justified by the anticipated benefits of GSK2894512 cream for patients with atopic dermatitis or psoriasis.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary:
- To evaluate the cumulative irritation potential of GSK2894512 cream.
Secondary:
- To evaluate the safety profile of topical application of GSK2894512 cream.
- To quantify plasma concentrations of GSK2894512.

2.2. Endpoints

Primary:
- Mean cumulative irritation scores.
- Total cumulative irritation scores.

Secondary:
- The incidence of AEs and treatment-related AEs.
- Change from baseline in vital signs, clinical laboratory parameters, and electrocardiogram (ECG) findings.
- Plasma trough concentrations of GSK2894512.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase I, multicenter, randomized, controlled, evaluator-blinded, 21-day cumulative irritation study to evaluate the potential of 3 concentrations of GSK2894512 (0.5%, 1%, and 2%) cream to induce skin irritation following repeated exposures under exaggerated conditions (ie, constant exposure under semi-occlusion) in healthy adult subjects. Up to 46 subjects will be enrolled in order to have at least 30 evaluable subjects patched under semi-occlusive conditions. Eligible subjects will be 18 to 65 years of age, inclusive, in generally good overall health with healthy skin in the potential test sites, and have skin tone in the potential test sites on the back such that erythema and other dermal reactions can be easily visualized (ie, Fitzpatrick skin types I, II, III, or IV).

The primary endpoints are the mean and total cumulative irritation scores. There are no efficacy evaluations in this study. Safety will be assessed throughout the study by evaluating AEs, vital signs, ECGs, clinical laboratory test results, and reasons for withdrawal from the study.

Screening will occur within 28 days of the Baseline visit. Study visits will occur daily from Baseline/Day 1 through Day 22 for applications of study product patches and evaluations of dermal reactions (see Figure 1). Subjects must provide written informed consent before any study-specific procedures are performed. The total duration of subject participation may be up to 50 days. A completed subject is one who has completed Day 22. The end of the study is defined as the last subject’s last visit.
All subjects will have a set of 6 patches applied to randomized test sites on their backs once daily. A total of 21 applications will be made over a period of 22 days. Each set will consist of the following study products: GSK2894512 0.5% cream, GSK2894512 1% cream, GSK2894512 2% cream, the cream vehicle (without the active ingredient), a positive control (sodium lauryl sulfate [SLS] 2% solution), and a negative control (petrolatum). Patches will be removed after approximately 23 hours, and the test sites will be evaluated for signs of erythema and dermal reactions within 30 minutes of removal. A new set of patches will be applied to the same randomized test sites after evaluation (within 1 hour after removal). The final evaluations will be performed on Day 22, at approximately 23 hours after application of the final set of patches. Conditions under which applications of an individual study product may be discontinued are described in Section 5.1.

Protocol waivers, exemptions, or deviations 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 (see Table 3), are essential and required for study conduct.

Within the protocol, reference to GlaxoSmithKline (GSK) and/or Stiefel, a GSK company (Stiefel) is inclusive of tasks and responsibilities that will be performed by a contract research organization (ie, PAREXEL or bioskin GmbH). Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying study procedures manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2. Discussion of Design

3.2.1. Design Rationale

The study design is based on the general principles outlined in the former United States Food and Drug Administration Guidance for Industry, *Skin irritation and sensitization testing of generic transdermal drug products* [FDA 1999] and the European Medicines Agency Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, *Appendix 1* [EMA 2013].
Each subject will be exposed to all 6 study products simultaneously to minimize the effects of inter-subject variability. Study products are randomly assigned to each application area/test site to control for the possibility of a treatment-by-site interaction.

To ensure that irritation can be recognized under the test conditions, SLS 2% is included as a positive control. In the majority of cases, SLS induces irritation following repetitive application, thereby demonstrating the skin’s susceptibility to react to irritant exposure.

Examination of a test field treated with a negative control (petrolatum) will be performed to assess possible effects resulting from the study design, such as reactions to the patches, adhesives, or occlusion. Petrolatum is not anticipated to induce irritation following repetitive application.

The vehicle cream is included to differentiate any irritation related to the active pharmaceutical ingredient versus irritation related to components of the vehicle itself.

3.2.2. Dose Rationale

An initial proof-of-concept study in subjects with psoriasis evaluated the safety, systemic exposure, and efficacy of 3 concentrations of GSK2894512 (0.5%, 1%, and 2%) cream (in the first clinical formulation) applied once or twice daily for a period of 28 days. Results of this study indicated the 2% concentration was associated with a higher incidence of application site reactions than the lower concentrations; therefore, only 0.5% and 1% were included in subsequent studies.

Stiefel has reformulated the cream vehicle in order to stabilize the active pharmaceutical ingredient in the vehicle and also to potentially improve tolerability of the drug product. The current study will evaluate the tolerability and irritancy potential of all 3 previously-tested concentrations of GSK2894512 in the reformulated cream vehicle. Results of this study will contribute to selection of the most appropriate maximum concentration of GSK2894512 cream to be further evaluated in subsequent studies.

The systemic exposure to GSK2894512 during this patch-test study in healthy subjects is expected to be lower than the exposure in 2 previous studies, where GSK2894512 was applied to a mean of 1.4% to 4.0% of the total body surface area in subjects with psoriasis and atopic dermatitis, respectively. The predicted maximum systemic exposure to GSK2894512 during this study assuming fully occlusive testing conditions is summarized in Appendix 1. It is anticipated that semi-occlusive testing will result in a materially lower systemic exposure to GSK2894512; however, the exact level of GSK2894512 percutaneous absorption and its consequent systemic bioavailability are difficult to predict.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

This study will enroll up to 46 subjects in order to have at least 30 evaluable subjects patched under semi-occlusive conditions. No subject prematurely discontinued from the study for any reason will be replaced.
Deviations from inclusion and exclusion criteria are not allowed, as 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.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK2894512 that may impact subject eligibility is provided in the Investigator’s Brochure.

4.2. Inclusion Criteria

It is the investigator’s responsibility to confirm, before enrollment into the study, that potential subjects are willing and able to provide written informed consent, participate in the study as an outpatient, make frequent visits to the study site, and comply with all study requirements including restrictions on usage of concomitant medications and other treatments. Informed consent must be obtained prior to any study-specific procedures being performed.

Subjects eligible for study participation must meet all of the following criteria:

1. Aged 18 to 65 years, inclusive, at time of consent.
2. In generally good overall health with healthy skin in the potential test sites on the back.
3. Skin tone in the potential test sites on the back such that erythema and other dermal reactions can be easily visualized, ie, Fitzpatrick skin types I (always burns; never tans), II (usually burns; tans with difficulty), III (sometimes mild burn; gradually tans), or IV (rarely burns; tans with ease) (see Section 6.1, Table 4). Determination of skin types is based on sunburn and tanning history in response to the first 30 to 45 minutes of sun exposure.
4. A woman is eligible to participate if she is of nonchildbearing potential, defined as a woman with functioning ovaries who has a documented bilateral tubal ligation/sterilization or hysterectomy, bilateral oopherectomy, or postmenopausal with at least 12 months of spontaneous amenorrhea.

4.3. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. History of known or suspected intolerance to GSK2894512, any of the ingredients of the study products, adhesive tape/plaster, or the patches.
2. Inability to evaluate the skin at and around the potential test sites on the back due to sunburns, unevenness in skin tone, tattoos, scars, excessive hair, freckles, birthmarks, moles, or other skin damage or abnormality.
3. Clinically-relevant skin disease, including psoriasis, eczema, atopic dermatitis, acne, dysplastic nevi, or other skin pathologies, or a history of skin cancer, that may, in the opinion of the investigator, contraindicate participation or interfere with test site evaluations.
4. Considered immunocompromised, or has a clinically-relevant history of or currently suffering from any disease or condition that, in the opinion of the investigator, might affect the evaluation of the study product or place the subject at undue risk.

5. Used prohibited concomitant medications or products within the defined washout periods before the Day 1 visit (see Section 5.6.2, Table 2). This includes investigational products, allergy injections, immunizations, corticosteroids, immunomodulators, anti-inflammatories, antihistamines, selective leukotriene receptor antagonists, mast cell stabilizers, and topical medications or products at and around the potential test sites.

6. Participation in any interventional clinical study within 4 weeks of the Day 1 Visit.

7. A clinically relevant history of or current evidence of abuse of alcohol or other drugs.

8. Considered vulnerable (eg, individuals in detention/institutionalized due to legal or regulatory order).

9. Employee of the study center, bioskin GmbH, PAREXEL, GSK, or Stiefel who is involved in the study, or an immediate family member (eg, partner, offspring, parents, siblings, or sibling’s offspring) of an employee who is involved in the study.

10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin >1.5x upper limit of normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%).

11. QTc ≥450msec or QTc ≥480msec for subjects with bundle branch block. The QTc is the QT interval corrected for heart rate according to Fridericia’s formula (QTcF), with machine overread. The QTc should be based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period.

4.4. Lifestyle Restrictions

- Patches and test areas must be kept dry. Subjects should not go swimming, sit in a hot tub, or take deep baths, but may take showers if their back does not get wet.

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

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

- Test areas 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.
4.5. Withdrawal Criteria

4.5.1. Subject Discontinuation

A subject may voluntarily 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.

The following criteria may lead to discontinuation of an individual subject from the clinical study:

- Occurrence of a dermatosis in the test fields or any dermatosis requiring treatment with a prohibited medication.
- Serious concomitant symptoms such as the occurrence of blisters or erosions in several test fields, as well as a local or generalized allergic reaction to the study products or procedures.
- Illness during the study that could influence the results.
- Evidence of the use of drugs or prohibited medications during the clinical study.
- Protocol violation, failure to comply with the study stipulations/poor compliance.
- Withdrawal of consent.
- Liver chemistry: ALT ≥3xULN (refer to Appendix 2 for details of the required assessments).
- QTc:
  - QTc >500 msec or uncorrected QT >600 msec
  - Change from baseline QTc >60 msec
  - For subjects with underlying bundle branch block:
    | Baseline QTc with Bundle Branch Block | Discontinuation QTc with Bundle Branch Block |
    |--------------------------------------|---------------------------------------------|
    | <450 msec                            | >500 msec (or >600 msec uncorrected)        |
    | 450-480 msec                         | ≥530 msec                                   |

Note: These criteria should be based on the average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

The reason for a subject’s premature discontinuation from the study must be fully documented in the source documents and CRF. Subjects who have failed to attend follow-up evaluations will be contacted to determine if they have withdrawn themselves from the study. The study site should attempt to contact the subject 3 times via phone calls and/or e-mail and send a certified letter before considering a subject lost to follow-up.

If the subject withdraws consent, no further study evaluations should be performed. No subject prematurely discontinued from the study for any reason will be replaced.
4.5.2. Termination of the Study

The following criteria may lead to termination of the study:

- Severe, unexpected, study product-related AEs in one or more subjects.
- Mutual agreement between the sponsor and investigator.
- Sponsor business decision.

If the clinical study is terminated prematurely, there will be no disadvantages regarding the medical care of subjects.

4.6. Screening/Run-in Failures

Subjects who sign the informed consent form and who are discontinued or withdraw from the study before randomization and the first exposure to study products are defined as screen failures. Data for screen failures will be collected in source documentation at the study center but will not be entered into a CRF.

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 if their potential eligibility status has changed. Eligible subjects may then be enrolled in the study.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatments

The following investigational products will be supplied by Stiefel in open-label containers:

- GSK2894512 0.5% cream (5 mg/g): ~ 0.75 mg active per patch
- GSK2894512 1% cream (10 mg/g): ~ 1.5 mg active per patch
- GSK2894512 2% cream (20 mg/g): ~ 3 mg active per patch
- Vehicle cream

Subjects completing the study will be exposed to approximately 5.25 mg of GSK2894512 per day, with a total of approximately 111 mg over a period of 21 days.

GSK2894512 is a white to off-white cream packaged in 45-gram laminate tubes. The contents of the label will be in accordance with all applicable regulatory requirements.

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

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Storage temperature should be from 15°C to 30°C (59°F to
Site staff should monitor temperature, maintain a temperature log, and notify the study monitor of any deviations outside of the specified range.

Investigational product will be shipped to the study center after receipt of required documents in accordance with Stiefel/GSK procedures and applicable regulatory requirements. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be administered only to subjects enrolled in the study and in accordance with the protocol.

The following control agents will be supplied by the study centers:

- Positive control: SLS 2% (20 mg/g) solution
- Negative control: Petrolatum

The study centers will also provide specialized semi-occlusive patches/test strips and semi-occlusive tape.

### 5.1.1. Application of Study Products

Each of the 6 study products (tests and controls) will be applied to the respective test fields (approximately 2 cm x 2 cm) using the specialized patches. Approximately 150 μL (0.15 mL) of the creams and petrolatum will be applied to the respective patches using a 1-mL tuberculin syringe. Approximately 150 μL (0.15 mL) of the SLS 2% solution will be pipetted onto a patch using a Pipette. The respective amounts ensure continuous contact of the skin with the study products over the entire exposure period.

A trained technician will concurrently apply each set of 6 patches to the designated test sites on the subject’s back in accordance with the permutation in the randomization list once daily for a total of 21 days. The distance between test fields will be at least 1.3 cm. The patches will be fixed to the skin with adhesive and the outline of the test field will be drawn on the skin using a stencil. If additional fixation of patches is needed, an adhesive bandage will be applied to the edges of the patch(es).

All patches will be prepared, applied, and removed by a trained technician at the study center. Subjects will be instructed to return to the study center with patches in place. Approximately 23 ±2 hours after each application, all patches will be removed by a trained technician. Any remaining residue from the study products will be removed with a clean soft towel or gauze before the blinded evaluator assesses the test sites for signs of dermal reactions. New patches will be applied to the same test sites immediately after clinical assessments.

In the event of scheduling conflicts, subjects may miss a maximum of 2 application visits; however, the missed visits may not be on consecutive days and all patches should remain in place until the next visit (approximately 46 hours after the last application of study products). In case of dislodgment or misplacement of a patch during the study, the responsible investigator will assess whether this application should be considered as a missing application. Unless criteria for discontinuing patch applications are met (see Section 5.1.2), no other modifications of the dosing regimen are allowed.
The dates and times of application and removal will be recorded on the source documents and the CRF.

5.1.2. Criteria for Discontinuing Individual Study Products

If the evaluator for a test site notes a score ≥3 on the dermal response grading scale or a letter score of F, G, or H for other effects, applications of the study product at the affected site should be discontinued permanently for the affected subject. It is recommended that a photograph of the back showing all test sites be taken for sponsor review. Photographs will not be used for grading or analysis purposes.

The evaluator will continue with assessments of the dermal reactions after discontinuation of the test field. The subject should remain in the study and applications at all other test sites should continue per protocol, unless discontinuation criteria are also met at those sites. The assessment score for the discontinued test site will be carried forward (i.e., last observation carried forward method) as the final score for the purposes of the statistical analysis.

In case of severe reactions related to a specific study product, the investigator, after consultation with the sponsor, may prematurely discontinue applications of this product for all subjects. To keep the evaluator blinded, the investigator will inform the study nurse/coordinator who is responsible for the product application about which test field(s) is deemed necessary to be discontinued.

5.2. Treatment Assignment

All subjects will be exposed to the same study products. There will be no subdivision into separate dosing groups. The specific locations of application (i.e., test sites) of each study product for an individual subject will be determined on Day 1 according to the overall randomization schedule, which will be computer generated by the designated contract research organization. Once a randomization number has been assigned to a subject, it should not be re-assigned to any other subject.

The 4 study products will be assigned the codes A, B, C, and D. The negative and positive controls will be assigned the codes E and F, respectively. Randomization will be performed using PROC PLAN method and SAS software Version 9.1.3 or higher (SAS Institute Inc, Cary, NC) by assignment of random permutations of the treatment codes (i.e., A through F) to the random numbers for each test field (i.e., 1 through 6). The treatment listed first in the respective permutation will be assigned to Field 1, the second to Field 2, the third to Field 3, etc. A permutation will be randomly assigned to each subject.

Special treatment code templates will be prepared for each randomization number for use at the clinical site. These templates show the layout of the test fields as specified in the clinical protocol in such a way that the technician can use the template as a guide for application (Figure 2).
5.3. Blinding

This is an evaluator-blinded study; therefore, the designated evaluator will be unaware of which study products are applied to which test sites. Study-center staff responsible for preparation and application of the patches will not be blinded to the test site allocations and will be instructed not to reveal the identity of the allocations to the blinded evaluator.

Individuals, other than the blinded evaluator, who are involved with the conduct, analysis, and reporting of clinical study data (e.g., the sponsor) will not be blinded to test site allocations.

The randomization list and a sealed envelope containing the list with the treatment codes will be 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 both study products concurrently and there will be no subdivision into separate dosing groups, it is unlikely that unblinding the randomized test site allocations will provide any additional knowledge that would be essential. However, if the investigator determines that the occurrence of a test site-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 patches (who are unblinded to the randomization list) will determine which treatment is assigned to the test area(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 Stiefel medical monitor or appropriate Stiefel study personnel to discuss options before unblinding the subject’s treatment assignment. If Stiefel study personnel are not contacted before the unblinding, the investigator must notify Stiefel as soon as possible after unblinding. The date and reason for the unblinding must be fully documented in the appropriate data collection tool. For any AE or serious adverse event (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 site allocations (ie, is unblinded). The primary reason for discontinuation (the event or condition that led to the unblinding) will be recorded in the CRF.

GSK Global Clinical Safety and Pharmacovigilance will be sent a copy of the randomization list. If an SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject’s randomized assignments, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

5.4. Product Accountability

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.

All unused study product containers must be kept until the monitor has reconciled delivery records with accountability logs. After reconciliation of any discrepancies between the amount of GSK2894512 and vehicle cream received and dispensed, the site may destroy the containers, unless otherwise directed by the sponsor. An accounting must be made of any drug deliberately or accidentally destroyed.

5.5. Compliance

Detailed instructions concerning protocol requirements will be provided to the subject at Screening and Baseline. Subject compliance with the study procedures will be documented by study personnel at the study center.

At each visit, designated study staff will check if the patches remain in place to ensure continuous contact of the study products with the subject’s skin since the previous visit. In case of dislodgment or misplacement of a patch, the responsible investigator will assess whether this application should be considered as a missing treatment.
5.6. Concomitant Medications and Nondrug 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 CRF with end dates, if end dates are available.

5.6.1. Permitted Medications and Nondrug Therapies

Subjects are allowed to use contraceptives (for indications other than pregnancy prevention), acetaminophen/paracetamol, vitamin and mineral supplements, medications for regulation of thyroid function, 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.

5.6.2. Prohibited Medications and Nondrug 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>
<tbody>
<tr>
<td>Systemic immunomodulators or slow-release corticosteroids</td>
<td>3 months</td>
</tr>
<tr>
<td>Investigational products or procedures (including other patch testing studies)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Immunizations</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Antihistamines, selective leukotriene receptor antagonists (eg, montelukast sodium, zafirlukast), or mast cell stabilizers (eg, cromolyn sodium or nedocromil sodium)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Systemic nonsteroidal anti-inflammatory medications (stable, low dose nonsteroidal anti-inflammatory use is permitted)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Topical corticosteroids, anti-inflammatories, or immunomodulators, or other topical medications or products (including, but not limited to, self-tanning products, waxing products, benzoyl peroxide, salicylic acid, or sulfur) in the areas of testing</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Allergy injections (immunotherapy)</td>
<td>1 week</td>
</tr>
<tr>
<td>Personal care products in the areas of testing (including, but not limited to, body oils, moisturizers, creams, lotions, astringents, soaps, body washes, or cosmetics)</td>
<td>1 day</td>
</tr>
</tbody>
</table>
5.7. Treatment of Study Treatment Overdose

Not applicable. Patches will be prepared and applied at the study center by trained technicians; therefore, overdose is unlikely.

6. STUDY ASSESSMENTS AND PROCEDURES

Subjects will have study visits once daily, at approximately the same time each day, for 22 consecutive days (Table 3). Visit schedules should be timed such that test site evaluations are conducted approximately 23 ± 2 hours after the patches were applied.

Table 3 Time and Events Table

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen</th>
<th>Baseline</th>
<th>Exposure Period: Daily Clinic Visits</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>X</td>
<td></td>
<td>Day 2 through Day 21</td>
<td>Day 22/ Early WD</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Exposure Period: Daily Clinic Visits</td>
<td>Up to Day -28 a</td>
<td>Day 1 a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Study</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

- **Written informed consent**: X
- **Inclusion/exclusion criteria**: X X
- **Demographics & medical history**: X
- **Vital signs**: X X Every other day b X
- **Electrocardiogram**: X Day 11 (+2 days) X (+2 days)
- **Clinical laboratory testing**: X Day 11 (+2 days) X
- **Plasma concentration of GSK2894512**: Day 11 (+2 days) X
- **Concomitant medications**: X X X X
- **Adverse event query**: X X X X
- **Compliance instructions/query**: X X X X
- **Apply patches (all 6 concurrently)**: X X
- **Remove patches**: X X
- **Evaluate test sites for skin reactions**: X c X

- a. The Screening Visit may be conducted up to 28 days before the Baseline/Day 1 visit, or the Screening and Baseline Visits may be combined.
- b. 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. During the Exposure Period, vital signs should be obtained every other day on even study days (ie, Day 2, Day 4, Day 6, etc).
- c. If a score ≥3 on the dermal response grading scale or a letter score of F, G, or H for other effects is noted, subsequent applications of that study product should be discontinued for the subject for the remainder of the study; however, evaluations of the test site should continue. Applications of the other study products should be continued per protocol.

6.1. Screening and Baseline

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 4 weeks prior to the Baseline visit. Baseline tests and procedures must be performed before randomization and the first application of study products.

The subject’s Fitzpatrick skin type (Table 4) should be documented with demographics.

**Table 4**  
**Fitzpatrick Skin Type Classification**

<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.

6.2. **Completion of Study**

Whether a subject completed the study and the last date of study participation will be recorded in the source documents and CRF. Subjects who complete the study are those who complete the final visit on Day 22. The last date of study participation is the date of the last visit (ie, Day 22).

6.3. **Efficacy**

There are no efficacy assessments in this study.

6.4. **Assessment of Cumulative Irritation**

All evaluations will be performed by a qualified investigator or designated evaluator (ie, dermatologist or physician with dermatological training) who is experienced in assessing dermal reactions in similarly-designed patch test studies and who is blinded to the randomized test site assignments. 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.

Each set of 6 patches will be removed by appropriately-trained study center staff after 23 ±2 hours, and a clean soft towel or gauze will be used to gently wipe residual material from the test sites before evaluation by the investigator.

Within 30 minutes after patch removal, the investigator or designee will visually assess and grade erythema and dermal reactions at each test site using the scale in Table 5 and
noting any other effects as described in Table 6. Scoring will be conducted under daylight conditions. Additionally, a handheld lamp with a 100-watt incandescent blue bulb may be used as an artificial light source to illuminate the test areas. The evaluator should not refer to scores from previous time points.

Application of an individual study product will be discontinued in the event of an erythema score ≥3 or a letter of F, G, or H for other effects at the associated test site (see Section 5.1.2); however, assessments of dermal reactions at that test site will continue.

Any skin reaction not captured by the grading scale (eg, deemed related to the patches or tape) will be documented as an AE.

### Table 5  Erythema and Dermal Response Grading Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of irritation</td>
</tr>
<tr>
<td>1</td>
<td>Minimal erythema; barely perceptible</td>
</tr>
<tr>
<td>2</td>
<td>Definite erythema, readily visible, or minimal edema, or minimal papular response</td>
</tr>
<tr>
<td>3</td>
<td>Erythema and papules</td>
</tr>
<tr>
<td>4</td>
<td>Definite edema</td>
</tr>
<tr>
<td>5</td>
<td>Erythema, edema, and papules</td>
</tr>
<tr>
<td>6</td>
<td>Vesicular eruption</td>
</tr>
<tr>
<td>7</td>
<td>Strong reaction spreading beyond test site</td>
</tr>
</tbody>
</table>

Source: [FDA, 1999]

### Table 6  Other Effects

<table>
<thead>
<tr>
<th>Notation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Slight glazed appearance</td>
</tr>
<tr>
<td>B</td>
<td>Marked glazing</td>
</tr>
<tr>
<td>C</td>
<td>Glazing with peeling and cracking</td>
</tr>
<tr>
<td>F</td>
<td>Glazing with fissures</td>
</tr>
<tr>
<td>G</td>
<td>Film of dried serous exudate covering all or portion of the test site</td>
</tr>
<tr>
<td>H</td>
<td>Small petechial erosions and/or scabs</td>
</tr>
</tbody>
</table>

Source: [FDA, 1999]
Table 7  Additional Definitions and Descriptions of Reaction Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>Pink or red coloration</td>
</tr>
<tr>
<td>Edema</td>
<td>Swelling, spongy feeling when palpated</td>
</tr>
<tr>
<td>Papule</td>
<td>Red, solid elevation</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Small elevation containing fluid; &lt;0.5 cm</td>
</tr>
<tr>
<td>Bulla</td>
<td>Fluid-filled lesion (blister); &gt;0.5 cm</td>
</tr>
<tr>
<td>Spreading</td>
<td>Evidence of the reaction extending beyond the area of the test site</td>
</tr>
<tr>
<td>Weeping</td>
<td>Serous exudate, result of a vesicular or bullous reaction</td>
</tr>
<tr>
<td>Induration</td>
<td>Solid, elevated, hardened, thickened skin</td>
</tr>
<tr>
<td>Fissures</td>
<td>Grooves in the superficial layers of the skin</td>
</tr>
</tbody>
</table>

6.5. Safety

Safety will be assessed by evaluation of AEs, vital signs, ECGs, clinical laboratory test results, and reasons for withdrawal from the study.

6.5.1. Electrocardiogram

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, QTcF) should be used for subject eligibility, withdrawal criteria, and data analysis. Refer to Section 4.5.1 for QTc withdrawal criteria and additional readings that may be necessary.

6.5.2. Clinical Laboratory Assessments

The following laboratory parameters will be assessed:

<table>
<thead>
<tr>
<th>Hematology</th>
<th>RBC Indices:</th>
<th>Automated WBC Differential:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cell count</td>
<td>Mean corpuscular volume</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>White blood cell count (absolute)</td>
<td>Mean corpuscular hemoglobin</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Mean corpuscular hemoglobin concentration</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td>Basophils</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Chemistry</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>Blood urea nitrogen</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Glucose, fasting</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>Chloride</td>
<td>Carbon dioxide, total</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>Sodium</td>
<td>Calcium</td>
<td>Alkaline phosphatase</td>
</tr>
</tbody>
</table>
Note: Details of liver chemistry stopping criteria and follow-up procedures are given in Section 4.5.1 and Appendix 2.

If additional laboratory assessments not specified in the protocol are performed and result in a change in subject management or are considered clinically significant (for example an SAE or AE or dose modification) by the investigator, the results must be captured and sent to the sponsor along with other study data.

6.5.3. Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or an SAE.

6.5.3.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (eg, 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.
6.5.3.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization
   - NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
   - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity
   - NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, 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. 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. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) (or ALT ≥3xULN and international normalized ratio (INR) >1.5, if INR measured) termed ‘Hy’s Law’ events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).
NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin $\geq 2 \times$ ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations $>1.5$ suggest severe liver injury.

### 6.5.4. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator’s clinical judgment.

The intensity of each AE and SAE will be recorded in the appropriate AE/SAE data collection tool as per the instructions and will be assigned 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 is 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.

### 6.5.5. Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The following terms are to be used for causality: “yes” or “no.” “Yes” denotes a *reasonable possibility* that a causal relationship exists between the study product and the AE, which 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 investigational product will be considered and investigated. The investigator will also consult the investigator’s brochure (IB) in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to the sponsor. The investigator may change their 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.
The investigator will provide the assessment of causality as per instructions for completion of the AE/SAE data collection tool.

6.5.6. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Whether or not a protocol-specified procedure, any abnormal laboratory test result (ie, hematology, clinical chemistry, or urinalysis) or other safety assessment (eg, ECGs, radiological scans, or vital signs measurements) felt to be clinically significant in the medical and scientific judgment of the investigator, that occurs on the day of informed consent and before first dose of study product will be recorded on the Medical History CRF. New or worsening clinically significant abnormal laboratory test results or other safety assessments that occur subsequently are to be recorded as AEs or SAEs. If the cause of or condition associated with the abnormal result is known, then the cause or condition will be recorded on the CRF; otherwise, the abnormal finding will be recorded on the CRF.

6.5.7. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

All AEs and SAEs will be recorded from the time a subject consents to participate in the study through the final study visit. All SAEs will be reported to the sponsor within 24 hours, as indicated in Section 6.5.8.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE detection period as defined in the protocol. Investigators are not obligated to actively seek AEs or SAEs in former 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 considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify the sponsor.

6.5.8. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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?”
6.5.9. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subject’s condition. All AEs and SAEs documented at a previous visit/contact and that are designated as ongoing, will be reviewed at subsequent visits/contacts.

All SAEs and related AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely.

6.5.10. Prompt Reporting of Serious Adverse Events and Other Events to the Sponsor

SAEs meeting predefined criteria will be reported promptly by the investigator to the sponsor as described in Table 8 once the investigator determines that the event meets the protocol definition for that event.

A copy of the SAE notification form should be completed as fully as possible. Complete details for SAE reporting are provided in the SPM.

Table 8 Reporting of Serious Adverse Events and Other Events

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Initial Reports</th>
<th>Follow-up Information on a Previous Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time Frame</td>
<td>Documents</td>
</tr>
<tr>
<td>All SAEs</td>
<td>24 hours</td>
<td>“SAE” data collection tool</td>
</tr>
<tr>
<td>Nonserious AEs related to study treatment</td>
<td>5 calendar days</td>
<td>“Adverse Reaction” data collection tool</td>
</tr>
</tbody>
</table>

Abbreviations: AE=adverse event; SAE=serious adverse event

The method of recording, evaluating, and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to the sponsor are provided in the SPM. Procedures for poststudy AEs/SAEs are provided in the SPM.

6.5.10.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Stiefel/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. Stiefel/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 Stiefel/GSK policy and are forwarded to investigators as necessary.

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

6.6. Pharmacokinetics

Plasma trough concentrations of GSK2894512 will be measured at Day 11 (±2 days) and Day 22.

Plasma analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, DMPK, GlaxoSmithKline. Concentrations of GSK2894512 will be determined in plasma using the currently-approved analytical methodology. Raw data will be stored in the GLP archives at the site of analysis.

7. DATA MANAGEMENT

For this study, subject data will be collected using Stiefel/GSK-approved CRFs and combined with data provided from other sources (if applicable) in a validated data system.

Management of clinical data will be performed in accordance with applicable Stiefel/GSK standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and concomitant medications terms will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to Stiefel/GSK according to Stiefel/GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

There is no formal hypothesis testing. This study will assess if there is skin irritation related to the use of study products and describe the observed and relative frequency of dermal reactions.

8.2. Study Design Considerations

8.2.1. Sample Size

Up to 46 healthy subjects will be enrolled in this study to have evaluable data from at least 30 subjects patched under semi-occlusive conditions. Sample size is based on the former United States Food and Drug Administration Guidance for Industry, *Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* [FDA 1999].
A formal sample size calculation was not performed. Sample size re-estimation is not planned.

8.3. Data Analysis Considerations

8.3.1. Analysis Data Sets

The Safety analysis set will include all subjects exposed to at least 1 application of study product.

The Per Protocol analysis set will include subjects exposed to study products under semi-occlusive conditions and who complete the study. This analysis set will be used for the analysis of cumulative irritation.

8.3.2. Treatment Comparisons

The primary endpoints are the mean cumulative irritation score and total cumulative irritation score for each concentration of GSK2894512 versus the controls.

The mean cumulative irritation score will be computed by study product for each subject in the Per Protocol analysis set as the sum of dermal response irritation scores from Day 2 through Day 22 divided by the number of nonmissing observations (total of 21 possible scores). The total cumulative irritation score will be computed by study product for each subject as the sum of dermal response irritation scores from Day 2 through Day 22. If a patch is removed due to excessive irritation, the last observation carried forward method will be used to impute scores.

The mean and total cumulative irritation scores will be analyzed using a repeated measures mixed model, provided there are enough non-zero responses for the model to converge and provide estimates of the fixed effects. Treatments (ie, GSK2894512, vehicle, and controls) will be treated as repeated measures within the same subject. Location (ie, test site) will be included in the model as a fixed effect. Prespecified pair-wise treatment comparisons (see Table 9) will be performed within the context of the repeated measures mixed model. Point estimates and 90% confidence intervals for the treatment differences will be computed using model-based estimates from the repeated measures mixed model. The statistical analysis will use SAS software Version 9.1.3 or higher (SAS Institute Inc, Cary, NC, United States).
Table 9  
**Pair-wise Comparisons of Test and Control Products**

<table>
<thead>
<tr>
<th>Study products:</th>
<th>GSK2894512 Cream</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5%</td>
<td>1%</td>
</tr>
<tr>
<td>GSK2894512 Cream</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>0.5%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vehicle</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: SLS=sodium lauryl sulfate

The following comparisons will be done:

- T1 vs. R1;
- T1 vs. R2;
- T1 vs. R3;
- T2 vs. R1;
- T2 vs. R2;
- T2 vs. R3;
- T3 vs. R1;
- T3 vs. R2;
- T3 vs. R3;
- T1 vs. T2;
- T1 vs. T3;
- T2 vs. T3;
- R1 vs. R2;
- R1 vs. R3

Where, T1: GSK2894512 0.5% cream; T2: GSK2894512 1% cream; T3: GSK2894512 2% cream; R1: vehicle cream; R2: SLS 2% solution; R3: petrolatum

Frequency counts and percentages of subjects with dermal responses will be tabulated by visit and study product. Individual subject data for each visit and test site will be presented in a by-subject listing.

### 8.3.3. Key Elements of Analysis Plan

Descriptive statistics will be used to provide safety results by visit. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, minimum, and maximum. Appropriate inferential statistics will be used for the primary variables.

The number of subjects enrolled and the number of subjects included in each analysis set will be summarized. Reasons for withdrawal from the study will be summarized with frequencies and percentages.

Demographic data, including age, sex, race, ethnicity, and Fitzpatrick skin type, will be summarized and will be listed by subject.

#### 8.3.3.1. Efficacy Analyses

Not applicable.
8.3.3.2. Safety Analyses

Extent of exposure to each study product will be summarized and will be listed by subject.

Adverse events 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. Adverse event onset, severity, relationship to study product, action taken, and outcome will be listed by subject.

Vital sign and clinical laboratory absolute and change from baseline values will be summarized by time point. The number of subjects with abnormal ECG results will be summarized by time point.

Medical history and concomitant medications will be listed by subject.

8.3.3.3. Pharmacokinetic Analyses

Plasma concentration data will be presented in a tabular summary by collection day.

8.3.4. Interim Analysis

An interim analysis is not planned.

9. STUDY CONDUCT CONSIDERATIONS

9.1. 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.

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

The study will be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), all applicable regulatory requirements, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Stiefel will provide full details of the above procedures, either verbally, in writing, or both.
Written informed consent must be obtained from each subject prior to participation in the study.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information, approved by the IRB/IEC, regarding the objective and procedures of the study, the benefits of the study, and the possible risks involved. The information must be provided to the subject prior to undertaking any study-related procedures. The subjects must be informed about their right to withdraw from the study at any time. It is the responsibility of the investigator to obtain signed and dated informed consent from all subjects, and a signature from the person conducting the informed consent discussion, prior to undertaking any study-related procedures.

Informed consent must be obtained in accordance with ICH GCP and all applicable local and national regulations. In the United States, subjects must also understand and sign a Health Insurance Portability and Accountability Act authorization form (may be included in the informed consent form), before any study-related procedures can be performed.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Stiefel/GSK procedures, monitors designated by Stiefel 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 sponsor requirements. When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which the CRF will serve as the source document.

The study will be monitored to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the 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.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor 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.
9.5. Study and Site Closure

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

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and Stiefel/GSK standard operating procedures.

Stiefel reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Stiefel determines that such action is required, Stiefel will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Stiefel will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, Stiefel will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Stiefel will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or 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 easily accessible when needed (e.g., for a Stiefel/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 the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must 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. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Stiefel will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Stiefel/GSK standard operating procedures, and/or institutional requirements.
The investigator must notify Stiefel of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

**9.7. 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 Stiefel site or other mutually-agreeable location. Stiefel 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 results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject’s last visit. When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.
10. REFERENCES


11. APPENDICES

11.1. Appendix 1: Predicted Exposure to GSK2894512 under Maximized Occlusive Testing Conditions

Under Protocol Amendment 2, approximately 150 µL of GSK2894512 0.5%, 1%, and 2% creams will be applied to the respective test fields using patches approximately 2 cm x 2 cm. Up to 5.25 mg of GSK2894512 will be applied under semi-occlusion each day over 12 cm$^2$ of skin on the back, which is less than 0.07% of body surface area in an adult with a body surface area of 1.73 m$^2$. Over the 21-day study period, each subject will be exposed to up to 111 mg of GSK2894512.

The systemic exposure potential calculated below is based on the originally-planned fully occlusive patch-testing conditions. Although a slightly larger body surface area will now be exposed, it is anticipated that the semi-occlusive testing using a smaller volume of cream will result in a materially lower systemic exposure to GSK2894512, and the overall systemic exposure potential from the patch testing will be no greater than the originally calculated levels. However, the exact level of GSK2894512 percutaneous absorption and its consequent systemic bioavailability are difficult to predict.

**Systemic exposure potential based on original patch-testing assumptions**

Approximately 200 µL of the 0.5%, 1%, and 2% GSK2894512 creams will be applied to the respective test fields using the test chambers. Up to 7 mg of GSK2894512 will be applied with occlusion each day in each subject over 7.63 cm$^2$ of skin on the back, which is less than 0.05% of body surface area in an adult with a body surface area of 1.73 m$^2$. Over the 21-day study period, each subject will be exposed to up to 147 mg of GSK2894512. The systemic exposure potential of GSK2894512 was estimated by extrapolating from the pharmacokinetic data of the 4-week study in subjects with psoriasis (WBI-1001-101). To assume the worst case, data from the 2% treatment cohorts was used as the systemic exposure represented by mean AUC$_{0-8h}$ and mean $C_{max}$ was greatest in those cohorts when normalized by the percentage of body surface area treated. In addition, all 3 sites were assumed to be treated with 2% GSK2894512 in the cumulative irritation study for ease of extrapolation and added safety margin.

Assumptions and considerations:

- Assume linear relationship between the size of treatment area and systemic exposure.
- Application of GSK2894512 under the occluded conditions described in this protocol is likely to result in higher systemic exposure compared with the nonoccluded application in Study WBI-1001-101.
- Application of GSK2894512 to healthy skin is likely to result in similar or lower systemic exposure compared with application to psoriatic skin in Study WBI-1001-101 based on the difference in skin barrier function.

The effect of occlusion, and longer duration in some cases, of drug exposure on the percutaneous absorption of different compounds reported varies from a 1.4-fold increase to a 10-fold increase [Hafeez 2013]. In various human *in vivo* studies, the difference
between healthy skin and psoriatic skin in penetration of different substances is shown to vary from none to a 20-fold increase [Chiang 2012]. Although it is difficult to precisely predict the overall effect of the 2 opposing factors, conservatively assuming negligible difference in the skin conditions and maximum reported effect of occlusion, above mentioned differences in treatment condition are not expected to result in more than a 10-fold increase in systemic exposure in the irritation study. Based on these assumptions, the mean AUC\textsubscript{0-24h} is expected to be less than 1.11 ng*h/mL and C\textsubscript{max} less than 0.61 ng/mL (Table 10).

### Table 10: Estimated Systemic Exposure in Irritation Study IPS117191

<table>
<thead>
<tr>
<th></th>
<th>Mean AUC\textsubscript{0-24h} (ng*h/mL)</th>
<th>Mean C\textsubscript{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK2894512 2% cream once or twice daily over 1.26% BSA (mean) for up to 4 weeks (WBI-1001-101) – Observed on Day 0</td>
<td>2.765\textsuperscript{a}</td>
<td>1.51</td>
</tr>
<tr>
<td>GSK2894512 2% cream once daily over less than 0.05% BSA for 21 days (IPS117191) – Estimated</td>
<td>1.11</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Abbreviations: BSA=body surface area

\textsuperscript{a} Estimated to be equal to mean AUC\textsubscript{0-8h}. Only 3 of 36 subjects showed 3 consecutive blood samples with quantifiable levels of GSK2894512. In these subjects, extrapolation for AUC\textsubscript{0-24h} from AUC\textsubscript{0-8h} and concentration at t=8h using apparent first-order terminal elimination half-life revealed negligible increase.

**Comparison of predicted human plasma exposures to nonclinical toxicity study exposures**

In nonclinical toxicity studies, the principal test article-related findings were in the skin, liver, and thymus, with associated secondary hematological findings. A no observed adverse effects level (NOAEL) was identified in each of the nonclinical species for the dermal and subcutaneous administration. The mean systemic exposure corresponding to the identified NOAELs ranged from 99 to 2600 ng*h/mL in AUC and from 7.13 to 888 ng/mL in C\textsubscript{max} at study end.

In the 3-month dermal minipig study using up to 4% GSK2894512, the treatment effects of twice daily application of GSK2894512 at 37.8 mg/cm\textsuperscript{2} were limited to very mild, reversible dermal changes for all groups including controls and minor, reversible clinical pathology effects for animals dosed at 4%. Based on the findings, the NOAEL was identified as 4% with corresponding mean AUC\textsubscript{0-24h} of 99 ng*h/g/mL and mean C\textsubscript{max} of 7.13 ng/mL at Week 13. In the 13-week rat study with subcutaneous injection of GSK2894512, adverse dermal observations consisting of swelling, discoloration, firmness, and/or sores or scabs of the dermis were found in multiple animals at all dose levels. However, similar dermal lesions in control animals of lower severity and incidence suggested some effects from the vehicle, which is specific to the subcutaneous route, and hence NOAEL was not established. In rats given 10 mg/kg/day or more of GSK2894512, decreases in mean absolute and relative thymus weights were observed along with thymus lymphoid depletion. No systemic test article-related adversity was noted in animals given 3 mg/kg/day with corresponding AUC\textsubscript{0-24h} of 100 ng*h/mL and C\textsubscript{max} of 32 ng/mL at Week 13.
At the proposed dosage and concentrations for the clinical cumulative irritation study, the safety margins are approximately 90-fold (in minipigs and rats) for AUC and range from 12-fold (in minipigs) to 52-fold (in rats) for $C_{\text{max}}$ using data from the 13-week nonclinical studies (Table 11), and go as high as 2300-fold for AUC and 1400-fold for $C_{\text{max}}$ using data from the 28-day rat studies. These results support the evaluation of topically-applied GSK2894512 in the cumulative irritation study at the proposed dose with up to 2% GSK2894512 with appropriate monitoring of clinical parameters.

Table 11  Exposure Safety Margins for Predicted Clinical Exposure in Irritation Study IPS117191

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th></th>
<th>C$_{\text{max}}$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOAEL (ng*h/mL)</td>
<td>Predicted (ng*h/mL)</td>
<td>Safety Margin</td>
<td>NOAEL (ng/mL)</td>
</tr>
<tr>
<td>Dermal, Minipig, 13 weeks, 4%</td>
<td>99</td>
<td>1.11</td>
<td>90</td>
<td>7.13</td>
</tr>
<tr>
<td>Subcutaneous, Rat, 13 weeks, 3 mg/kg/day</td>
<td>99.2$^a$</td>
<td>1.11</td>
<td>90</td>
<td>32</td>
</tr>
</tbody>
</table>

$^a$ Skin lesions were observed at all doses including the vehicle (of lower severity and incidence compared with the active doses). No systemic test article-related adversity was noted at this level of exposure.

References


11.2. Appendix 2: Liver Safety Process

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the Food and Drug Administration premarketing clinical liver safety guidance).

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criterion of ALT $\geq 3x$ULN (Section 4.5.1):

- Immediately withdraw the subject from study treatment.
- Notify the medical monitor within 24 hours of learning of the abnormality to confirm the subject’s study treatment cessation and follow-up.
- Complete the “Safety Follow-Up Procedures” listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 6.5.3.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required.
- Do not restart the study product.

Safety follow-up procedures for subjects with ALT $\geq 3x$ULN:

- Monitor subjects weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) resolve, stabilize, or return to within screening/baseline values.

Safety follow-up procedures for subjects with ALT $\geq 3x$ULN and total bilirubin $\geq 2x$ULN (>35% direct); or ALT $\geq 3x$ULN and INR $>1.5$:

- This event is considered an SAE (see Section 6.5.3.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have the subject return to the clinic (within 24 hours) for repeat liver chemistries, additional testing, and to be monitored closely (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, and bilirubin) resolve, stabilize, or return to within screening/baseline values.

For all subjects with ALT $\geq 3x$ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.
- Hepatitis B surface antigen and Hepatitis B core antibody (IgM).
- Hepatitis C ribonucleic acid.
- Cytomegalovirus IgM antibody.
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
- Hepatitis E IgM antibody.
- Serum creatine phosphokinase and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) as relevant on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the concomitant medications CRF.
- Record alcohol use on the liver events CRF.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- Liver imaging and/or liver biopsy CRFs are also to be completed if these tests are performed.

Refer to Figure 3 for a visual presentation of the procedures listed above.
Figure 3  Liver Safety Flow Chart

ALT ≥ 3xULN?

No

Continue investigational product (IP)

Yes

Bilirubin ≥ 2xULN (or INR > 1.5 if measured)*?

No

Discontinue applications of IP
Notify GSK within 24 hrs
Obtain weekly liver chemistries until resolved, stabilized or returned to baseline values
Perform liver event follow up assessments (serology, PK sample, etc as in protocol)
Complete liver event CRF
Withdraw subject from study after liver chemistry monitoring complete + do not re-challenge with IP

Yes

Discontinue applications of IP
Notify GSK and arrange clinical followup within 24 hrs
Perform liver event follow up assessments (serology, PK sample etc as in protocol)
Report as SAE (excl. hepatic impairment or cirrhosis studies); complete SAE & liver event CRF + liver imaging and biopsy CRFs (if these tests are performed)
Obtain twice weekly liver chemistries until resolved, stabilized or returned to baseline values
Consultation with hepatologist/specialist recommended
Withdraw subject from study after liver chemistry monitoring complete + do not re-challenge with IP

*INR threshold does not apply to subjects receiving anticoagulants.
## 11.3. Appendix 3: Protocol Changes

**Protocol Amendment 1: 16 October 2013**

Applicable to all subjects.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Changes</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title page</td>
<td>NA</td>
<td>Protocol amendment number and revision chronology</td>
<td>NA</td>
</tr>
<tr>
<td>Protocol summary; Section 2.1</td>
<td>Secondary Objective:</td>
<td>• To determine plasma concentrations of GSK2894512.</td>
<td>New endpoint to determine systemic exposure.</td>
</tr>
<tr>
<td>Protocol summary; Section 3.1, Section 6.5</td>
<td>Safety will be assessed by evaluating adverse events and reasons for withdrawal from the study.</td>
<td>Safety will be assessed by evaluating adverse events, vital signs, electrocardiograms, clinical laboratory test results, and reasons for withdrawal from the study.</td>
<td>Additional safety evaluations added to the study.</td>
</tr>
<tr>
<td>Section 1.3.1</td>
<td>The clinical assessments of dermal reactions are noninvasive procedures...</td>
<td>The clinical assessments of dermal reactions (ie, visual evaluation and scoring) are noninvasive procedures...</td>
<td>Clarification.</td>
</tr>
<tr>
<td>NA</td>
<td>Nasopharyngitis and headache were the most frequently-reported (&gt;10% of subjects) nondermatological AEs overall.</td>
<td></td>
<td>Alignment with AE summary in IB.</td>
</tr>
<tr>
<td>Table 1</td>
<td>Systemic reactions:</td>
<td>In a nonclinical study in minipigs using intravenous administration, reversible decreases in arterial blood pressure and PR interval were observed; however, in dermal toxicity studies there were no effects on QT interval or heart rate. Vital signs will be taken at screening, baseline, and every other day during the study. An ECG will be performed and blood will be collected at screening, Day 11, and Day 22 to monitor cardiac safety, laboratory parameters, and plasma concentrations of GSK2894512.</td>
<td>Additional safety evaluations added to the study based on reversible cardiovascular findings in a nonclinical study of intravenous administration.</td>
</tr>
</tbody>
</table>
Table 1
Potential Risks and Mitigation Strategies

Reaction to the testing materials or exposure conditions:

The subject may be discontinued from the study at the discretion of the investigator (Section 4.5.1). If needed, appropriate topical or systemic treatment will be provided.

Section 2.2
Secondary Endpoints:

• Change from baseline in vital signs, clinical laboratory parameters, and electrocardiogram findings.
• Plasma trough concentrations of GSK2894512.

Section 4.2

...Fitzpatrick skin types I (always burns); never tans), II (always burns easily; tans minimally), III (burns moderately; tans gradually)...

...Fitzpatrick skin types I (always burns; never tans), II (usually burns; tans with difficulty), III (sometimes mild burn; gradually tans)...

Section 4.3

Exclusion Criteria:

10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Alanine aminotransferase, alkaline phosphatase, or bilirubin >1.5x upper limit of normal (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%).

11. QTc ≥450msec or QTc ≥480msec for subjects with bundle branch block.

Section 4.5.1

Subject Discontinuation:

• Liver chemistry: ALT ≥3xULN (refer to Appendix 2 for details of the required assessments).
• QTc >500 msec or uncorrected QT >600 msec; change from baseline QTc >60 msec.

Section 5.1.1

Application of Study Products:

In the event of scheduling conflicts, subjects may miss a maximum of 2 application visits; however, the missed visits may not be on consecutive days and all test chambers should remain in place until the next visit (approximately 46 hours after the last application of study products).

Considering the timing of the study, it may be challenging for subjects to attend all 22 visits. A missed application is not expected to affect the overall analysis of irritation.
<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Changes</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 5.6.1</td>
<td>…are allowed to use contraceptives…</td>
<td>…are allowed to use contraceptives (for indications other than pregnancy prevention)…</td>
<td>Clarification.</td>
</tr>
<tr>
<td>Table 3 Time and Events Table</td>
<td>Vital signs: screening</td>
<td>Vital signs at screening, baseline, every other day, Day 22 ECG, clinical laboratory testing, and plasma concentrations of GSK2894512 at screening, Day 11, and Day 22.</td>
<td>Added new assessments and timing to Time and Events table.</td>
</tr>
<tr>
<td>Section 6.1</td>
<td>Subject screening should be conducted within 4 weeks prior to the Baseline visit or may take place at the same time as the Baseline visit.</td>
<td>Subject screening should be conducted within 4 weeks prior to the Baseline visit.</td>
<td>Addition of laboratory tests at screening will make a combined screening/baseline visit impractical.</td>
</tr>
<tr>
<td>Section 6.5.1, Section 6.5.2</td>
<td>NA</td>
<td>New sections for descriptions of ECGs and clinical laboratory assessments and analyses.</td>
<td>New assessments.</td>
</tr>
<tr>
<td>Section 6.6</td>
<td>NA</td>
<td>Addition of description for plasma concentrations of GSK2894512.</td>
<td>New assessment.</td>
</tr>
<tr>
<td>Section 8.3.3.2</td>
<td>NA</td>
<td>Vital sign and clinical laboratory absolute and change from baseline values will be summarized by time point. The number of subjects with abnormal ECG results will be summarized by time point.</td>
<td>New assessments.</td>
</tr>
<tr>
<td>Section 8.3.3.3</td>
<td>NA</td>
<td>Plasma concentration data will be presented in a tabular summary by collection day.</td>
<td>Analysis of new secondary endpoint.</td>
</tr>
<tr>
<td>Appendix 1, Table 10</td>
<td>…over 1.24% BSA…</td>
<td>…over 1.26% BSA…</td>
<td>Correction.</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>NA</td>
<td>Addition of detailed description of liver safety monitoring process.</td>
<td>New criteria.</td>
</tr>
</tbody>
</table>
## Protocol Amendment 2: 13 December 2013

Applicable to all sites and to all subjects enrolled after the effective date of this amendment. At the time of this amendment, 6 subjects had been randomized in the study.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Changes</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title page</td>
<td>NA</td>
<td>Protocol amendment number and revision chronology</td>
<td>NA</td>
</tr>
<tr>
<td>Throughout the protocol</td>
<td>...test chambers...</td>
<td>...patches...</td>
<td>Revised patch-testing conditions.</td>
</tr>
<tr>
<td></td>
<td>...occlusion...</td>
<td>...semi-occlusion...</td>
<td></td>
</tr>
<tr>
<td>Sponsor Information Page</td>
<td>MD, FAAD Manager, Clinical Development, Dermatology</td>
<td>MD, PhD, MBA, FAAD Executive Director, Medicines Development, Dermatology</td>
<td>Change in medical monitor.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EudraCT Number 2013-005156-15</td>
<td>Addition of EudraCT number.</td>
</tr>
<tr>
<td>Section 1.3.1</td>
<td>...procedures that do not pose a risk...</td>
<td>...procedures that pose minimal risk...</td>
<td>Minimal risk is more accurate.</td>
</tr>
<tr>
<td>Section 2.1</td>
<td>•To determine plasma concentrations of GSK2894512.</td>
<td>•To quantify plasma concentrations of GSK2894512.</td>
<td>Quantify is more accurate.</td>
</tr>
<tr>
<td>Protocol summary; Section 3.1</td>
<td>...single-center...</td>
<td>...multicenter...</td>
<td>A second study center will be added to facilitate enrollment.</td>
</tr>
<tr>
<td>Protocol summary; Sections 3.1, 4.1, 8.2.1</td>
<td>...enroll approximately 40 subjects in order to have at least 30 evaluable subjects at the end of the study.</td>
<td>Up to 46 subjects will be enrolled in order to have at least 30 evaluable subjects patched under semi-occlusive conditions.</td>
<td>The total number of subjects was increased due to the nature of the amendment.</td>
</tr>
<tr>
<td>Sections 3.1, 3.2.1, 5.1, 8.3.2</td>
<td>...sodium lauryl sulfate 0.4% solution...</td>
<td>...sodium lauryl sulfate 2% solution...</td>
<td>Application of SLS 0.1% under semi-occlusive patch conditions is unlikely to produce the same degree of irritation that would be expected with full occlusion; therefore, the concentration will be increased to 2% to ensure a positive irritation response will be observed.</td>
</tr>
<tr>
<td>Section</td>
<td>Original Text</td>
<td>Changes</td>
<td>Rationale</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Section</td>
<td>Predicted Exposure to GSK2894512</td>
<td>Predicted Exposure to GSK2894512 under Maximized Occlusive Testing Conditions</td>
<td>Clarification that calculations were based on original assumptions.</td>
</tr>
<tr>
<td>3.2.2;</td>
<td>..predicted maximum systemic exposure...</td>
<td>...predicted maximum systemic exposure... assuming fully occlusive testing conditions... It is anticipated that semi-occlusive testing will result in a materially lower systemic exposure to GSK2894512; however, the exact level of GSK2894512 percutaneous absorption and its consequent systemic bioavailability are difficult to predict.</td>
<td></td>
</tr>
<tr>
<td>Appendix 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Re screening of subjects who were screen failures is not permitted.</td>
<td>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 if their potential eligibility status has changed. Eligible subjects may then be enrolled in the study.</td>
<td>The recruiting period for this study has been increased.</td>
</tr>
<tr>
<td>Section</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GSK2894512 0.5% cream (5 mg/g): ~0.9 to 1 mg</td>
<td>GSK2894512 0.5% cream (5 mg/g): ~0.75 mg active</td>
<td>Revised patch-testing conditions.</td>
</tr>
<tr>
<td></td>
<td>GSK2894512 1% cream (10 mg/g): ~1.7 to 2 mg</td>
<td>GSK2894512 1% cream (10 mg/g): ~1.5 mg active</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GSK2894512 2% cream (20 mg/g): ~3.5 to 4 mg</td>
<td>GSK2894512 2% cream (20 mg/g): ~3 mg active</td>
<td></td>
</tr>
<tr>
<td></td>
<td>...exposed to approximately 6 to 7 mg of GSK2894512 with a total of approximately 128 to 147 mg.</td>
<td>...exposed to approximately 5.25 mg of GSK2894512 with a total of approximately 111 mg.</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>...packaged in 45 gram laminate tubes or glass jars</td>
<td>...packaged in 45 gram laminate tubes.</td>
<td>Glass jars will not be utilized.</td>
</tr>
<tr>
<td>5.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Original Text</td>
<td>Changes</td>
<td>Rationale</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Section 5.1</td>
<td>...specialized polypropylene-coated test chambers (Finn Chambers; SmartPractice [formerly Epitest Ltd Oy]; 18 mm inside diameter) and occlusive hypoallergenic tape.</td>
<td>... specialized patches/test strips and semi-occlusive tape.</td>
<td>Irritation observed in the first cohort of subjects did not appear to permit differentiation between concentrations of GSK2894512; therefore, changing patch-testing conditions is expected to slow the appearance of irritation. Finn chambers are only used for full occlusion.</td>
</tr>
<tr>
<td>Section 5.1.1</td>
<td>...respective test fields (approximately 2.5 cm²)…</td>
<td>...respective test fields (approximately 2 cm x 2 cm)…</td>
<td>Revised patch-testing conditions.</td>
</tr>
<tr>
<td></td>
<td>...200 μL (0.2 mL)…</td>
<td>...150 μL (0.15 mL)…</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The distance between test fields will be at least 1.5 cm.</td>
<td>The distance between test fields will be at least 1.3 cm.</td>
<td></td>
</tr>
<tr>
<td>Section 5.1.2</td>
<td></td>
<td>It is recommended that a photograph of the back showing all test sites be taken for sponsor review. Photographs will not be used for grading or analysis purposes.</td>
<td>Photographs will provide visual information on the degree of irritation observed in the study to supplement evaluator scoring.</td>
</tr>
<tr>
<td>Table 3</td>
<td>ECG Day 22 (±2 days)</td>
<td>ECG Day 22 (+2 days)</td>
<td>ECG should be performed after the final exposure to study products.</td>
</tr>
<tr>
<td>Section 6.4</td>
<td>Scoring will be conducted using a handheld lamp with a 100-watt incandescent blue bulb…</td>
<td>Scoring will be conducted under daylight conditions. Additionally, a handheld lamp with a 100-watt incandescent blue bulb may be used…</td>
<td>Daylight is preferred.</td>
</tr>
<tr>
<td>Section 8.3.1</td>
<td>Per Protocol analysis set will include subjects exposed to study products in accordance with the protocol…</td>
<td>Per Protocol analysis set will include subjects exposed to study products under semi-occlusive conditions…</td>
<td>Due to the change in patch-testing conditions, only data from subjects exposed under the modified conditions will be used for the irritation analyses.</td>
</tr>
</tbody>
</table>