Clinical Protocol
212383

A Human Repeat Insult Patch Test (HRIPT) in Healthy Subjects to Assess the Cutaneous Irritation and Sensitization Potential of Three Developmental Cosmetic Facial Products.

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CLINICAL PROTOCOL

A Human Repeat Insult Patch Test (HRIPT) in Healthy Subjects to Assess the Cutaneous Irritation and Sensitization Potential of Three Developmental Cosmetic Facial Products.

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Sponsor Information

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1		
Amendment 2		

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

Background and Rationale

A cosmetic product that is freely available to the consumer must be safe and must not cause damage when applied under normal or reasonably foreseeable conditions of use. Thus, as a general requirement, the safety of a developmental formulation should be confirmed before it is marketed (Guideline for the Safety Evaluation of Cosmetic Products; Agência Nacional de Vigilância Sanitária, ANVISA, 2012; Cosmetics Europe, 2004).

The human repeated insult patch test (HRIPT) is a long standing, standard method to determine whether exposure to a topical product will elicit a cutaneous (dermal) irritant or allergic response under exaggerated (occluded) conditions. It is also routinely used and accepted as an appropriate methodology to establish the sensitization potential of topical medicated products by health authorities, including the US FDA and MHRA. The HRIPT requires approximately six weeks and involves three phases: induction, rest and challenge, and is based on the modified Draize test. (Draize *et al*, 1944)

In this randomized, single-center, evaluator-blind study, there will be three test products and a reference product (negative control; saline solution) tested. Controlled amounts of each of the products (0.02 mL/cm^2) will be dispensed into individual cells of defined surface area within a semi-occlusive adhesive patch and the adhesive patch applied to the dorsum of each subject.

The first phase of the study is an induction phase, in which subjects will undergo repeated adhesive patch application for 3 weeks. Patches will remain affixed to the skin for 48 (weekdays) or 72 (weekends) hours during the induction phase, after which they will be removed, the skin evaluated for signs of reactions, and new adhesive patches with all the test products applied to the same site on the dorsum.

After the induction phase is complete, subjects will enter a 2-week rest phase, during which no patches or products will be applied.

After the rest phase is complete, subjects will return to the clinical site for the challenge phase. In this phase, a new adhesive patch containing all the products will be affixed to virgin skin (i.e. previously unpatched) for 48 hours. The patch will then be removed, and the skin assessed for any signs of reactions shortly after patch removal, and the area assessed again after a further 24 and 48 hours.

Any observations that resolve within 48 hours are generally considered to be due to irritation instead of sensitization. An increased intensity over time should be present for the indication of sensitization. Indeed, a crescendo evolution of intensity of scoring or the presence of an eczema like reaction at any time suggests a possible sensitization response.

The objective of this clinical study is to assess the irritation and sensitization potential of 3 developmental cosmetic formulations by following a conventional HRIPT methodology.

Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the cutaneous sensitization potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects potentially sensitized, as assessed by a dermatologist.

Secondary	
To evaluate the cutaneous irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a positive reaction (score of '+' or greater) as assessed by a trained evaluator.
Safety	
To evaluate the general safety of three cosmetic facial skincare products	Frequency and severity of Adverse Events

Study Design

This will be a randomized, evaluator-blind, single-center, HRIPT study in healthy adult subjects aged 18 to 65 years to evaluate the cutaneous irritation and contact sensitization potential of three cosmetic facial skincare products compared to saline solution. Subjects will be exposed to repeated cutaneous (dermal) semi-occlusive application of 3 cosmetic facial skincare products and a negative control (saline solution).

Study Products

The 3 test products are developmental cosmetic moisturizers (a serum, lotion and cream), intended to be used topically by healthy individuals with dry facial skin. A fourth reference product will be used as a negative control; saline solution.

A controlled quantity (0.02 mL/cm^2) of each of the study products will be applied to a cell contained within an adhesive semi-occlusive patch system. The number of cells available in the patch system will be 6, of which 4 will be used for the products and 2 will be left blank. Each of the study products will be dispensed into 4 adjacent cells, per the randomization schedule. Three cells will be used for the test products (serum, lotion and cream) and a fourth for the negative control (saline solution). No other products will be applied to subjects enrolled in this study.

Type and Planned Number of Subjects

Healthy male and female volunteers aged 18 to 65 with Fitzpatrick skin phototype I to IV and no dermatological disorders will be enrolled into this study.

Approximately 470 healthy subjects will be screened to randomize at least 280 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is observed in 200 subjects, there is a 95% certainty that the actual rate of reaction in the wider population will be less or equal to 1.83%.

The focus of the statistical analysis will be the number of subjects potentially sensitized and evaluation of the frequency of subjects with positive reaction scores (i.e. of '+' or greater) for the investigational products.

1.1 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

	Screening	Induction									Rest	Challenge			
Study Week	-	Week 1			Week 2			Week 3			Week 4-5	Week 6			
Study Day / Procedure/ Assessment	VISIT 1 DAY -14 to DAY 0	VISIT 2 DAY 1	VISIT 3 DAY 3	VISIT 4 DAY 5	VISIT 5 DAY 8	VISIT 6 DAY 10	VISIT 7 DAY 12	VISIT 8 DAY 15	VISIT 9 DAY 17	VISIT 10 DAY 19	VISIT 11 DAY 22	VISIT 12 DAY 36	VISIT 13 DAY 38	VISIT 14 DAY 39	VISIT 15 DAY 40
Day of Week	-	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Mon	Wed	Thu	Fri
Informed Consent *(date and time captured)*	X														
Demographics	X														
Medical History	X														
Current/Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fitzpatrick Skin Type Assessment	X														
Inclusion/Exclusion Criteria	X	X [a]													
Dermatologist Assessment [b]	X											X	X	X	X

	Screening	Induction									Rest	Challenge			
Study Week	-	Week 1			Week 2			Week 3			Week 4-5	Week 6			
Study Day / Procedure/ Assessment	VISIT 1 DAY -14 to DAY 0	VISIT 2 DAY 1	VISIT 3 DAY 3	VISIT 4 DAY 5	VISIT 5 DAY 8	VISIT 6 DAY 10	VISIT 7 DAY 12	VISIT 8 DAY 15	VISIT 9 DAY 17	VISIT 10 DAY 19	VISIT 11 DAY 22	VISIT 12 DAY 36	VISIT 13 DAY 38	VISIT 14 DAY 39	VISIT 15 DAY 40
Day of Week	-	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Mon	Wed	Thu	Fri
Subject Eligibility	X														
Continued Eligibility		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization *(sequence of products to cells within the patch)*		X										X			
Patch (product) Application [c]		X	X	X	X	X	X	X	X	X		X [g]			
Patch Removal [d]			X	X	X	X	X	X	X	X	X [h]		X [j]		
Assessment of the test sites [e]		X [f]	X	X	X	X	X	X	X	X	X	X [i]	X [k]	X [l]	X [l]
Adverse Events [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Conclusion/ Discharge from Study															X

Notes:

- Visit 1 and Visit 2 could occur on the same day but Visit 2 must be within 14 days of Visit 1.
- A 'patch' contains individual cells, each of the test products and the saline solution (reference product) will be applied into separate single cells. The order of application of the products into the cells will be randomized for each subject. The same sequence within each subject will be used throughout the induction phase. But the sequence will change for each subject for the challenge phase.
- Subjects should avoid missing the first day of application during the Induction Phase, or the day of application during the Challenge Phase.
- Subjects should avoid missing 2 or more consecutive visits or more than 2 alternate visits.

Footnotes:

a. Only inclusion criterion 6 will be assessed (by a qualified dermatologist) if visits are not combined.
b. A blinded dermatologist will review overall subject eligibility at the screening visit and the final visit and review any evaluator reaction score that is '+' or greater in the challenge phase to provide a narrative and classification as a potential sensitization reaction.
c. Patch Application; Patches will remain in place on the back for 48 (±4) hours during the week. If a patch is applied on a Friday it will remain in place for approximately 72 (±4) hours until Monday.
d. Patch Removal; Approximately 15-30 (maximum 1 hour) minutes following patch removal, subjects will rest in standard room conditions (18-26°C) prior to the test area assessment. Approximately 30 minutes up to 1 hour after each patch is removed, a trained, blinded evaluator will evaluate the test sites for visual signs of reactions using the scoring system detailed in Appendix 2.
e. Patch Assessment - A trained blinded evaluator will perform assessments of all test site areas (where each cell was in contact with the skin) for reactions using the scoring system detailed in Appendix 2.
f. Visit 2 (Day 1) - Baseline assessments of the proposed induction phase area on the subjects back will be made prior to product application.
g. Visit 12 (Day 36) - Challenge Phase patch application (after a 2-week Rest Phase of no patch /product application). The challenge patch will be applied to a naïve site on the subjects back and remain in place for 48 (±4) hours.
h. Visit 11 (Day 22) will be the final induction phase patch removal and test site area assessment.
i. Visit 12 (Day 36) - Baseline assessments of the proposed challenge phase area on the subjects back will be performed prior to the challenge patch (product) application.
j. Challenge patch removal.
k. Approximately 15-30 minutes (maximum 1 hour) following challenge patch removal, subjects will rest in standard room conditions (18-26°C) prior to the test area assessment. Approximately 30 minutes up to 1 hour following naïve site challenge patch removal a trained blinded evaluator will perform an assessment of the challenge test site areas (where each cell was in contact with the skin) for reactions using the scoring system detailed in Appendix 2.
l. Further challenge phase test site assessments will take place 24 (±4) and 48 (±4) hours after challenge patch removal.
m. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides written consent to participate in the study by completing the Informed Consent Form (ICF).

2 INTRODUCTION

In recent years the cosmetic industry has grown considerably, along with its concern for developing safe and effective products. Heightened industry awareness, consumer and regulatory agency requirements have led cosmetic manufacturers to adopt procedures that provide a robust assessment of the risks and benefits of their products. This includes the conduct of clinical tests to assess safety and efficacy, which are often coordinated by dermatologists or other experts before marketing a new product. These procedures provide greater assurance of safety for cosmetic manufacturers, increasing their credibility and confidence among consumers.

A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use (ANVISA, 2012; Cosmetics Europe, 2004). As a general requirement, the safety of the final formulation must also be confirmed before it is marketed.

Skin contact with topical products such as cosmetics may trigger different types of reactions including eczematous contact dermatitis, urticaria, acne and spots. Contact dermatitis can arise from two mechanisms: primary irritation, through the action of irritant substances; or sensitization, in the presence of an allergenic ingredient. Skin sensitization is an immunological process in which the responsiveness to a specific chemical allergen is increased. By definition, skin sensitization is induced when a susceptible individual is exposed to an inductive chemical allergen. This allergen causes a skin immune response that, at a certain range, will result in the development of contact sensitization (Kimber et al, 2001).

An irritation reaction is typically a surface reaction on the skin due to a stimulant, that presents immediately, or over some time. A sensitization reaction is an immune response that is slower to develop, typically following a repeated exposure. An increased intensity over time should be present for the indication of sensitization. Indeed, a crescendo evolution of intensity of scoring or the presence of an eczema like reaction at any time suggests a possible sensitization response.

Clinical compatibility studies which evaluate the irritation and sensitization potential of a product must take into account a number of variables: components used in the formulation, ingredient concentration, absorption, amount applied, skin condition, application directions and frequency, as well as the cumulative effect (Dooms-Goossens, 1993).

The objective of such compatibility studies is to evaluate potential untoward effects during exaggerated application to the skin, therefore providing assurance that the test product is well tolerated and safe under normal or foreseeable conditions of use. A common method to assess the potential of topically applied products to cause irritation or sensitization involves repeated patch applications of a product to the skin (Basketter *et al*, 2004).

Semi-occlusive administration provides a higher degree of contact between the components of the product formula and the skin. Therefore, it is considered to be a sensitive method to assess the irritation and sensitization potential of topically applied products. Clinical outcomes are typically reported by visual grading of the skin for signs of reactions by an experienced, trained evaluator (Ivens et al, 2007).

The objective of this clinical study is to assess the irritation and sensitization potential of 3 developmental cosmetic formulations by following a conventional HRIPT methodology.

2.1 Study Rationale

GSK CH has developed 3 new cosmetic formulations; a serum, lotion and cream, intended to be used as topical moisturizers by healthy adult consumers with dry facial skin.

Clinical data are required to demonstrate that the developmental formulations have favourable local tolerance profiles. Among the several types of safety assays in humans, patch tests are currently the most widespread protocols conducted to investigate the potential risk of local irritation and contact sensitization.

Complete information for the developmental cosmetic facial serum, lotion and cream may be found in the single reference safety document (SRSD), which for this study is the Safety Statement.

2.2 Background

To make an adequate risk assessment or safety evaluation, it can be argued that a safety test has to be performed in naive human subjects. For this purpose, a number of sensitization tests have been developed. The most common design is the HRIPT, originating from a test described by Draize in 1944 (Draize *et al*, 1944). The test repeatedly exposes subjects to the products during a 3-week induction period, which is followed by a 2-week rest period and a final challenge at a previously unexposed site. The test sites are graded for visual signs of reactions throughout the induction and challenge periods. Generally, the classification of clinical outcomes follows the scale recommended by the International Contact Dermatitis Research group (ICDRG) (Fregert, 1974).

The objective of this clinical study is to assess the irritation and sensitization potential of 3 developmental cosmetic formulations by following a conventional HRIPT methodology.

2.3 Mechanism of Action/Indication

The European Union Cosmetics Directive defines a cosmetic as any substance or preparation intended to be placed in contact with the external parts of the human body with a view exclusively or mainly to cleaning, perfuming, changing appearance and/or correcting body odours and/or protecting or keeping in good condition (European Commission (EC), 2009). This is a consistent definition of cosmetic products per ANVISA (ANVISA, 2012)

The investigational products in this study are cosmetic moisturisers; a serum, lotion and cream intended for topical application to healthy adults with dry skin immediately after cleansing.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the cutaneous sensitization potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects potentially sensitized, as assessed by a dermatologist.

Secondary	
To evaluate the cutaneous irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a positive reaction (score of '+' or greater) as assessed by a trained evaluator.
Safety	
To evaluate the general safety of three cosmetic facial skincare products	Frequency and severity of Adverse Events

4 STUDY DESIGN

4.1 Overall Design

This will be a randomized, single blind (evaluator), single-center, HRIPT study in healthy adult subjects aged 18 to 65 years to evaluate the cutaneous irritation and contact sensitization potential of 3 cosmetic facial skincare products. Subjects will be exposed to repeated cutaneous (dermal) semi-occlusive application of 3 cosmetic facial skincare products and a reference product as a negative control (saline solution).

A sufficient number of subjects will be screened (approximately 470) to randomize approximately 280 subjects to ensure that at least 200 subjects complete the study.

During the screening visit (Visit 1), subjects will sign an informed consent form and then a dermatological assessment will be conducted to ensure subjects have no dermatological conditions on their dorsum that might impact subject safety or study results and to ensure subjects have a Fitzpatrick Phototype I to IV (per APPENDIX 3 – Fitzpatrick Skin Type Grading).

Each subject's medical history and medication history will be reviewed, as well as inclusion and exclusion criteria. After which, site staff will review lifestyle considerations and study visit requirements with eligible subjects.

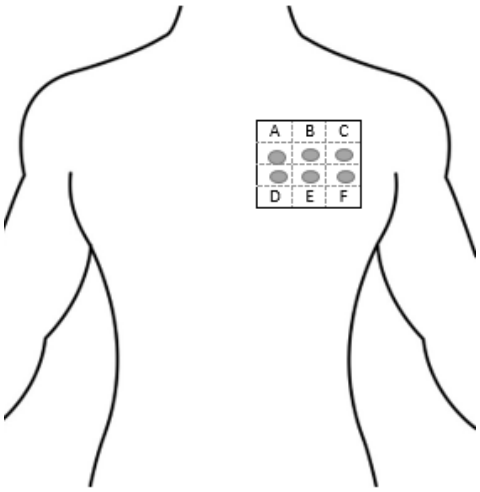
The study will progress in 3-phases, as follows:

Induction Phase:

Visit 2/Day 1 of the induction phase could be combined with visit 1. If visits 1 and 2 are not combined, then visit 2 will occur within 14 days of visit 1.

At visit 2, eligible subjects will return to the study site and be re-evaluated by a dermatologist against inclusion criterion 6 to ensure they remain eligible to continue in the study. A review of any current/concomitant medications taken since screening will also be made. The area for patch application will be designated between the scapula and waistline and away from the spinal mid-line. Baseline assessment of the test site area will then be performed by a blinded trained evaluator.

Figure 4-1 Example layout of the patch on the dorsum (shown adhesive side down)



A semi-occlusive adhesive patch with 6 cells labelled A-F will be used. Four cells (A-D) will be used in this study (1 for each test product and 1 for the saline solution). Two cells (E-F) will remain empty.

A controlled amount (0.02 mL/cm^2) of each study product will be dispensed using suitable measuring apparatus (e.g. a pipette) into the appropriate separate cell, 3 cells for each of the test products and 1 cell for the saline solution. The assignment of the study products to the cells within the patch system within each subject will be randomly assigned per the randomization schedule provided (5.4 Randomization Criteria). The sequence of the products to the cells for each subject will remain the same for the induction phase, and a different sequence will be generated for each subject for the challenge phase (8.1.7 Randomization). Once the products have been dispensed into the cells the adhesive patch will be applied to the identified dorsum site of the subject.

During the induction phase there will be a total of 9 patch applications over 3 consecutive weeks, with patches applied to the same location on alternate weekdays each week (Monday, Wednesday, and Friday).

Each patch will remain in place for 48 (± 4) hours on weekdays and 72 (± 4) hours on weekends. The patch will then be removed, and the area may be gently wiped with saline solution. Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area with any other surface. After 30 minutes (maximum of 1 hour), the test sites will be evaluated as per the scale in Appendix 2.

A new adhesive patch with each of the products applied to the same cells per the allocation of that subject will then be reapplied to the same area on the dorsum.

Rest Phase:

At visit 11, after the final induction patch removal and evaluation, subjects will enter a minimum 2-week rest phase. During this time there will be no product or patch applications. Subjects will be reminded to continue to follow the Lifestyle Considerations throughout the rest phase

Challenge Phase:

At visit 12 (or visit 11, if visit 1 and visit 2 were combined), after completing the rest phase, subjects will return for the challenge phase. A naïve (i.e. previously untreated/patched) area of skin on the back, between the shoulder line and waist and away from the spinal mid-line, will be selected for the challenge patch. This area will be evaluated by the blinded evaluator prior to any patch application to provide a baseline for interpretation. A new patch, with each of the cells filled with study products as per the sequence for the subject's challenge phase, will then be applied.

After 48 (±4) hours, subjects will return to the site, the patch will be removed, and the area may be gently wiped with saline solution, Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area with any other surface. After 30 minutes (maximum of 1 hour), the test sites will be evaluated as per the scale in Appendix 2. Subjects will return to site for subsequent test-site evaluations 24 (±4) hours - Visit 13 and 48 (±4) hours - Visit 14 post patch removal as per the scale in Appendix 2

End of Study:

At visit 15 (or visit 14, if visit 1 and visit 2 were combined), after the 48 (±4) hour assessment, a final examination by a dermatologist will be performed to confirm it is medically appropriate to exit the subject from the study. After all study assessments are completed, subjects will be discharged from the study site.

Adverse events and current/concomitant medications will be assessed throughout the study from the point at which subjects sign the informed consent form.

Patch Test Site Assessments:

Any skin response at a patched site will be clinically assessed by a trained blinded evaluator using the scale recommended by the ICDRG, per Appendix 2

Assessment of the test site areas will be conducted once at baseline (Visit 2/Day 1) prior to any patch (or product) application and then a further 8 times post-baseline during the induction phase, once during the rest phase (for the final induction phase patch removal), and 4 times during the challenge phase (prior to challenge patch application (baseline) and post) by a, trained evaluator who will be blinded to the treatment sequence allocation for both the induction and challenge phases.

During the induction phase; a trained, blinded evaluator will score the test sites for signs of irritation per ICDRG scale (Appendix 2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

During the challenge phase patch test site assessment will be conducted in a 2-step process:

Step 1: A trained, blinded evaluator will score the test sites for signs of reactions per ICDRG scale (Appendix 2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

Step 2: For each subject who presents a positive reaction (a score of '+' or greater), a blinded dermatologist will further classify the reaction as potential sensitization (or not) at the final visit and provide a narrative description of the event. The dermatologist will not be scoring the

reaction. A single event may occur over multiple visits. Only one narrative should be made. The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken, and diagnosis (potential sensitization reaction, or not, as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

If a score (per Appendix 2) of '++' (Strong) or greater at any point during the induction phase is reported, the next patch will be applied to an adjacent naïve (i.e. previously untreated) site. If a score of '++' (Strong) or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will, however, progress to the challenge phase unless, in the opinion of the Investigator (or medically qualified designee), it would be unwise to do so.

The negative control (saline solution) will be used as a reference to contextualise clinical outcomes for the test products by the Sponsor after the study completes and unblinding.

Any cutaneous (dermal) irritation or sensitization reactions which occur within the patch application area and can be completely described by the scale in Appendix 2 will not be recorded as AEs during the study. These responses are typical effects of occluded application of topical products. Reactions to the patch itself or the adhesive will also not be recorded as AEs.

Unexpected or unusual reactions which occur within the patch test area that cannot be completely described by the scale in Appendix 2 (e.g., rash, hives) will be recorded as AEs.

4.2 Rationale for Study Design

Compatibility studies represent the first contact of the finished product in humans and seek to demonstrate the safety of topical products under maximised conditions.

The human repeated insult patch test (HRIPT) is a long standing, standard method to determine whether exposure to a topical product will elicit a cutaneous (dermal) irritant or allergic response (sensitization) under exaggerated (occluded) conditions. It is also routinely used and accepted as an appropriate methodology to establish the sensitization potential of topical medicated products by health authorities, including the US FDA and MHRA. The HRIPT requires approximately six weeks and involves three phases: induction, rest and challenge, and is based on the modified Draize test. (Draize *et al*, 1944).

Patch testing techniques and scoring reactions by a grading scale were first standardized in the 1930s. The International Contact Dermatitis Research Group (ICDRG) published the following nonlinear, descriptive grading scale in 1970's (Fregert, 1974) which continues to be widely used and will be adopted for this clinical study (Appendix 2). A suitable trained (blinded) evaluator will assess the subjects prior and during the induction and challenge phases of the study per the scale in Appendix 2.

The semi occlusive adhesive patch allows an assessment in maximized condition, with adequate contact of the product with the skin and is globally accepted, being widely used in the literature.

Subjects will be assessed by a dermatologist as a prerequisite to enrollment, and again at study end. This study will be conducted under the supervision of a dermatologist.

4.3 Justification for Dose

A critical aspect of a patch test is that the whole test area of the cell is covered with the test product, without spreading or overlapping into other test sites (cells). Previous work has shown that the optimal dose to fulfil these requirements is 0.02 mL/cm^2 (Isaksson *et al*, 2007).

Therefore, in this study each of the test products will be dispensed at a dose of 0.02 mL/cm^2 into individual cells of a semi-occlusive adhesive patch system using an electronic pipette with disposable tips and applied to the designated area on the back. A sodium chloride (NaCl) saline solution (0.9%) will be used as a negative control product and dispensed at the same dose.

The semi-occlusive adhesive patches will be made of a hypoallergenic material and contain round cells of an absorbent material. One of the cells will contain the negative control and 3 other cells will be filled with each the test products according to the supplied randomization allocation for the induction and challenge phase. Only products of the sponsor, GSK CH, will be tested in this study.

4.4 End of Study Definition

A subject will be considered to have completed the study if he or she completes all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Healthy male and female subjects ages 18 to 65, with a Fitzpatrick skin phototype I to IV and no dermatological disorders will be enrolled into this study.

Approximately 470 healthy subjects will be screened to randomize at least 280 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is observed in 200 subjects, there is a 95% certainty that the actual rate of reaction in the wider population would be less or equal to 1.83%. (Clopper and Pearson, 1934)

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorized representative and successfully met eligibility criteria to proceed beyond the screening visit.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

Subject eligibility to participate in the clinical study should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Site personnel assessing the subject inclusion and exclusion criteria and subject eligibility should be the investigator, a suitable qualified medically qualified person or designee as per the needs of the study.

5.2 Inclusion Criteria

An individual must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 and 65 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan, and study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, with no clinically significant or relevant abnormalities in medical history or upon dermal examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. Fitzpatrick phototype I to IV (see Appendix 3).
6. Healthy, intact skin at the proposed test area dorsum (below the shoulder, above the waist), as evaluated by a dermatologist, to ensure subject is free of clinically relevant dermatological conditions.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrollment into the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies involving investigational product(s) within 30 Days prior to study entry and/or during study participation.
3. A subject who has participated in other studies including non-medicinal, cosmetic studies within 7 Days prior to study entry and/or during study participation.
4. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
5. A subject who is pregnant or intends to become pregnant during the study duration (self-reported).
6. A subject who is breastfeeding.
7. A subject with known or suspected intolerance or hypersensitivity to the study materials/product (or closely related compounds) or any of their stated ingredients, to hypoallergenic tape, or to the cotton patches.

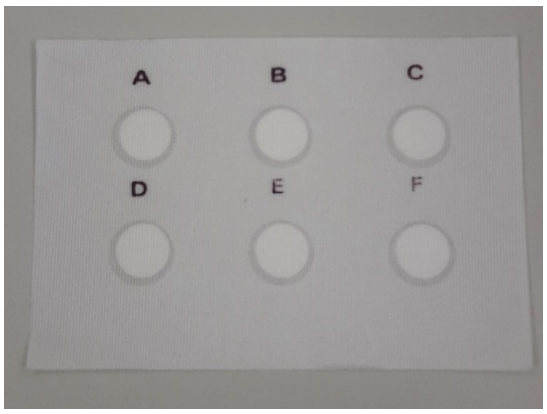
8. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
9. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
10. A subject with current or recent (within last 6 months before the start of the study) history of atopic lesions and/or eczema.
11. A subject with a history of allergic reactions to topical-use products, cosmetics or medications or their ingredients.
12. A subject with any history of significant diseases or medical conditions known to alter skin appearance or physiologic response (e.g. uncontrolled diabetes) which could, in the opinion of the Investigator, preclude topical application of the investigational products and/or interfere with the evaluation of the test site reaction.
13. A subject considered immune-compromised.
14. A subject with active dermatosis (local or disseminated) that might interfere with the results of the study.
15. A subject currently using any medication which in the opinion of the investigator, may affect the evaluation of the investigational product, or place the subject at undue risk.
16. A subject who has used any of the following topical or systemic medications up to two weeks before the screening visit: immuno-suppressants, antihistamines, non-steroidal anti-inflammatory drugs (NSAIDS, high dose aspirin), and/or corticosteroids.
17. A subject who has used a transcutaneous electrical nerve stimulation (TENS) machine 1 day before the screening visit.
18. A subject who has used oral or topical treatment with vitamin A acid and/or its derivatives up to 1 month before the screening visit.
19. A subject who has been vaccinated up to 1 month before the screening visit or is intending to receive a vaccination during their participation in the study.
20. A subject with any skin marks on the back that might interfere with the evaluation of possible skin reactions (e.g. pigmentation disorders, open sores, pimples, cysts, vascular malformations, scars, tattoos, excessive hair, numerous freckles).
21. A subject that intends bathing (in the sea or a pool), using sauna, or partaking in water sports, or activities that lead to intense sweating.
22. A subject that is a prisoner or involuntary incarcerated.
23. A subject from an indigenous tribe.
24. A subject who has previously been enrolled in this study.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

A semi-occlusive adhesive patch with 6 cells labelled A-F will be used. Four cells (A-D) will be used in this study (1 for each test product and 1 for the saline solution). Two cells (E-F) will remain empty.

Figure 5-1 Example of the semi-occlusive adhesive patch system (shown adhesive side down)



The sequence of each of the study products to the cells within the patch system for each subject will be randomly assigned per the randomization sequence provided. The sequence of the products to the cells within each subject will remain the same for the induction phase, and a different sequence will be generated for each subject for the challenge phase. For more details on the randomization, please refer to section 8.1.7

5.5 Lifestyle Considerations

During the entire study (Screening – Last Subject Last Visit (LSLV) including the rest phase) the following should be avoided:

- Applying any other product to the test site (dorsum).
- Use of cosmetics, moisturisers, and other topical products on the back area.
- Changing any cosmetic habits, including personal hygiene.
- Changing dietary habits.
- Getting the patch test site wet: during showers or bathing, in pools or lakes/ocean, sauna or activities that cause excessive sweating. The study site will provide instructions on how to shower or bathe throughout the study.
- Removing the patches.
- Wearing tight or restrictive clothing that can remove the patch through friction or cause redness.
- Intentional exposure to artificial ultraviolet (UV) light or cosmetic procedures (includes tanning beds, Intense Pulsed Light, etc.) are prohibited on the test areas for the duration of the study.
- Introduction of new products during the study including but not limited to soap, laundry detergent, or fabric softener.
- Engaging in activities that result in excessive sweating.
- Missing the first day of application during the Induction Phase, or the day of application during the Challenge Phase.
- Missing 2 or more consecutive visits or more than 2 alternate visits.

5.5.1 Pregnancy

For GSK CH studies in which no drug is utilized a pregnancy test will not be required. Subjects will need to provide verbal confirmation of negative pregnancy status.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, and any adverse events or incidents as applicable.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical questions or problems in the event that the established communication pathways between the investigational site and the study team are not available.

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Clinical Evaluator Qualifications

For products with specific safety appeals, the study must be followed up by a specialist (ANVISA, 2012). A dermatologist will assess the overall subject eligibility at the Screening Visit and continued eligibility in the study at Visit 2 (if not combined) to ensure the subject is free of any pre-existing dermatological pathology. Additionally, a final assessment at Visit 15 (Last Visit) by a qualified dermatologist will confirm it is medically appropriate to exit the subject from the study at the final visit (Edward and Norman, 1982).

A trained, blinded evaluator will score the patch test sites for signs of irritation per ICDRG scale (Appendix 2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

During the challenge phase a blinded dermatologist will further classify any assessor positive reaction (a score of '+' or greater), as potential sensitization (or not) at the final visit and provide a narrative description of the event. The dermatologist will not be scoring the reaction. All practical efforts will be made to ensure the same dermatologist will be used to evaluate all subjects in the study.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, investigational product is defined as a pharmaceutical form of an active ingredient, a non-medicinal product (marketed or investigational), or a placebo, being tested or used as a reference (positive or negative control), in a clinical trial. This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Investigational/Study Product Supplies

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Investigational/Study Product Supplies

	Test Product 1	**Test Product 2**	**Test Product 3**	**Reference Product (Negative control)**
Product Name	Developmental Serum	Developmental Lotion	Developmental Cream	Saline Solution: Sodium Chloride (NaCl; 0.9%)
Pack Design	40 mL pump pack	50 mL tube	50 mL tube	500ml
Product Master Formulation Code (MFC)	CCI [redacted]	CCI [redacted]	CCI [redacted]	N/A Commercial Product
Application Quantity	0.02 mL/cm^2 Each product will be dispensed into an individual cell within the adhesive patch system according to the randomization sequence for the induction phase and the challenge phase and removed/reapplied as per study schedule.			
Route of Administration	Topical cutaneous (dermal) application via semi-occlusive adhesive patch to the dorsum.			
Application Instruction	Applied on-site by technician			

The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Clinical Supplies Department, GSKCH.

Other sundry items to be supplied by the clinical investigational site:

- Semi-occlusive adhesive patch system (Durapore® tape 3M™ and paper filter)
- Saline solution (for cleansing the patched sites as needed, following patch removal)
- Cotton pads/wool (for cleansing the patched sites as needed, following patch removal)

Supplies provided by the clinical investigational site must also be stored in compliance with the label requirements in a secure place with limited or controlled access.

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSK CH during the study in time for study close out visit.

6.1.1 Dosage Form and Packaging

The 3 developmental formulations will be supplied to the clinical site as labelled packaged bottles or tubes for dispensing and application by the site staff. The saline solution as the reference product will be supplied in its commercial packaging for dispensing and application by the site staff. Additional saline solution for cleansing of the test site areas as needed will be provided by the investigational site.

The content of the study product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group.

Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study.

All products supplied are for use only in this clinical study and should not be used for any other purpose.

6.1.2 Preparation and Dispensing

The products; 3 developmental formulations and the saline solution will be dispensed by qualified unblinded site personnel according to the randomization sequence into the cells of the adhesive patch system for the induction phase and the challenge phase per the application schedules.

In this study each of the products will be dispensed at a dose of 0.02 mL/cm^2 using suitable measuring apparatus (e.g. a pipette) into the individual cells of a semi-occlusive adhesive patch system and applied to the designated area on the back.

Subjects will be assigned to the sequence of products within the cells of the patch in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the induction phase, and a different sequence will be followed for the challenge phase, using validated software. See sections 5.4 Randomization Criteria and 8.1.7 Randomization.

The study products will be applied to the cells of the patch by qualified unblinded site personnel. The patch will then be applied to dorsum of each subject as per the study schedule. These staff members will not be involved in any safety assessments or other aspects of the study that could be influenced by the knowledge of product/sequence a subject has been assigned to.

An additional unblinded site member of site staff, should ensure the dispensing procedures are completed accurately per the randomization sequence for each subject for each application day of the induction phase and the challenge as per study schedule and the randomization sequences provided.

6.2 Administration

The study will progress in 3-phases, as follows:

Induction Phase:

Visit 2/Day 1 of the induction phase could be combined with visit 1. If visits 1 and 2 are not combined, then visit 2 will occur within 14 days of visit 1.

At visit 2, eligible subjects will return to the study site and be re-evaluated by a dermatologist against inclusion criterion 6 to ensure they remain eligible to continue in the study. A review of any current/concomitant medications taken since screening will also be made. The area for patch application will be designated between the scapula and waistline and away from the spinal mid-line. Baseline assessment of the test site area will then be performed by a blinded trained evaluator.

A semi-occlusive adhesive patch with 6 cells labelled A-F will be used. Four cells (A-D) will be used in this study (1 for each test product and 1 for the saline solution). Two cells (E-F) will remain empty. See 5.4 Randomization Criteria and 8.1.7 Randomization.

A controlled amount (0.02 mL/cm^2) of each study product will be dispensed using suitable measuring apparatus (e.g. pipette) into the appropriate separate cell, 3 cells for each of the test products and 1 cell for the saline solution. The adhesive patch is then applied to the dorsum of the subject.

The assignment of the study products to the cells within the patch system within each subject will be randomly assigned per the randomization schedule provided. The sequence of the products to the cells for each subject will remain the same for the induction phase, and a different sequence per the randomization provided will be generated for each subject for the challenge phase.

During the induction phase there will be a total of 9 patch applications over 3 consecutive weeks, with patches applied on alternate weekdays each week (Monday, Wednesday, and Friday).

Each patch will remain in place for 48 (±4) hours on weekdays and 72 (±4) hours on weekends. The patch will then be removed, and the area may be gently wiped with saline solution. Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area with any other surface. After 30 minutes (maximum of 1 hour), the test sites will be evaluated as per the scale in Appendix 2.

A new adhesive patch with each of the products applied to the same cells will then be reapplied to the same area on the dorsum.

Rest Phase:

At visit 11, after the final induction patch removal and evaluation, subjects will enter a minimum 2-week rest phase. During this time there will be no product or patch applications. Subjects will be reminded to continue to follow the Lifestyle Considerations throughout the rest phase.

Challenge Phase:

At visit 12, after completing the rest phase, subjects will return for the challenge phase. A naïve (i.e. previously untreated/patched) area of skin on the back, between the shoulder line and waist and away from the spinal mid-line, will be selected for the challenge patch. This area will be evaluated by the blinded evaluator prior to any patch application to provide a baseline for interpretation. A new adhesive patch, with each of the cells filled with study products as per the randomization sequence for the subject's challenge phase, will then be applied.

After 48 (±4) hours, subjects will return to the site, the patch will be removed, and the area may be gently wiped with saline solution, Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area

with any other surface. After 30 minutes (maximum of 1 hour), the test sites will be evaluated as per the scale in Appendix 2. Subjects will return to site for subsequent test-site evaluations 24 (±4) hours - Visit 13 and 48 (±4) hours - Visit 14 post patch removal as per the scale in Appendix 2.

6.2.1 Dosing Errors

Dosing errors may result, in this study, from the administration of:

- the wrong product sequence,
- to the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such dosing errors occurring to a study subject are to be captured in the CRF. In the event of dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

Dosing errors are reportable irrespective of the presence of an associated AE, including:

- Dosing errors involving subject exposure to any of the study products;
- Potential dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a dosing error is accompanied by an AE, as determined by the investigator, the dosing error and, any associated adverse event(s) are to be captured in the CRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study.

Limited quantities of the study product(s) will be supplied, dispensed by the site staff and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

6.3 Investigational/Study Product Storage

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label and the clinical study supplies checklist.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions

should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible as per the information provided in the clinical study supplies checklist. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation and reported to the Sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

6.4 Investigational/Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

All study products must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels and the clinical study supplies checklist. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study will be returned for destruction to the GSK CH clinical supplies department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and instructions for the IRT will be provided to the site staff.

The study products will be dispensed to the appropriate cells of the patch according to the instruction received (sequence) through the IRT at the appropriate study visits for the induction phase and the challenge phase.

The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.

This is a single-blind study in which the outcome evaluator for the reaction score will be blinded to the product sequence received. The dermatologist will also be blind to the product sequence. The study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation.

To ensure the examiner remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area. The examiner is not permitted in any area where study product is stored, dispensed, or in use.

Dispensing staff will not be involved in any assessment procedures during the study.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product sequence assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding, unless this could delay emergency treatment of the subject.

If a subject's product application sequence assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Any AE associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required to inform the IRB/EC if the blind is broken.

6.7 Compliance

All study products will be dispensed and administered by suitably trained investigator site personnel at the study site.

6.8 Current and Concomitant Medication/Treatment(s)

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about current/concomitant medication/treatments at each site visit.

Medication or treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications or treatments taken after signing the informed consent, will be documented as concomitant medication/treatments.

Subjects will abstain from all concomitant treatments, except for contraceptives and those used for the treatment of adverse events.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF. If a subject is discontinued, they will not be replaced.

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls. These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent, if the subject has provided consent for this.

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

Adherence to the study design requirements, including all procedures are essential and required for study conduct.

8.1 Visit 1/Screening

Visit 1 may be combined with Visit 2 but should be no more than 14 days following Visit 1. If visits are combined all procedures will be conducted at Visit 1.

Prior to the screening visit, telephone screening of interested subjects may be conducted using a telephone script. This will be conducted by the site recruitment staff or designee.

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

The following procedures will be completed:

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSK CH.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will also be captured on the Informed Consent Form as this is the point at which all Adverse Events will be captured from. The date and time of consent will be transcribed to the CRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race. Fitzpatrick skin type assessment (Appendix 3 - Fitzpatrick Skin Type Grading) will also be conducted by a trained assessor and recorded on the CRF.

Race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.3 Inclusion/Exclusion Criteria

Subject compliance with all inclusion and exclusion criteria will be documented in the CRF.

8.1.4 Dermatologist Assessment

A dermatologist will perform a visual assessment of the subject to confirm they are free of any pre-existing dermatological pathology at the screening visit.

This assessment will be repeated at Visit 2 (if not combined with visit 1) to ensure the subject remains free of any pre-existing dermatological pathology and that they are therefore suitable to continue in the study.

For each reaction score of '+' or greater during the challenge phase, a blinded dermatologist will further classify the reaction as potential sensitization (or not) and provide a narrative description of the event. The dermatologist will not be scoring the reaction. All practical efforts will be made to ensure the same dermatologist will be used to evaluate all subjects in the study.

Additionally, a final assessment at Visit 15 by a dermatologist will confirm it is medically appropriate to exit the subject from the study at the final visit. (Edward and Norman, 1982). The dermatologist may request further investigation as needed.

Confirmation of subject eligibility and continued eligibility will be documented in the CRF. Any subject narrative will also be documented in the CRF.

8.1.5 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 1 year), including allergies or drug sensitivity, will be documented in the CRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.6 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines and any Current and Concomitant Medication/Treatment(s) requirements of the protocol.

8.1.7 Randomization

This assessment will be conducted at visit 2 (if not combined with visit 1).

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number. This will remain the same for each subject throughout the study duration.

All subjects who meet the criteria for entry into the study will be centrally randomized using Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the study site. Study products will be dispensed according to the instruction received through the IRT system at the appropriate study visits.

At visit 2, (or visit 1 if combined) a randomization number will be assigned electronically in ascending numerical order to each subject who is determined to be fully eligible. This randomization number will include the sites of application for each of the products into each cell for the induction phase. See also 5.4 Randomization Criteria and 6.1.2 Preparation and Dispensing.

At visit 12 (challenge phase), another randomization number will be assigned electronically in ascending numerical order to each subject that completed the induction phase and meets the continued eligibility criteria. This randomization number will be different from the first one assigned at visit 2 (or visit 1) and will include the sites of application for each of the products into each cell for the challenge phase.

Randomization schedules for induction phase and challenge phase will follow respectively a 4x4 Latin Square (Williams) design.

The sequence of product application will remain the same within the subject for the induction phase, but a new sequence will be generated for each subject for the challenge phase.

Table 8-1 Application site sequences – induction phase

An example of the randomization schedule for the induction phase is shown below:

Randomization Number / Patch Cell	Induction phase			
	Cell A	**Cell B**	**Cell C**	**Cell D**
PPD	Test Product 1	Reference Product	Test Product 2	Test Product 3
	Test Product 3	Test Product 1	Reference Product	Test Product 2
	Test Product 2	Test Product 3	Test Product 1	Reference Product
	Reference Product	Test Product 2	Test Product 3	Test Product 1

Table 8-2 Application site sequences – challenge phase

An example of the randomization schedule for the challenge phase is shown below:

Randomization Number / Patch Cell	Challenge phase			
	Cell A	**Cell B**	**Cell C**	**Cell D**

PPD	Test Product 2	Test Product 3	Test Product 1	Reference Product
	Reference Product	Test Product 1	Test Product 3	Test Product 2
	Test Product 3	Reference Product	Test Product 2	Test Product 1
	Test Product 1	Test Product 2	Reference Product	Test Product 3

8.2 Study Period – Baseline to Visit 14

Visit 2 may be combined with Visit 1 (Screening) but should be no more than 14 days following Visit 1.

During the study period subjects should be reminded to inform the site if they experience any untoward medical occurrence or if they use any new medications or treatments and report at their next visit.

8.2.1 Visit 2/Day 1

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

A qualified dermatologist will check for subject continued eligibility in the study (at Visit 2 only if Visits are not combined).

8.2.1.1 Baseline Grading

Visit 2/Day 1 (or Visit 1 if visits combined), the induction phase; the test area for the application of the adhesive patch will be designated between the scapula and waistline and away from the spinal mid-line. Baseline assessment of the application test sites will then be performed by a blinded trained evaluator per the assessment scale in Appendix 2.

Baseline assessment scores will be documented in the CRF.

8.2.1.2 Patch (Product) Application

The study will progress in 3-phases, as follows:

Induction Phase:

A semi-occlusive adhesive patch with 6 cells labelled A-F will be used. Four cells (A-D) will be used in this study (1 for each test product and 1 for the saline solution). Two cells (E-F) will remain empty. See also 5.4 Randomization Criteria and 6.1.2 Preparation and Dispensing.

A controlled amount (0.02 mL/cm^2) of each study product will be dispensed using suitable measuring apparatus (e.g. a pipette) into the appropriate separate cell, 3 cells for each of the test products and 1 cell for the saline solution. The assignment of the study products to the cells within the patch system within each subject will be randomly assigned per the randomization schedule provided. The sequence of the products to the cells for each subject will remain the same for the induction phase, and a different sequence per the randomization provided will be

generated for each subject for the challenge phase. The adhesive patch will then be applied to the dorsum of the subject.

During the induction phase there will be a total of 9 patch applications over 3 consecutive weeks, with patches applied on alternate weekdays each week (Monday, Wednesday, and Friday).

Each patch will remain in place for 48 (±4) hours on weekdays and 72 (±4) hours on weekends. The patch will then be removed, and the area may be gently wiped with saline solution. Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area with any other surface. After 30 minutes (maximum of 1 hour), the test sites will be evaluated as per the scale in Appendix 2. Assessment scores will be documented in the CRF.

A new adhesive patch with each of the products applied to the same cells will then be applied to the same area on the dorsum.

Rest Phase:

At visit 11, after the final induction patch removal and evaluation, subjects will enter a minimum 2-week rest phase. During this time there will be no product or patch applications. Subjects will be reminded to continue to follow the Lifestyle Considerations throughout the rest phase

Challenge Phase:

At visit 12, after completing the rest phase, subjects will return for the challenge phase. A naïve (i.e. previously untreated/patched) area of skin on the back, between the shoulder line and waist and away from the spinal mid-line, will be selected for the challenge patch. This area will be evaluated by the blinded evaluator prior to any patch application to provide a baseline for interpretation. A new patch, with each of the cells filled with study products as per the randomization sequence for the subject's challenge phase, will then be applied.

After 48 (±4) hours, subjects will return to the site, the patch will be removed, and the area may be gently wiped with saline solution, Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area with any other surface. After 30 minutes (maximum of 1 hour), the test sites will be evaluated as per the scale in Appendix 2. Subjects will return to site for subsequent test-site evaluations 24 (±4) hours - Visit 13 and 48 (±4) hours - Visit 14 post patch removal as per the scale in Appendix 2. Assessment scores will be documented in the CRF.

8.2.1.3 Patch Test Site Assessment

Each adhesive patch will remain in place for 48 (±4) hours on weekdays and 72 (±4) hours on weekends. The patch will then be removed, and the area may be gently wiped with saline solution before visual assessment. Subjects will be instructed to rest for 15-30 minutes (maximum 1 hour) in standard room conditions (18-26°C) avoiding contact of the back area with any other surface. After 30 minutes (maximum of 1 hour), a trained, blinded evaluator will evaluate the test sites for visual signs of reaction using the scoring system detailed in Appendix 2.

Any skin response at a patched site will be clinically assessed by an experienced, trained evaluator for reactions for the duration of the study according to the scoring scale in Appendix 2. The evaluator will be blinded to the treatment allocation location. Test sites will be graded using a magnifying glass with a fluorescent daylight lamp as needed. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

During the induction phase; a trained, blinded evaluator will score the test sites for signs of irritation per ICDRG scale (Appendix 2) at all time points specified in the study schedule.

During the challenge phase patch test site assessment will be conducted in a 2-step process:

Step 1: A trained, blinded evaluator will score the test sites for signs of reactions per ICDRG scale (Appendix 2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

Step 2: For each subject who presents a positive reaction (a score of '+' or greater), a blinded dermatologist will further classify the reaction as potential sensitization (or not) at the final visit and provide a narrative description of the event. The dermatologist will not be scoring the reaction. Details will be documented in the CRF.

If a score of '++' (Strong) or greater at any point during the induction phase is reported, the next patch will be applied to an adjacent naïve (i.e. previously untreated) site. If a score of '++' (Strong) or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will, however, progress to the challenge phase unless, in the opinion of the Investigator (or medically qualified designee), it would be unwise to do so.

Assessment of the test sites will be conducted once at baseline (Visit 2/Day 1) prior to any patch (or product) application and then a further 8 times post-baseline during the induction phase, once during the rest phase (for the final induction phase patch removal), and 4 times during the challenge phase (prior to challenge patch application (baseline) and post) by a, trained evaluator who will be blinded to the treatment sequence allocation.

8.2.2 Visit 15/Day 40

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

Final challenge test site assessment 48 ± 4 hours (Visit 15) post patch removal will take place.

A final evaluation by a dermatologist will be conducted to confirm it is medically appropriate to exist the subject from the study. The outcome of this evaluation will be documented on the CRF.

8.3 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the GSK CH medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.4 Follow-up Visit

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol

9.2 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.2.1 Patch Test Site Assessments

Any skin response at a patched site will be clinically assessed by a trained blinded evaluator using the scale recommended by the ICDRG, per Appendix 2

Each patch will be removed, and the treated areas may be cleaned with saline solution before visual assessment.

During the induction phase; a trained, blinded evaluator will score the test sites for signs of irritation per ICDRG scale (Appendix 2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

During the challenge phase patch test site assessment will be conducted in a 2-step process:

Step 1: A trained, blinded evaluator will score the test sites for signs of reactions per ICDRG scale (Appendix 2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

Step 2: For each subject who presents a positive reaction (a score of '+' or greater), a blinded dermatologist will further classify the reaction as potential sensitization (or not) at the final visit and provide a narrative description. The dermatologist will not be scoring the reaction. A single event may occur over multiple visits. Only one narrative should be made. The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken and diagnosis (potential sensitization reaction, or not as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

If a score (per Appendix 2) of '++' (Strong) or greater at any point during the induction phase is reported, the next patch will be applied to an adjacent naïve (i.e. previously untreated) site. If a score of '++' (Strong) or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will, however, progress to the challenge phase unless, in the opinion of the Investigator (or medically qualified designee), it would be unwise to do so.

The negative control (saline solution) will be used as a reference to contextualise clinical outcomes for the test products by the Sponsor after the study completes and unblinding.

Any cutaneous (dermal) irritation or sensitization reactions which occur within the patch application area and can be completely described by the scale in Appendix 2 will not be recorded as AEs during the study. These responses are typical effects of occluded application of topical products. Reactions to the patch itself or the adhesive will also not be recorded as AEs.

Unexpected or unusual reactions which occur within the patch test area that cannot be completely described by the scale in Appendix 2 (e.g., rash, hives) will be recorded as AEs.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- 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.
- Any cutaneous (dermal) irritation or sensitization reactions which occur within the patch application area and can be completely described by the scale in Appendix 2 will not be recorded as AEs. Reactions to the patch or adhesive tape will also not be recorded as AEs.

10.2 Definition of a Serious Adverse Event (SAE)

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

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - 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;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - 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.

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

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)

- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available. The GSK CH Study Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox (PPD).

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria

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

10.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD). The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD).

The investigator will submit any updated SAE data to GSK CH within the designated reporting time frames.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.7.1 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 5 days after last administration of study product.

10.8.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box (PPD) within 24 hours of learning of the subject becoming pregnant. The GSK CH

Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox (PPD). Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD). Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Any female subject who becomes pregnant while participating will discontinue study treatment and be withdrawn from the study.

11 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, dispensing records, subject files and records kept at the site, involved in the clinical study) which contain the source of data recorded in the CRF should be specified. The CRF can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

A CRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party BDM Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary, GSKDrug.

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Approximately 470 healthy subjects will be screened to randomize at least 280 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is observed in 200 subjects, the 95% exact confidence interval (Clopper-Pearson method for binomial proportions) for the true of rate of positive reactions (in the general population) would be [0, 1.83%]. (Clopper and Pearson, 1934)

12.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (RAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate).

12.2.1 Definition of Analysis Populations

This safety study is designed to evaluate cutaneous irritation and sensitization (local tolerance). There are no efficacy outcomes. Therefore, analyses will be conducted on the Safety population.

The Safety population will comprise of all randomized subjects who receive any application of the study products.

12.2.2 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable. No data will be excluded from analysis post database lock.

12.2.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the safety population.

Age will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group. Gender, race, and Fitzpatrick skin type will be summarized using frequency counts for the safety population.

12.2.4 Study Product Compliance

Product application will be conducted at study site. Any protocol deviations associated with treatment applications or patch adherence will be reviewed during Blind Data Review Meeting prior to database lock.

12.2.4.1 Prior and Concomitant Medications

Prior medications, concomitant medications and significant non-drug therapies taken during treatment will be listed for the safety population.

12.2.5 Primary Analysis(es)

The primary analysis will be based on potential sensitization reactions as assessed by a dermatologist and will be conducted on the Safety population.

The number and percentage of subjects with any potential sensitization reactions versus those without any potential sensitization reactions will be presented by visit and treatment group.

The 95% exact confidence intervals for binomial proportions using the Clopper-Pearson method (Clopper and Pearson, 1934) will be computed for the proportion of subjects with potential sensitization reactions.

Narrative description of all potential sensitization reactions will be provided.

12.2.6 Secondary Analysis(es)

The secondary analysis will be based on the positive reactions scores (scores of '+' or greater) as assessed using the scale described in Appendix 2 and will be conducted on the Safety population.

The number and percentage of subjects with each category of score versus those without any skin response will be presented by phase, visit and treatment group using the maximum score.

The number and proportion of subjects with any positive reactions scores (scores of '+' or greater) will be summarized by phase and across both phases by treatment group and 95% exact confidence intervals for binomial proportions using the Clopper-Pearson method will be computed. (Clopper and Pearson, 1934).

Narrative descriptions of all positive responses (scores of + or greater), in the challenge phase, will be provided.

12.2.7 Safety Analysis(es)

Safety analyses will be performed according to the treatment that the subject received, and Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be regarded as treatment emergent if they occur on or after the first treatment application.

Treatment Emergent Adverse Events by System Organ Class (SOC) and Preferred Term (PT), Treatment Emergent Adverse Events (skin site related/non-skin site related), treatment-related AEs (skin site related/non-skin site related), will be summarized overall and by treatment group.

Deaths, Non-fatal Serious Adverse Events, Treatment Emergent Adverse Events leading to study or drug discontinuation will be listed.

12.2.8 Handling of Dropouts and Missing Data

Missing data will not be replaced or imputed. Dropouts will be included in analyses up to the last assessments at the point of discontinuation.

12.2.9 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH or designee (i.e. third-party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK CH 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.

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

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

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH 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.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the**,** guidelines for Good Clinical Practice (International Code for Harmonisation 1996 and revision 2), the Declaration of Helsinki (World Medical Association 2013), and the Brazil National Resolution 466. In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This

generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH-sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13.4 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 in accordance with applicable GSK CH processes.

GSK intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK CH site or other mutually-agreeable location.

GSK CH will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK CH Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, the investigator 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 (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g. for a GSK CH audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of developmental skin care products at any time. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

14 REFERENCES

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14. APPENDICES

14.1 APPENDIX 1 - ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Table 14-1 Abbreviations

Abbreviation	Term
AE	adverse event
CRF	case report form

Abbreviation	Term
EC	ethics committee
eCRF	Electronic Case Report Form
FSFV	First Subject First Visit
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRB	institutional review board
IRC	internal review committee
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
N/A	not applicable
PI	principal investigator
PI	personal information
PT	Preferred Term
cm^2	Centimeter squared
SAE	serious adverse event
SmPC	summary of product characteristics
SOC	System Organ Class
mL	Milliliter
SRSD	single reference study document
SS	safety statement

14.2 APPENDIX 2 – Scoring of patch test reactions according to ICDRG

Patch testing techniques and scoring reactions by a grading scale were first standardized in the 1930s. The International Contact Dermatitis Research Group (ICDRG) published the following nonlinear, descriptive grading scale in 1970's (Fregert, 1974) which continues to be widely used and will be adopted for this clinical study (Table 15-2). Therefore, any skin response at a patched site will be clinically assessed using scale recommended by the ICDRG.

A trained, blinded evaluator will score the test sites for signs of reactions per ICDRG scale at all time points specified in the study schedule. The evaluator score will be considered final.

During the induction phase; a trained, blinded evaluator will score the test sites for signs of irritation per ICDRG scale (Table 14-2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

During the challenge phase patch test site assessment will be conducted in a 2-step process:

Step 1: A trained, blinded evaluator will score the test sites for signs of reactions per ICDRG scale (Table 14-2) at all time points specified in the study schedule. The trained evaluator score will be considered final. The trained evaluator does not need to be medically qualified.

Step 2: For each subject who presents a positive reaction (a score of '+' or greater), a blinded dermatologist will further classify the reaction as potential sensitization (or not) at the final visit

and provide a narrative description of the event. The dermatologist will not be scoring the reaction. A single event may occur over multiple visits. Only one narrative should be made. The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken and diagnosis (potential sensitization reaction, or not as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

The negative control (saline solution) will be used as a reference to contextualise clinical outcomes for the test products by the Sponsor after the study completes and unblinding.

Any cutaneous (dermal) irritation or sensitization reactions which occur within the patch application area and can be completely described by the scale in Table 14-2 will not be recorded as AEs during the study. These responses are typical effects of occluded application of topical products. Reactions to the patch itself or the adhesive will also not be recorded as AEs.

Unexpected or unusual reactions which occur within the patch test area that cannot be completely described by the scale in Table 14-2 (e.g., rash, hives) will be recorded as AEs.

Table 14-2 Scoring of patch test reactions according to ICDRG

-	Negative reaction
?+	Doubtful reaction; faint erythema only
+	Weak (non-vesicular) positive reaction; erythema, infiltration and possibly papules
++	Strong (vesicular) positive reaction; erythema, infiltration, papules and vesicles
+++	Extreme positive reaction; bullous reaction, intense erythema and infiltration, coalescing vesicles
IR	**Irritant reaction**
NT	**Not tested**

If a score of '++' (Strong) or greater at any point during the induction phase is reported, the next patch will be applied to an adjacent naïve (i.e. previously untreated) site. If a score of '++' (Strong) or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will, however, progress to the challenge phase unless, in the opinion of the Investigator (or medically qualified designee), it would be unwise to do so.

14.3 APPENDIX 3 – Fitzpatrick Skin Type Grading

The Fitzpatrick scale is a numerical classification that is widely used by dermatologists to classify a person's skin type by their response to sun exposure (Fitzpatrick, 1988)

Skin Type	Sunburn and Tanning History
I	Always burns easily; never tans (pale white skin)
II	Always burns easily; tans minimally (white skin)
III	Burns moderately; tans gradually (light brown skin)
IV	Burns minimally, always tans well (moderate brown skin)
V	Rarely burns, tans profusely (dark brown skin)
VI	Never burns (deeply pigmented dark brown to black skin)