Clinical Protocol

212378

A Photo-irritation and Photo-sensitisation study in Healthy Subjects for Three Developmental Cosmetic Facial Products

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GlaxoSmithKline Consumer Healthcare

980 Great West Road, Brentford,
Middlesex, TW8 9GS,
United Kingdom (UK)

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CLINICAL PROTOCOL

A Photo-irritation and Photo-sensitisation study in Healthy Subjects for Three Developmental Cosmetic Facial Products

Protocol Number:	212378
Compound/Product Name:	Developmental cosmetic facial serum, lotion and cream
United States (US) Investigational New Drug (IND) Number:	Not Applicable
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Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSKCH)** Rua Hungria 1240 - 4º andar, Jardim Europa São Paulo/SP – Brazil, CEP 01455-000

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Minor changes to increase the product drying time before irradiation, clarify ITA section (8.1.6) and amend the presentation of tables in section 12.
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

Table of Contents

List of in text tables

1 PROTOCOL SUMMARY

Background and Rationale

A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use. As a general requirement, the safety and compatibility of a new formulation should be confirmed before it is commercialised (Guideline for the Safety Evaluation of Cosmetic Products; Agência Nacional de Vigilância Sanitária, ANVISA, 2012), (Cosmetics Europe, 2004).

Compatibility studies, performed as patch tests, aim to confirm the local tolerance of topical cosmetic products during the first application to the skin, therefore providing assurance that the product is safe for use under maximized conditions (ANVISA, 2012).

Photo-irritation assessments aim to demonstrate the absence of irritation potential of a product when applied to the skin and exposed to ultraviolet radiation (UVR). Photo-sensitisation assessments aim to demonstrate the absence of allergic potential of a product applied to the skin when exposed to UVR.

Photo-irritation potential will primarily be evaluated through the repeated occluded application and UV exposure of the study products over 3 weeks (induction phase). Photo-sensitisation potential will primarily be evaluated through a subsequent semi-occluded application and UV exposure (challenge phase) after a 2-week rest period. Subjects who participate in this study shall be healthy adult males and females with no prior hypersensitivity to topical products with no active dermatoses on their upper back.

Prior to the conduct of any study procedures or application of study products, prospective test areas will be evaluated by a trained blinded evaluator to confirm they are free any signs or symptoms of cutaneous irritation.

At screening, the minimal erythema dose (MED) will be determined for each subject to ensure the dose of UV radiation to be administered in the induction and challenge phase is controlled appropriately. Only subjects who present a valid MED will be considered eligible for randomisation.

Once randomised, controlled amounts of each of the three test products and a reference product (0.9M saline) will then be applied in duplicate to defined areas of skin (0.02 mL/cm^2 of each product) via cells within semi-occlusive patch system to the upper back of each subject. Each patch shall remain in place for 24 hours, after which it will be removed, and each test site evaluated and recorded by a trained evaluator for signs of cutaneous irritation.

Study products will then be reapplied to the skin test sites, and one series of test sites will be exposed to a controlled dose of UV radiation and the other series will not. Both the irradiated and non-irradiated sites will be evaluated immediately after completion of the UV exposure procedures and again the following day. This procedure shall be repeated twice-weekly for 3 weeks (a total of 6 patch applications per series).

Subjects will then enter a 2-week rest phase during where no interventions are made. This will be followed by a 24-hour challenge exposure of each study product under semi-occlusive conditions. Test materials will be applied to naïve test sites on the upper back in duplicate. Once the patch systems are removed, one series will be exposed to UV radiation and the other shall

not. Both sets of test sites will be evaluated by a trained evaluator for signs of cutaneous irritation immediately, 24, 48 and 72-hours after UV exposure of the irradiated sites.

Photo-irritant reactions are most often characterised by intense delayed erythema (i.e. an exaggerated sunburn reaction) and are frequently followed by hyperpigmentation and peeling of damaged skin. The acute aspects of photo-irritant reactions may begin within a few minutes to hours after irradiation and tend to resolve within a few days to weeks. Hyperpigmentation may take several months to years to clear. Whereas the acute aspects of photo- irritant reactions typically present soon after irradiation, photo-sensitisation reactions seldom occur after the first exposure to the photo-allergen. Since photo-sensitisation is an immunological process in nature, multiple exposures to the photo-activated allergen and a latent period of several days to weeks are typically required before the immune system is ready to respond. Once a subject has been sensitised, subsequent exposures to the photo-allergen and UV radiation will elicit cutaneous responses quite rapidly within 24-72 hours (Beani 2017).

After the trained evaluator has graded all the patch cells according to the ICDRG scoring Table 15-2 (Appendix 2), a blinded dermatologist will evaluate every positive reaction (defined as a score of '+' or greater) in the challenge phase to further classify it as potential sensitisation (or not) and provide a narrative description of the event. The location of positive reactions will be determined after unblinding to determine whether a reaction was potentially photo-initiated.

The objective of this clinical study is to assess the photo-irritation and photo-sensitisation potential of three developmental cosmetic formulations compared to a reference product (negative control) after duplicate, repeated semi-occlusive patch applications to healthy human subjects by following a conventional photo-irritation and photo-sensitisation methodology under supervision of a dermatologist.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the cutaneous photo-sensitisation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a potential sensitisation reaction which is considered photo-initiated.
Secondary	
To evaluate the cutaneous photo-irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a photo-initiated reaction score of '+' or greater which not considered a potential sensitisation reaction.
To evaluate the cutaneous sensitisation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a potential sensitisation reaction which is not considered photo-initiated.
To evaluate the cutaneous irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a non-photoinitiated reaction score of '+' or greater which is not considered a potential sensitisation reaction.
Safety	
To evaluate the general safety of three cosmetic facial skincare products	Frequency and severity of Adverse Events

Study Design

This will be a single-center, randomised, evaluator (single) blind study in healthy adult subjects with no dermatological disorders and with a Fitzpatrick skin phototype II to IV. Subjects will be exposed to a duplicate series of repeated semi-occlusive patch applications of 3 topical cosmetic formulations and a reference product (saline solution) to evaluate the photo-sensitisation and photo-irritation potential of the study products under maximized conditions of use. Only one series of patches will be exposed to UV radiation. The study will be conducted under the supervision of a dermatologist.

Study Products

The three study products are developmental cosmetic moisturisers (a serum, lotion and cream), intended to be used topically by healthy individuals with dry facial skin.

In both the induction and challenge phases, 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 each patch system will be 6, of which 4 will be used for the products and 2 will be left blank. In this study, each of the study products will be dispensed into 4 adjacent cells, in two duplicate series of patches, as per the randomisation schedule. Three cells will be used for the test products (serum, lotion and cream) and a fourth for the reference product (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 II to IV and no dermatological disorders will be enrolled into this study.

Approximately 80 healthy subjects will be screened to randomise at least 40 subjects to ensure at least 25 evaluable subjects complete the entire study. No formal power calculation has been performed as the sample size is standard in clinical testing practices and is consistent with the ANVISA guidelines (ANVISA, 2012).

The focus of the statistical analysis will be the evaluation the proportion of subjects potentially photo-sensitised (potential sensitisation reaction in the UV-exposed series of patches) and the frequency of positive irritation reactions (scores of '+' or greater) to 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 Study Schedule

Study Phase	Screening			Induction														Rest	Challenge				
Study Week	Maximum 2 Week Duration			1					2					3					4/5	6				
Procedure/ Assessment \ Study	VISIT 1	VISIT 2	VISIT 3	VISIT 4 DAY 1	VISIT 5 DAY 2	VISIT 6 DAY 3	VISIT 7 DAY 4	VISIT 8 DAY 5	VISIT 9 DAY 8	VISIT 10 DAY 9	VISIT 11 DAY 10	VISIT 12 DAY 11	VISIT 13 DAY 12	VISIT 14 DAY 15	VISIT 15 DAY 16	VISIT 16 DAY 17	VISIT 17 DAY 18	VISIT 18 DAY 19	-	VISIT 19 DAY 36	VISIT 20 DAY 37	VISIT 21 DAY 38	VISIT 22 DAY 39	VISIT 23 DAY 40
Day of Week	-	-	-	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	-	Mon	Tue	Wed	Thu	Fri
Informed Consent	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	X	X	X		X	X	X	X	X
Fitzpatrick Skin Type Assessment	X																							
Individual Typology Angle ITA°	X																							

Study Phase	Screening			Induction															Rest	Challenge				
Study Week	Maximum 2 Week Duration			1					2					3					4/5	6				
Study / Procedure/ Assessment	VISIT 1	VISIT 2	VISIT 3	VISIT 4 DAY 1	VISIT 5 DAY 2	VISIT 6 DAY 3	VISIT 7 DAY 4	VISIT 8 DAY 5	VISIT 9 DAY 8	VISIT 10 DAY 9	VISIT 11 DAY 10	VISIT 12 DAY 11	VISIT 13 DAY 12	VISIT 14 DAY 15	VISIT 15 DAY 16	VISIT 16 DAY 17	VISIT 17 DAY 18	VISIT 18 DAY 19	-	VISIT 19 DAY 36	VISIT 20 DAY 37	VISIT 21 DAY 38	VISIT 22 DAY 39	VISIT 23 DAY 40
Day of Week	-	-	-	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	-	Mon	Tue	Wed	Thu	Fri
Inclusion/Exclusion Criteria	X	X [a]																						
Dermatologist Assessment [b]	X																			X	X	X	X	X
Subject Eligibility	X																							
Continued Eligibility		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Provisional MEDu irradiation		X																						
MEDu Determination			X [c]																					
Randomisation				X																X				
Acclimatization to Standard Conditions [d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Baseline Grading of Test Sites [e]				X																X				

Study Phase	Screening			Induction															Rest	Challenge				
Study Week	Maximum 2 Week Duration			1					2					3					4/5	6				
Study / Procedure/ Assessment	VISIT 1	VISIT 2	VISIT 3	VISIT 4 DAY 1	VISIT 5 DAY 2	VISIT 6 DAY 3	VISIT 7 DAY 4	VISIT 8 DAY 5	VISIT 9 DAY 8	VISIT 10 DAY 9	VISIT 11 DAY 10	VISIT 12 DAY 11	VISIT 13 DAY 12	VISIT 14 DAY 15	VISIT 15 DAY 16	VISIT 16 DAY 17	VISIT 17 DAY 18	VISIT 18 DAY 19	-	VISIT 19 DAY 36	VISIT 20 DAY 37	VISIT 21 DAY 38	VISIT 22 DAY 39	VISIT 23 DAY 40
Day of Week	-	-	-	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	Mon	Tue	Wed	Thu	Fri	-	Mon	Tue	Wed	Thu	Fri
Patch Removal					X		X			X		X			X		X				X			
Grading of Test Sites Prior to UV Irradiation [f,]					X		X			X		X			X		X				X			
Product Application and UV Irradiation [g]					X		X			X		X			X		X				X			
Grading of Test Sites After UV Irradiation [h,]					X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X [i]	X [i]	X [i]
Product and Patch Application				X		X			X		X			X		X				X				
Adverse Events [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Study Conclusion/ Exit from Study/																								X

Notes:

- Visit 1 and Visit 2 could occur on the same day but Visit 2 must be within 7 days of Visit 1.
- Visit 4 will start on the first Monday after a valid MED has been recorded.
- A 'patch system' contains individual cells. Each of the study 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 randomised for each subject. The same sequence within each subject will be used throughout the induction phase on both patches, 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. Assessment of inclusion criteria 6 (only) by a qualified dermatologist.

b. A blinded dermatologist will review overall subject eligibility at the screening visit and the final visit and will also review any evaluator reaction score that is '+' or greater in the challenge Phase to provide a narrative and interpretation whether the reaction is a potential sensitisation reaction.

c. Provisional MEDu grading must occur 16-24 hours after completion of the MEDu irradiation. It may take multiple attempts to record a valid MED for a subject.

d. Approximately 15-30 minutes following patch removal, subjects will rest in standard room conditions (18-26 °C) prior to the test area assessment.

e. Baseline grading of naïve test sites will be performed prior to the patch application at Visit 4 (induction phase) and Visit 19 (challenge phase) using the scoring system detailed in grading scale Table 15-2 Appendix 2.

f. 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 Table 15-2 Appendix 2.

g. UV irradiation will occur after product application. One series of test sites will be exposed to UV radiation while the second series of test sites will not be exposed to UV radiation.

h. Both series of test sites will be evaluated by a blinded and trained evaluator, immediately after UV exposure of the irradiated series of sites using the scoring system detailed in grading scale Table 15-2 Appendix 2.

i. Grading of challenge sites (irradiated and non-irradiated) will occur 24 (±4), 48 (±4) and 72 (±4) hours after UV exposure of the irradiated series of sites.

j. 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. This industry awareness, and consumer and regulatory agency requirements have led cosmetic manufacturers to adopt procedures that provide them with a better understanding 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 product. These procedures provide greater assurance of safety for the companies, increase their credibility, and increase 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). Thus, the raw materials used in the product formulation must be of proven safety and with established use in the cosmetic industry. 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 sensitisation, in the presence of an allergenic ingredient.

Clinical studies to evaluate the irritation and sensitisation 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).

A common method to assess the potential of a topical product to cause irritation or sensitisation involves repeated applications of a product to the skin under semi-occlusive patches (Basketter, 2008). The semi-occlusion provides a higher degree of contact between the components of the product formula and the skin (exaggerated use conditions). Therefore, it is considered to be a sensitive method to assess the photo-irritation and photo-sensitisation potential of topically applied products.

Several types of substances do not present an inherent irritant or allergenic potential; however, they may provoke skin reactions when exposed to sunlight, either because ultraviolet radiation converts them into other substances, or because they are photo-initiated to excited states capable of interacting with the skin (Billhimer, 1990). Specifically, topically applied agents can cause contact dermatitis or interact with sunlight to cause photo-irritant reactions. These reactions occur on first exposure to the product and usually resemble exaggerated sunburn and may be characterised by a sensation of prickling and burning.

Skin sensitisation is an immunological process in which the responsiveness to a specific chemical allergen is increased. By definition, skin sensitisation 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 sensitisation (Kimber *et al.*).

The photo-irritation test measures the potential of a test product to produce photo-irritant reactions in human subjects upon exaggerated application. Evaluator comparison of cutaneous responses to test product alone, test product exposed to UV radiation and an irradiated,

reference product site provides an assessment of the photo-irritant toxic potential of the test product.

Topically applied products may contain one or more ingredients that can be converted to a photo-antigen by UV radiation. In certain individuals, the photo-antigen can then trigger an inflammatory response by the immune system and produce an allergic reaction upon subsequent exposure to the product in sunlight.

The photo-sensitisation test measures the potential of study products to produce allergic reactions in the presence of UV radiation. This test consists of three phases: a 3-week induction phase consisting of two parallel repeated 24 hour patch applications on the backs of healthy subjects (one of which is subsequently exposed to UV radiation upon patch removal, and evaluation of cutaneous responses of both sites) after each patch removal; a 2 week Rest phase; and a final challenge phase, consisting of two parallel 24 hour semi-occlusive patch applications to naive sites, one set of which is subsequently exposed to UV radiation upon patch removal, and evaluation of cutaneous responses of both sites 24, 48 and 72 hours after patch removal.

The inclusion of an induction and challenge phase for two series of patches (one with and one without exposure to UV radiation) enables simultaneous evaluation of the potential for contact irritation, photo-irritation, contact sensitisation and photo-sensitisation.

The objective of this clinical study is to assess the photo-sensitisation and photo-irritation potential of three cosmetic study products under exaggerated conditions of use with controlled product application and under supervision of a dermatologist.

2.1 Study Rationale

GSK CH has developed three topical cosmetic formulations (a lotion, cream and serum) intended to be used in daily facial skin care routines. These products are designed to be suitable for use by healthy adult consumers with dry facial skin. The study products are to be applied directly to the skin after cleansing, with the intent of delivering ingredients directly onto the skin.

As the new formulations are intended for facial application, consumers who apply the products will be exposed to ultraviolet radiation from the sun. Therefore, clinical data is required to confirm that the developmental formulations have low photo-sensitisation potential.

Among the several types of safety assays in humans, patch tests are currently the most widespread protocols conducted in order to investigate the potential risk for possible irritation and sensitisation agents that, when in contact with the human skin and exposure to UVR may trigger a reaction.

Visual assessment will be performed in a room with matte, neutral wall colours with sufficient and uniform illumination. As only one series of unprotected skin sites will be exposed to UV radiation for the detection of the provisional MEDu, the grader will, necessarily, not be blinded at this point in the study.

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

2.2 Background

Clinical studies to evaluate the irritation and sensitisation 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). Compatibility studies, performed as patch tests, aim to confirm the local tolerance of topical cosmetic products during the first application to the skin, therefore providing assurance that the product is safe for use under maximized conditions (ANVISA, 2012).

A common method to assess the potential of a topical product to cause irritation or sensitisation involves repeated applications of a product to the skin under semi-occlusive patches (Basketter, 2008). 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 semi-occlusion 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 photo-irritation and photo-sensitisation potential of topically applied products.

The objective of this clinical study is to assess the photo-sensitisation and photo-irritation potential of three developmental cosmetic formulations and a reference product (saline solution) by repeated semi-occlusive patch applications to healthy human subjects, under the supervision of a dermatologist.

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

Objectives	Endpoints
Primary	
To evaluate the cutaneous photo-sensitisation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a potential sensitisation reaction which is considered photo-initiated.
Secondary	
To evaluate the cutaneous photo-irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a photo-initiated reaction score of '+' or greater which not considered a potential sensitisation reaction.
To evaluate the cutaneous sensitisation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a potential sensitisation reaction which is not considered photo-initiated.
To evaluate the cutaneous irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a non-photo-initiated reaction score of '+' or greater which is not considered a potential sensitisation reaction.
Safety	
To evaluate the general safety of three cosmetic facial skincare products	Frequency and severity of Adverse Events

Success criteria:

A test product will be considered to have low photo-sensitisation potential if the proportion of subjects with a potential photo-sensitisation reaction are comparable for the test product and saline.

The hypothesis is that the study products will have low photo-sensitisation potential. Therefore, it is expected that the vast majority of responses will be negative. No formal statistical comparison between treatment groups shall be made.

4 STUDY DESIGN

4.1 Overall Design

This will be a single-center, randomised, evaluator (single) blind study in healthy adult subjects aged 18 to 65 years with no dermatological disorders to evaluate the cutaneous photo- irritation and photo- sensitisation potential of three cosmetic facial skincare products.

Approximately 80 healthy subjects will be screened to randomise at least 40 subjects to ensure at least 25 evaluable subjects complete the entire study.

There will be a total of 5 different test areas, located on the back of each subject, which will be used in this study across the screening, induction and challenge phases:

- 1 test area to determine the provisional MEDu in screening;

- 2 test areas for test products and reference product (saline solution) in the induction phase (1 series will be exposed to UV radiation, the other series will not);
- 2 test areas for test products and reference product (saline solution) in the challenge Phase (1 series will be exposed to UV radiation, the other series will not).

The 4 test areas in the induction and challenge phases will each undergo applications of an adhesive patch system. Within each patch system, there will be 6 circular cells, of which 4 will be used to host the study products and 2 will be left blank. In this study, each of the study products will be dispensed into 4 adjacent cells, in two duplicate series of patches, as per the randomisation schedule. Three cells will be used for the test products (serum, lotion and cream) and a fourth for the reference product (saline solution).

Subjects will be exposed to duplicate, repeated insult semi-occlusive patch applications of the test products and reference product (saline solution) over a three-week induction phase, and a further single application of the test products and reference product in a challenge phase.

During screening, subjects will sign an informed consent form and undergo a dermatological assessment to ensure they have no dermatoses on their dorsum (back) that might impact their safety or confound study outcomes, and to ensure a Fitzpatrick Phototype of II to IV.

Subjects will also undergo a colorimetry analysis of their skin type using the Individual Typology Angle (ITA°) which will be used to estimate MED.

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.

Subjects who meet all specified inclusion and exclusion criteria and who agree to comply with all lifestyle guidelines and restrictions will be considered eligible for enrollment in this study.

Visit 1 (screening) may be combined with visit 2 (MED irradiation) if convenient for the subject and study site. However, visit 2 should occur no later than 7 days after visit 1.

At visit 2, eligible subjects will return to the study site and another dermatological assessment will be conducted for inclusion criterion 6 to ensure subjects remain eligible to continue in the study (if visits 1 and 2 are not combined). Any changes to concomitant medications will also be reviewed.

The MED of each subject will then be determined in a two-step procedure, see section 8.2.1 (MED Irradiation) and 8.3.1 (MED Determination) for details. This step is critical to ensure the selection of UV doses for the assessment of photo-sensitisation and photo-irritation are appropriate for each subject, enabling a robust UV-challenge of the patched sites without resulting in UV-induced erythema (sunburn).

In this study, one series of patched sites will be repeatedly exposed to 0.3 MED of UV radiation (290-400 nm) and a second controlled dose of 2.5 J/cm^2 UVA (340-400 nm) radiation per the study schedule.

Induction Phase (visits 4-18):

During the induction phase (visits 4-18) there will be 6 patch application visits over 3 weeks. Each patch will contain a segregated sample of each of the test products and saline solution.

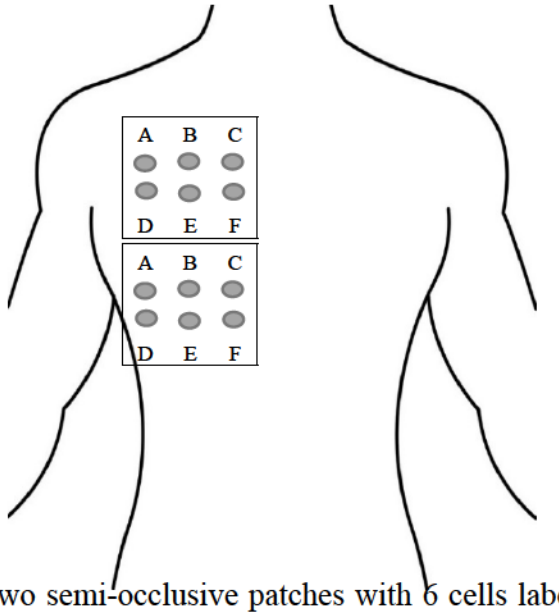
Duplicate series of each patch will be applied to the assigned test areas on Mondays and Wednesdays and shall remain in place for 24 (± 4) hours.

Monday: Subjects will arrive at site and will assigned to a random sequence of study products within the 4 cells of the patch system, per the randomisation schedule. The location of the test areas on the back of each subject will be determined by the investigator or designee based on the condition of the skin (e.g. free of moles, dermatoses etc.) and will not be randomised.

Subjects will be seated in standard room conditions (18-26°C) and instructed to avoid contact between the test area on their back and any other surface. 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 trained, blinded evaluator per the grading scale in Table 15-2 (Appendix 2). This will act as the baseline reading for the induction phase.

Note, the second and third Monday visits (i.e. visits 9 and 14) will not include the randomisation step. However, these visits will include an assessment for signs and symptoms of irritation by a trained, blinded evaluator following UV irradiation the preceding Thursday (i.e. visits 7 and 12).

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



Two semi-occlusive patches 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 into the appropriate separate cell, 3 cells for each of the test products and 1 cell for the saline solution to each of the patch systems. The assignment of the study products to the cells within the patch system for each subject will be randomly assigned per the randomisation schedule provided. The sequence of the products to the cells for each subject will remain the same throughout the induction phase. A different sequence per the randomisation provided will be used for each subject for the challenge phase.

Tuesday: Subjects will arrive at site after 24 (±4) hours of patch application. The patches will be removed, and the treated areas can be lightly wiped with saline solution. Subjects will be instructed to rest for 15-30 minutes in standard room conditions (temperature 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 by a trained, blinded evaluator per the scale in Table 15-2 Appendix 2.

After assessment of the test sites, study products will be reapplied directly to the previously treated skin sites in the same sequence (per the randomisation schedule). After a 15- 30 minute drying period, one area of skin treated with the study products will be irradiated with 2.5 J/cm^2 UVA radiation with a Schott UG11+WG335 filter (or equivalent) in place, and then with 0.3 MEDs of UVA+UVB radiation (filters UG11+WG320). The duplicate area treated with the study products will not receive irradiation during the irradiation procedure. Assessment of the irradiated and non-irradiated sites for signs of irritation will occur immediately after the UV exposure procedures are completed, and any reaction will be graded as per grading scale Table 15-2 (Appendix 2).

For each positive reaction (a score of '+' or greater) in the challenge phase, a dermatologist (blinded) will further classify it as potential sensitisation (or not) and provide a narrative description of the event. The dermatologist will not be scoring the reactions.

If a subject develops a score of 'Strong' (++) or greater at any point during the induction phase, 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 rest and challenge phase unless, in the opinion of the Investigator, it would be unwise to do so.

Wednesday: Subjects will arrive at site after 24 (±4) hours after irradiation and will be seated for at least 15-30 minutes to the environment of standard room conditions (18-26°C) and instructed to avoid contact of the back area with any other surface. Test sites will be evaluated for signs of irritation by a trained, blinded evaluator as per grading scale Table 15-2 (Appendix 2).

Duplicate patches will then be applied to the back, please see Monday assessments for further details on patch application.

Thursday: Tuesday assessments to be repeated.

Friday: Subjects will arrive at site after 24 (±4) hours after irradiation and will be seated for at least 15-30 minutes to the environment of standard room conditions (18-26°C) and instructed to avoid contact of the back area with any other surface. Test sites will be evaluated for signs of irritation by a trained, blinded evaluator as per grading scale Table 15-2 (Appendix 2).

The process of patch applications, grading and UV-exposure shall be repeated for an additional two weeks.

Rest Phase (2 weeks):

Once the induction phase is complete, subjects will enter a 2-week rest phase, during which there will be no product or patch applications.

Challenge Phase (Visits 19-23):

Once the rest phase in complete, subjects will return for the challenge phase (visits 19-23). Randomisation for challenge phase will occur on visit 19 (day 36). The order to which the study products are assigned to the cells within the patch system are randomise to reduce the opportunity for bias through outcomes observed in the induction phase.

The challenge phase will consist of a duplicate parallel series of product applications under semi-occlusive patches to 2 naïve areas (i.e. previously untreated) of the back, between the shoulder line and waist, and away from the spinal mid-line.

These areas will be evaluated by the trained, blinded evaluator prior to any patch application to provide a baseline for interpretation. Two patches containing study products as per the randomisation sequence for the subject's challenge phase, will then be applied.

Monday/Tuesday: After randomisation for the challenge phase all assessments as per the Induction phase are to be repeated.

Wednesday/Thursday/Friday: Further test site assessments for signs of cutaneous irritation will be conducted 24 (± 4), 48 (± 4), and 72 (± 4) hours after UV exposure as per grading scale Table 15-2 (Appendix 2).

End of Study (Visit 23):

At visit 23/Day 40, after the challenge phase is complete, a final clinical assessment by a qualified dermatologist will be performed to ensure that it is medically appropriate to exit each subject from the study. After all study assessments are completed, subjects will be discharged from the study site.

Additionally, the dermatologist will use the total body of data for a subject (any positive reactions which occurred over the challenge phase) to judge whether a positive reaction is a potential sensitisation reaction or not.

Adverse events and concomitant medications will be assessed throughout the study.

4.2 Rationale for Study Design

Compatibility studies represent the first contact of the finished product in humans and seek to prove the safety of product under maximised conditions, with controlled amount and application area. The application of study products within a semi occlusive patch allows for a clinical assessment under maximized conditions and is globally accepted, being widely used in the literature.

There will be a blinded evaluator (trained on the ICDRG scoring system) to assess all patch sites for the duration of the study. The intensity of any visual signs of irritation will be recorded according to the quantity and grade of the reactions, Table 15-2 (Appendix 2). The trained evaluator is responsible for grading the reactions, and the trained evaluator's score will be considered is final.

This study will be conducted under the supervision of a dermatologist. Subjects will be assessed by a dermatologist as a prerequisite to enrolment, and again at study end. For products with specific safety appeals, the study must be followed up by a specialist (dermatologist) (ANVISA, 2012).

For each subject who presents a positive reaction (i.e. a reaction score of '+' or greater) in the challenge phase a blinded dermatologist will further classify the reaction as potential sensitisation (or not) at the final visit and provide a single narrative description to summarise the entirety of the subject's experience of the event. As sensitisation and irritation can occur in the challenge phase, it is possible to record a positive reaction in the challenge phase which is not a sensitisation reaction. The dermatologist must consider how the reaction presents/evolves over time, to ascertain whether it is characteristic of a sensitisation reaction. The dermatologist will record their opinion in the narrative and with a check-box in the CRF.

The narrative must include the test site, start and finish date of the event, a description of how the event evolves over time, any action taken (e.g. moved patch) and whether the dermatologist considers the reaction to be a potential sensitisation reaction. If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

The acute aspects of photo-irritant reactions may begin within a few minutes to hours after irradiation and tend to resolve within a few days to weeks. Whereas the acute aspects of photo-irritant reactions typically present soon after irradiation, photo- sensitisation reactions seldom occur after the first exposure to the photo-allergen. Since photo-sensitisation is an immunological process in nature, multiple exposures to the photo-activated allergen and a latent period of several days to weeks are typically required before the immune system is ready to respond. Once a subject has been sensitised, subsequent exposures to the photo-allergen and light will elicit cutaneous responses quite rapidly within 24-72 hours (Beani 2017).

A subject may experience positive reactions in any of the following patterns:

1. At ONLY the UV-exposed site,
2. At ONLY the Non-UV-exposed site,
3. At BOTH the UV-exposed and non-UV-exposed sites.

The location of positive reactions will be determined after unblinding to determine whether a reaction is potentially photo-initiated:

- Positive reactions which occur at ONLY the UV-exposed site will be considered photo-initiated.
- Positive reactions which occur at ONLY the non-UV-exposed site will not be considered photo-initiated.
- Positive reactions which occur at BOTH the UV-exposed and non-UV-exposed sites will be considered photo-initiated if the maximum score at the UV-exposed site is more severe than the maximum score at the non-UV-exposed site. If the maximum score at the UV-exposed site is equal to or lower than the non-UV-exposed site, then it will not be considered photo-initiated.

The inclusion of evaluations at 24, 48 and 72-hours for duplicate sites treated with study products, with or without UVR, in a cumulative application via an induction phase, latent rest phase, and challenge phase, permits simultaneous evaluation of the potential for contact irritation, photo-irritation, contact sensitisation and photo-sensitisation.

4.3 Justification for Dose

The prerequisite for a patch test is the requirement that the whole test site is covered with the test product, without spreading or overlapping into other test sites. Previous work (Isaksson, 2007) has shown that the optimal dose to fulfil these requirements is 0.02 ml/cm^2.

The test product will be distributed over the patch test filter paper discs (semi occlusive patch application) in the amount of 0.02 ml and applied to designated sites on the back. A sodium chloride (NaCl) saline solution (0.9%) will be used as the reference product and will also be applied to the back through semi-occlusive application and dispensed at the same dose.

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

Photoreactions to exogenous agents typically occur in response to UVA light (315-400 nanometers (nm) rather than at the shorter wavelengths of UVB or UVC. Therefore, UVA irradiation is mandatory. However, some molecules have their action spectrum in UVB. Consequently, to prevent missing detection of any photoreactions, both UVA and UVB irradiation in parallel are now considered mandatory (Beani 1987). The photo- reactions can be divided into two types of responses; photo-irritation and photo-sensitisation (Norbert, 2005).

A dose of 0.3 MED and 2.5 J/cm^2 has been chosen to ensure that the total dose administered will be sufficient to provide evaluation of photo-sensitising and photo-irritant reaction potential with consideration of the exposure of the subjects (Beani 2017).

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed 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 aged 18 to 65 with no dermatological disorders, and with a Fitzpatrick skin phototype II to IV will be enrolled into this study.

Approximately 80 healthy subjects will be screened to randomise at least 40 subjects to ensure at least 25 evaluable subjects with no dermatological disorders and with a Fitzpatrick skin prototype II to IV complete the entire study. This sample size is standard in clinical testing practices and is consistent with the ANVISA guidelines (ANVISA, 2012).

This study can fulfill its objectives only if appropriate subjects are enrolled. 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 authorised representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

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.

5.2 Inclusion Criteria

Subject eligibility should be reviewed and documented by the Investigator or a medically qualified person or designee before subjects are included in the study.

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 other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, 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 II 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 (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, psoriasis or skin cancer
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. 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. History of diseases aggravated or triggered by ultraviolet radiation.
16. 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 (e.g. any photosensitising medication such as tetracycline, thiazides, fluoroquinolones, etc.) within one month prior to inclusion.
17. 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), and particular aspirin (>200mg/d), within two weeks prior to inclusion and/or corticosteroids.
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. Currently receiving allergy injections or received an allergy injection within 7 days prior to Visit 1 or expects to begin injections during study participation.
21. A subject with any skin marks on the back that might interfere with the evaluation of possible skin reactions (e.g. pigmentation disorders, vascular malformations, scars, tattoos, excessive hair, numerous freckles, open sores, pimples, or cysts).
22. A subject that intends bathing (in the sea or a pool), using a sauna, or partaking in water sports, or activities that lead to intense sweating for the duration of the study.

23. A subject who has used a transcutaneous electrical nerve stimulation (TENS) machine 1 day before the screening visit or intends to use a TENS machine at any point during the study.
24. History of sensitisation in a previous patch study.
25. History of abnormal reaction to sun exposure.
26. Intense sunlight exposure or sun tanning sessions up to 30 days before the Screening evaluation.
27. Recent history (within the last 5 years) of alcohol or other substance abuse.
28. A subject who has previously been enrolled in this study.

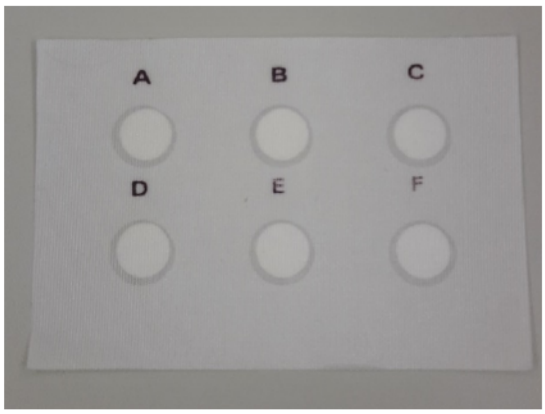
5.4 Randomisation Criteria

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

Please note that subjects will be randomised twice in this study. Randomisation for induction phase will occur on Monday Visit 4, day 1 and randomisation for challenge phase will occur on Monday Visit 19, day 36.)

Two semi-occlusive patches 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 test products to the cells within the patch system for each subject will be randomly assigned per the randomisation sequences provided. The sequence of the products to the cells for each subject will remain the same throughout the induction phase, and a different sequence per the randomisation provided will be provided for each subject for the challenge phase. For more details on the randomisation, please refer to sections 8.4.1 Induction Phase Randomisation and 8.10.1 Challenge Phase Randomisation.

5.5 Lifestyle Considerations

During the entire study (Screening – Last Subject Last Visit (LSLV)) 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 e.g. introduction of new products during the study including but not limited to soap, laundry detergent, or fabric softener.
- Getting the patch test site wet: during showers, bathing, swimming, hot tubs, saunas and steam rooms. 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.
- Use of a TENS machine
- Missing the first day of application during the induction phase or the day of application during the challenge phase.
- Missing two or more consecutive visits or more than 2 alternative visits.

5.5.1 Pregnancy

For GSK CH studies in which no drug is utilised 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 randomised. 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 Trained Evaluator and Dermatologist Qualifications

The 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 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. All practical efforts will be made to ensure the same trained evaluator will be used to evaluate all subjects in the study. The evaluator(s) will be trained by a dermatologist in the ICDRG scale, this will be documented in the site master file.

Step 2: For each subject who presents a positive reaction (i.e. a reaction score of '+' or greater) in the challenge phase a blinded dermatologist will further classify the reaction as potential sensitisation (or not) at the final visit and provide a single narrative description to summarise the entirety of the subject's experience of the event. As sensitisation and irritation can occur in the challenge phase, it is possible to record a positive reaction in the challenge phase which is not a sensitisation reaction. The dermatologist must consider how the reaction presents/evolves over time, to ascertain whether it is characteristic of a sensitisation reaction. The dermatologist will record their opinion in the narrative and with a check-box in the CRF.

The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken (e.g. moved patch), and diagnosis (potential sensitisation reaction, or other as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

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. This will confirm if subjects would require any follow up assessments. Additionally, a final assessment at Visit 23 (Last Visit) by a qualified dermatologist will confirm if it is medically appropriate to exit the subject from the study at the final visit (Edward and Norman, 1982).

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 authorisation 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	40mL Pump Pack	50mL Tube	50mL Tube	500 mL
Product Manufacturing Code (MFC)	CCI	CCI	CCI	N/A – Commercial Product
Application quantity	Dose: 0.02 mL/cm^2 Each product will be dispensed into an individual cell within the patch system according to the randomisation sequence for the induction phase and the challenge phase and removed/reapplied as per study schedule.			
Route of administration	Topical dermal application via semi-occlusive patch to the dorsum.			
Application Instruction	Applied on-site by technician			

Other items to be supplied by the clinical investigational site:

- Semi-occlusive 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 course of the study in time for study close out visit.

6.1.1 Dosage Form and Packaging

The three 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 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 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. Subjects should be instructed to not remove or deface any part of the study label.

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 test products; three developmental formulations and the saline solution will be dispensed by qualified unblinded site personnel according to the randomisation sequence into the cells of the patch system for the induction phase and the challenge phase and application schedules.

Subjects will be assigned to the sequence of products within the patch in accordance with the randomisation schedule generated by an approved GSK CH vendor, prior to the start of the induction phase and a different sequence for the challenge phase, using validated software. See section 8.4.1 Randomisation criteria and 8.10.1 Randomisation.

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

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

6.2 Administration

Induction Phase:

On Visit 4/Day 1 of the induction phase, the test site for the application of the patch will be designated above the waist between the scapula and waistline and away from the spinal mid-line. Test sites will not overlap with the site previously used for the provisional MEDu assessment. Baseline grading/assessment of the application test site will then be performed. The site of each of the products to the individual cells of the patch will then be randomly assigned, per the supplied randomisation schedule. This sequence will be different within the induction and challenge phase.

Two semi-occlusive patches 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 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 randomisation 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 randomisation provided will be generated for each subject for the challenge phase.

There will be six patch applications to duplicate sites on the dorsum over three consecutive weeks in the induction phase, with patches being applied on Monday and Wednesday. During the challenge phase, application will be made to duplicate naïve sites once on a Monday.

Each patch will remain in place for 24 (± 4) hours. The patch will contain each of the test products and the saline solution within individual cells of the patch system. 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 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.

Rest Phase:

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:

Two 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 a controlled amount (0.02 mL/cm^2) of the allocated study products as per the randomisation sequence for the subject's challenge phase, will then be applied.

The application process will follow the same process as the induction phase.

6.2.1 Dosing Errors

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

- the wrong product application sequence before and after patch removal
- at the wrong time,
- or at the wrong dosage.
- incorrect irradiation application.

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 products will be supplied, dispensed by 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 sites, 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. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorised 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 conclusion 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 (including empty containers), will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

6.5 Blinding and Allocation/Randomisation

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

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

Please note that subjects will be randomised twice in this study. Randomisation for induction phase will occur on Monday Visit 4, day 1 and randomisation for challenge phase will occur on Monday Visit 19, day 36.) For more details on the randomisation, please refer to sections 8.4.1. Randomisation criteria and 8.10.1. Randomisation.

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

This study is described as examiner-blind (the clinical evaluator and dermatologist will be blinded to the product and irradiations received). 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 and irradiations received. Dispensing staff will not be involved in any assessment procedures during this study

To ensure the trained evaluator and dermatologists remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area. The trained evaluator or Dermatologist 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 this 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 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 a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's product 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 be required to inform the IRB/EC if the blind is broken.

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel at the clinical site.

6.8 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, after 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 concomitant medication/treatments at each site visit.

Medication/treatments taken within 30 days of first application of product will be documented as a prior medication/treatment. Medications/treatments taken after first application of product 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.

7.2 Lost to Follow up

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.

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 or not the subject wishes to and/or should continue in the study.

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 and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). 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, which could include the following:

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 also 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.

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

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 dermatologist 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 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.

8.1.4 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF.

8.1.5 Dermatologist Assessment

A dermatologist will assess 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.

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

8.1.6 Individual Typology Angle (ITA°)

A tri-stimulus spectrophotometer, model Kônica Minolta CM2500D which utilizes the L*, a*, b* colour space will be used to measure the colour of each subject's skin (dorsum).
The spectrophotometer will measure three L* and three b* colour coordinates of the skin on different locations on the back (between the shoulder line and waist, on either side of the spinal mid-line) for each subject. The average (mean) L* and b* values are to be inputted into the eCRF and the ITA mean will be calculated automatically in the CRF as per equation 1.

$$\text{ITA}^\circ = \left\{ \text{arc tangent} \left[\frac{(L^* - 50)}{b^*} \right] \right\} \frac{180}{3.14159}$$

*arc tangent is expressed in radians.

The mean ITA° and historical data will be used to estimate the MEDu for each subject. The estimated MEDu will be recorded on the CRF.

8.1.7 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 Concomitant Medication/Treatment(s) requirements of the protocol.

8.2 Visit 2

Visit 1 can be combined with Visit 2.

At Visit 2 any current and concomitant therapy taken will be reviewed, and continued eligibility will be checked before any patch application. This will be reviewed again before each subsequent visit.

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

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

Spontaneous reporting of adverse events 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.

8.2.1 MED Irradiation

A UV dose is the result of multiplying the UV source irradiance by the episode duration. In this study, a solar simulator with 6 light guides exposing all sub-sites will be used. Before UVR exposure of each test site, irradiance values will be measured and recorded with a radiometer which has been calibrated with a spectroradiometric measurement of the solar simulator output.

A suitable warm-up time of at least 10 minutes will be allowed for the UVR solar simulator to stabilise before starting exposures. This is to ensure a consistent irradiance over the whole exposure period. UV exposures and MED assessments will be conducted in stable conditions, with the subject lying horizontally on their front (prone) and in a room with standard room conditions (18-26°C).

Test sites intended for UVR exposure shall be free from blemishes and have an even colour tone.

The MED of each subject will be determined in a two-step procedure. Firstly, the investigator or designee will administer a series of 6 controlled doses of UV radiation (290-400 nm) to the back of each subject (either side of the spine, between the shoulder line and waist) using a multiport solar simulator light 150 or 300 W. UV irradiation will be conducted by a trained technician with the subject lying horizontally on their front and in a room with controlled temperature (18-26°C).

The total dose of UV radiation administered by each port of the solar simulator will progressively increase by 1.25 units. The preliminary dose (MEDu) will be defined by the mean ITA° and the time of irradiation for each subject will vary to reach the dose.

In this study, the 1st sub-site will have the most intense form of radiation and the 6th sub-site will have the least intense form of radiation. The dose of UV radiation administered for the MED assessment will be chosen so that the 3rd of the 6 sub-sites will be irradiated with the estimated MED.

The minimum area of each exposure sub-site will be 0.5 cm^2. The minimum distance between borders of each exposure sub-site (spots) will be at least 0.8 cm.

Any extraneous exposure of the test sites to UVR light (artificial or natural) will be avoided during this period and for a period of 24 hours after exposure. Any additional UV exposure to the test area will invalidate the whole test for the subject concerned.

Successful conduct of the MED irradiation procedure will be recorded in the CRF.

8.3 Visit 3

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

Spontaneous reporting of adverse events 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.

8.3.1 MED Determination

At visit 3 (16-24 hours after UV irradiation), a trained evaluator will evaluate the exposed skin for signs of visible erythema. The MED is determined as the lowest dose of UV radiation required to induce uniform, unambiguous erythema. The MED will be used to determine the subsequent doses of UV radiation to be administered in the induction and challenge phases of the study and will vary from subject to subject. It may not be possible to read a valid MED for some subjects, in which case this process should be repeated by adjusting the range of UV doses administered.

The MED assessment will be assessed visually by a trained evaluator with the subject lying horizontally on their front and in a room-controlled temperature (18-26°C). Visual assessment will be performed in a room with matte, neutral wall colours with sufficient and uniform illumination.

The provisional MED of each subject will be recorded on the CRF with units of mJ/cm^2.

If a subject fails to present a valid MED, further irradiation at a naïve site may be required with an adjusted range of UV doses. In order for a subject to progress to randomisation, they must present a valid MED.

Successful conduct of the MED determination procedure will be recorded in the CRF.

8.4 Induction Phase - Day 1 Visit 4 (Monday)

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

Spontaneous reporting of adverse events 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.

8.4.1 Induction Phase Randomisation

Each subject will be assigned and identified by a unique Screening Subject Number sequentially as they sign their informed consent. 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 randomised 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.

Two semi-occlusive patches with 6 cells applied on the subject dorsum. Four cells (A, B, C and D) of the patch will be used in this study (3 cells for each of the test products and 1 cell for the reference product (saline solution). The two cells E and F will always remain empty. See also 5.4 Randomisation Criteria and 6.1.2 Preparation and Dispensing.

At Visit 4, a randomisation number will be assigned electronically in ascending numerical order to each subject who is determined to be fully eligible. This randomisation number will include

the sites of applications on the patch of each treatment. The sites of application will be the same for the two patches (UV-irradiated, non-UV-irradiated).

The randomisation schedule for the induction phase will follow a 4x4 Latin Square (Williams) design. An example of a randomisation schedule for the induction phase is shown below:

Table 8-1 Application site sequences- induction phase

Randomisation Number / **Patch cell**	**Induction phase** (*same sequence to be used for the UV-irradiated, non-UV-irradiated patches)*			
	Cell A	**Cell B**	**Cell C**	**Cell D**
PPD	Test Product 1	Reference product	Test Product 2	Test Product 3
PPD	Test Product 3	Test Product 1	Reference product	Test Product 2
PPD	Test Product 2	Test Product 3	Test Product 1	Reference product
PPD	Reference product	Test Product 2	Test Product 3	Test Product 1

8.4.2 Baseline Grading

Subjects will be seated for at least 15-30 minutes to the environment with standard room conditions (18-26°C) avoiding contact of the back area with any other surface. The test sites for the application of the patch will be designated above the waist between the scapula and waistline and away from the spinal mid-line. A blinded, trained evaluator will assess the test sites for signs of cutaneous irritation per grading scale Table 15-2 (Appendix 2).

8.4.3 Product Application and Patch Application

The location of the products within the individual cells of the patch will be randomly assigned, per the supplied randomisation schedule.

There will be 6 patch applications to the same site on the dorsum on duplicate patches, over 3 consecutive weeks during the induction phase, with a patch will be applied on Mondays and Wednesday. Each patch will remain in place for 24 (± 4) hours.

Approximately 0.02 mL/cm^2 of each of the study products will be applied to segregated cells within duplicate semi-occlusive patches on designated locations on the back in the induction and challenge phase using suitable measuring apparatus (for e.g. a pipette).

Once the product is applied to the patch cells, the patch will be applied to the designated naïve area on the back as per the example shown in Figure 4-1 adhesive side down.

8.5 Induction Phase - Day 2 Visit 5 (Tuesday)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF. Spontaneous reporting of adverse events 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.

8.5.1 Patch Removal

Subjects will arrive at site after 24 (±4) hours of patch application. 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 in standard room conditions (18-26°C) avoiding contact of the back area with any other surface.

8.5.2 Cutaneous Irritation Assessments

Any skin response at a patched site will be clinically assessed using scale recommended by the ICDRG.

After 30 minutes (maximum of 1 hour) of patch removal, the test sites will be evaluated as per the scale in Table 15-2 Appendix 2. The trained evaluator will be blinded to treatment and which patch has been UV irradiated. Patch sites will be graded using a magnifying glass with a fluorescent daylight lamp. Where ever possible the same experienced trained evaluator will perform will be used to evaluate all subjects in the study. The trained examiner is responsible for grading the reactions, and the trained examiner's score is final.

Any cutaneous (dermal) irritation or sensitisation reactions which occur within the patch application area and can be completely described by the scale in Table 15-2 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 Table 15-2 Appendix 2 (e.g., rash, hives) will be recorded as AEs.

Irritation assessments will be recorded in the CRF.

8.5.3 Test Site Irradiation

After assessment of the test sites, approximately 0.02 mL/cm^2 of each of the study products will be reapplied directly to the previously treated duplicate sites on the skin. After a 15- 30 minute drying period, one area of skin treated with the study products will be irradiated with 2.5 J/cm^2 UVA radiation with a Schott UG11+WG335 filter (or equivalent) in place, and then with 0.3 MEDs of UVA+UVB radiation (filters UG11+WG320). The duplicate area treated with the study products will not receive irradiation during the irradiation procedure.

8.5.4 Cutaneous Irritation Assessment Post Irradiations

Assessment of the irradiated and non-irradiated sites by the blinded, trained evaluator will occur immediately after the UV exposure procedures are completed, and any reaction will be graded as per grading scale Table 15-2 (Appendix 2).

Additionally, the dermatologist conducts an evaluation of every positive reaction (defined as a score of '+' or greater) in the challenge phase to further classify it as a potential sensitisation reaction (or not).

8.6 Induction Phase Day 3 Visit 6 (Wednesday)

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

Spontaneous reporting of adverse events 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.

Subjects will be seated for at least 15-30 minutes to the environment with standard room conditions (18-26°C) avoiding contact of the back area with any other surface. A trained evaluator will assess the test sites for signs of cutaneous irritation per grading scale Table 15-2 (Appendix 2).

Patches will be re-applied to the assigned test areas. Please see section 8.4 (Induction Phase Day 1 Visit 4 Monday) for details on patch application (please note randomisation only occurs on Monday Visit 4, Day 1).

8.7 Induction Phase Day 4 Visit 7 (Thursday)

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

Spontaneous reporting of adverse events 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.

The UV-exposure procedures and patch assessments will be repeated. Please see section 8.5 (Induction Phase Day 2 Visit 5 Tuesday) for details (please note randomisation only occurs on Monday Visit 4, Day 1).

8.8 Induction Phase Day 5 Visit 8 (Friday)

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

Spontaneous reporting of adverse events 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.

Subjects will be seated for at least 15-30 minutes to the environment with standard room conditions (18-26°C) avoiding contact of the back area with any other surface. A trained evaluator will assess the test sites for signs of cutaneous irritation per grading scale Table 15-2 (Appendix 2).

Induction week 2 and week 3 (Monday-Friday) will follow the same assessments as above, per the visit schedule. Please note randomisation only occurs on Monday, visit 4 (Day 1). At Monday visits 9 and 14, the patched sites will be assessed by a trained, blinded evaluator for signs and symptoms of irritation. Please see section 8.5 (Induction Phase Day 2 Visit 5 Tuesday) for details.

8.9 Rest Phase

Once the induction phase is complete, subjects will enter a 2-week rest phase, during which there will be no product or patch applications.

8.10 Challenge Phase Day 36 Visit 19 (Monday)

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

Spontaneous reporting of adverse events 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.

Subjects will be seated for at least 15-30 minutes to the environment of standard room conditions (18-26°C) avoiding contact of the back area with any other surface. A trained evaluator will assess the test sites for signs of cutaneous irritation per grading scale Table 15-2 (Appendix 2).

8.10.1 Challenge Phase Randomisation

At visit 19, another randomisation number will be assigned to each subject that completed the induction phase using the IRT system. This randomisation number will be different from the one previously assigned at Visit 4 and will include the sites of applications of each treatment for the challenge phase. The test sites of study products application will be previously untreated (naive) skin sites in the back, between shoulder blade and waistline for the duplicate UV-irradiated and non-UV-irradiated patch systems.

Randomisation schedule for the challenge phase will follow a 4x4 Latin Square (Williams) design. An example of the randomisation schedule is shown below:

Table 8-2 Application site sequences- challenge phase

Randomisation Number / **Patch cell**	**Challenge phase** (*same sequence to be used for the UV-irradiated, non-UV-irradiated patches)*			
	Cell A	**Cell B**	**Cell C**	**Cell D**
PPD	Test Product 2	Test Product 3	Test Product 1	Reference product
PPD	Reference product	Test Product 1	Test Product 3	Test Product 2
PPD	Test Product 3	Reference product	Test Product 2	Test Product 1
PPD	Test Product 1	Test Product 2	Reference product	Test Product 3

Please refer to section 8.4 (Induction Phase Day 1 Visit 4 Monday) for assessments on this day.

8.11 Challenge Phase Day 37 Visit 20 (Tuesday)

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

Spontaneous reporting of adverse events 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.

Please refer to section 8.5 (Induction Phase Day 2 Visit 5 Tuesday) and the visit schedule for procedures and assessments to be conducted on this day.

8.12 Challenge Phase Day 37 to 40 Visit 21 to Visit 23 (Wednesday to Friday)

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

Spontaneous reporting of adverse events 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.

Further test site assessments for signs of irritation will be conducted 24 (± 4), 48 (± 4), and 72 (± 4) hours after UV exposure as per grading scale Table 15-2 (Appendix 2).

8.13 Final Visit Day 40 Visit 23

After all assessments for the challenge phase have been completed, a final clinical assessment by a qualified dermatologist will be performed to ensure that it is medically appropriate to exit each subject from the study. After all study assessments are completed, subjects will be discharged from the study site.

In addition, for each subject who presents a positive reaction (i.e. a reaction score of '+' or greater) in the challenge phase a blinded dermatologist will further classify the reaction as potential sensitisation (or not) at the final visit and provide a single narrative description to summarise the entirety of the subject's experience of the event. As sensitisation and irritation can occur in the challenge phase, it is possible to record a positive reaction in the challenge phase which is not a sensitisation reaction. The dermatologist must consider how the reaction presents/evolves over time, to ascertain whether it is characteristic of a sensitisation reaction. The dermatologist will record their opinion in the narrative and with a check-box in the CRF.

The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken (e.g. moved patch), and diagnosis (potential sensitisation reaction, or other as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

8.14 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 conclusion 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.

8.15 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 Assessments

Patch testing techniques and scoring reactions by a grading scale were first standardised 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 (Appendix 2). Therefore, any skin response at a patched site will be clinically assessed using scale recommended by the ICDRG, Table 15-2 (Appendix 2).

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 reaction 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 (i.e. a reaction score of '+' or greater) in the challenge phase a blinded dermatologist will further classify the reaction as potential sensitisation (or not) at the final visit and provide a single narrative description to summarise

the entirety of the subject's experience of the event. As sensitisation and irritation can occur in the challenge phase, it is possible to record a positive reaction in the challenge phase which is not a sensitisation reaction. The dermatologist must consider how the reaction presents/evolves over time, to ascertain whether it is characteristic of a sensitisation reaction. The dermatologist will record their opinion in the narrative and with a check-box in the CRF.

The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken (e.g. moved patch), and diagnosis (potential sensitisation reaction, or other as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

Please see section 4.2 Rationale for Study Design for details on patch assessment.

If a subject develops a score of 'Strong' (++) or greater at any point during the induction phase, 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, it would be unwise to do so.

Any cutaneous (dermal) irritation or sensitisation 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 Meeting 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 sensitisation 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. hospitalisation 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 hospitalisation or prolongation of existing hospitalisation**
  - In general, hospitalisation 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

hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred, or was necessary, the AE should be considered serious.
    - Hospitalisation 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, influensa, 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 hospitalisation but may jeopardise 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 hospitalisation, 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, with the exception of 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 utilised 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 product use 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, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments 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/assent the CRF must be completed and signed by the Principal Investigator (or authorised 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 Personally Identifiable Information (PII) (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 authorised 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 80 healthy subjects will be screened to randomise at least 40 subjects to ensure at least 25 evaluable subjects complete the entire study. No formal power calculations have been performed on this study. This sample size is standard in clinical testing practices and is consistent with the ANVISA guidelines (ANVISA, 2012).

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 finalisation of the protocol and prior to study unblinding/analysis (as appropriate).

12.2.1 Definition of Analysis Populations

The Safety population includes all randomised subjects who received at least one dose of any study product. This population will be based on the treatment sequence the subject received.

12.2.2 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.2.3 Demographic and Baseline Characteristics

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

Age will be summarised by the mean, standard deviation, median, minimum and maximum values in each treatment group. Gender, race, and Fitzpatrick skin type will be summarised using frequency counts and percentages for all subjects (overall).

Individual typology angle predicted MED and measured MED will be listed for each subject.

12.2.4 Study Product Compliance

Product application will be done at study site. Any protocol deviation associated with treatment applications will be reviewed during Blind Data Review Meeting prior to database lock.

12.2.5 Prior and Concomitant Medications

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

12.2.6 Primary Analysis(es)

The primary analysis will be based on the number of subjects with potential sensitisation reactions considered photo- initiated (i.e. potential photo-sensitisation reactions) and will be based on the safety population.

The assessment of potential sensitisation reactions in the challenge phase will be determined by the blinded dermatologist. Potential sensitisation reactions will be further classified as potential photo-sensitisation reactions using the following rules:

1. Positive reactions which occur at ONLY the UV-exposed site will be considered photo-initiated.
2. Positive reactions which occur at ONLY the non-UV-exposed site will not be considered photo-initiated.
3. Positive reactions which occur at BOTH the UV-exposed and non-UV-exposed sites will be considered photo-initiated if the maximum score at the UV-exposed site is more severe than the maximum score at the non-UV-exposed site. If the maximum score at the UV-exposed site is equal to or lower than the non-UV-exposed site, then it will not be considered photo-initiated.

The number and percentage of subjects with any potential sensitisation considered photo-initiated reactions versus those without any will be presented by treatment group. No formal statistical inference will be performed.

All potential sensitisation reactions considered photo-initiated will be listed.

12.2.7 Secondary Analysis(es)

The secondary analyses will be based on positive irritation reactions (score of '+' or greater in the UV-irradiated and non-UV irradiated series of patches) assessed using the scale described in Appendix 2 and will be conducted on the Safety population.

Evaluation of the cutaneous photo-irritation potential

The classification of a positive reaction as a photo-initiated reaction will use the same criteria described in the primary endpoint.

The number and percentage of subjects with any photo-initiated reaction that is not considered a potential sensitisation reaction, versus those without a reaction will be presented by treatment group. No formal statistical inference will be performed.

All photo-initiated reactions that are not considered as potential sensitisation reactions, will be listed.

Evaluation of the cutaneous sensitisation potential

The classification of a positive reaction as a potential sensitisation reaction not considered photo-initiated will use the same criteria described in the primary endpoint.

The number and percentage of subjects with any potential sensitisation not considered photo-initiated versus those without any will be presented by treatment group using the maximum score. No formal statistical inference will be performed.

All potential sensitisation reactions that are not considered photo-initiated will be listed.

Evaluation of the cutaneous irritation potential

The classification of a positive reaction as an irritation reaction not considered photo-initiated will use the same criteria described in the primary endpoint.

The number and percentage of subjects with reactions not considered potential sensitisation and not considered as photo-initiated versus those without any will be presented by treatment group using the maximum score. No formal statistical inference will be performed.

All irritation reactions that are not considered as photo-initiated, will be listed.

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

12.2.8 Safety Analysis(es)

Safety analyses will be performed using the safety population according to the treatment that the subject received. Adverse events (AEs) 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/Preferred Term), Treatment Emergent Adverse Events (skin site related/non-skin site related), treatment-related AEs (skin site related/non-skin site related) will be summarised overall and by treatment group.

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

12.2.9 Handling of Dropouts and Missing Data

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

12.2.10 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 International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002),

International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

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 authorised 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 study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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.

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 developmental skin care products at any time.

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

1. ANVISA, Guideline for the Safety Evaluation of Cosmetics Products, 2012
2. ANVISA; Resolution 79/00, Annex XXI and its updates
3. Basketter, D. A., York, M., McFadden, J. P et al (2004), Determination of skin irritation potential in the human 4-h patch test. Contact Dermatitis, 51: 1–4
4. Beani, Jean Claude Phototoxicity, (2017) photo irritation, and Photoallergy Detection and Assessment DOI 10.1007/978-3-319-32383-1_137,
5. Dooms-Goossens A. Cosmetics as causes of allergic contact dermatitis. *Cutis* 1993; 52: 316-320.

6. Edward, M. Jackson, and FMT Robillard Norman. "The controlled use test in a cosmetic product safety substantiation program." Journal of Toxicology: Cutaneous and Ocular Toxicology 1.2 (1982): 117-132
7. European Commission (EC) Regulation No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products
8. Fitzpatrick, T.B., The validity and practicability of sun-reactive skin types I through VI. *Arch. Dermatol.* 124, pp. 869-871, 1988
9. Fregert S. Manual of contact dermatitis: On behalf of the international contact dermatitis research group: Munksgaard; 1974.
10. Food and Drug Administration. ICH Topic E6: Guideline for Good Clinical Practice. *Fed Reg* 1997; **62**(90): 25691-709.
11. Guidance for Industry; Skin Irritation and Sensitisation Testing of Generic Transdermal Drug Products, U.S. Department of Health and Human Services
12. Food and Drug Administration Center for Drug Evaluation and Research (CDER) Federal Register. 1999; 64(38):9516.
13. ICH Topic 6 Guideline for Good Clinical Practice CPMP/ICH/135/95 17th July 1996.
14. Isaksson, M., GrUVAberger, B., Frick-Engfeldt, M. and Bruze, M. (2007), Which test chambers should be used for acetone, ethanol, and water solutions when patch testing? Contact Dermatitis, 57: 134–136. doi: 10.1111/j.1600-0536.2007.01094.x
15. Kimber I, Basketter D, Berthold K, *et al.* Skin sensitization testing in potency and risk assessment. Toxicological Sciences. 2001;59(2):198-208
16. McNamee PM, Api AM, Basketter DA, *et al.* A review of critical factors in the conduct and interpretation of the human repeat insult patch test. *Regul Toxicol Pharmacol* 2008; **52**: 24-34.
17. National Health Surveillance Agency Brazil (ANVISA). Guideline for the Safety Evaluation of Cosmetic Products. Brasília; 2012.
18. World Medical Association Declaration of Helsinki, 64th General Assembly, Fortaleza 2013.

15 APPENDICES

15.1 APPENDIX 1- ABBREVIATIONS

Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
CRF	case report form
cm^2	Centimeter squared
EC	ethics committee
eCRF	Electronic Case Report Form
FSFV	First Subject First Visit
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation

Abbreviation	Term
ID	identification
IEC	Independent Ethics Committee
IRB	institutional review board
IRC	internal review committee
LSLV	last subject last visit
MED	Minimal Erythemal Dose
MedDRA	medical Dictionary for Regulatory Activities
mL	Milliliter
N/A	not applicable
PI	principal investigator
PT	Preferred Term
SAE	serious adverse event
SmPC	summary of product characteristics
SOC	System Organ Class
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
UVR	Ultra Violet Radiation

15.2 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 irritation per ICDRG scale at all time points specified in the study schedule. The evaluator score will be considered final.

For each subject who presents a positive reaction (i.e. a reaction score of '+' or greater) in the challenge phase a blinded dermatologist will further classify the reaction as potential sensitisation (or not) at the final visit and provide a single narrative description to summarise the entirety of the subject's experience of the event. As sensitisation and irritation can occur in the challenge phase, it is possible to record a positive reaction in the challenge phase which is not a sensitisation reaction. The dermatologist must consider how the reaction presents/evolves over time, to ascertain whether it is characteristic of a sensitisation reaction. The dermatologist will record their opinion in the narrative and with a check-box in the CRF.

The narrative must include the start and finish date of the event, a description of how the event evolves over time, any action taken (e.g. moved patch), and diagnosis (potential sensitisation reaction, or other as appropriate). If a clear diagnosis cannot be made, then the dermatologist should include this in the narrative.

Table 15-2 Scoring of patch cells 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 subject develops a score of 'Strong' (++) or greater at any point during the induction phase, 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, it would be unwise to do so.

Any dermal irritation or sensitisation reactions which occur within the patch application area and can't be completely described by the scale in Table 15-2 (Appendix 2), will not be recorded as AEs during the study. Reactions to the patch itself will also not be recorded as AEs. These responses are typical effects of occluded application of topical products.

Unexpected or unusual reactions which occur within the patch area that cannot be completely described by the scale in Table 15-2 (Appendix 2), (e.g., rash, hives) will be recorded as AEs.

15.3 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)

15.4 Appendix 4 Specification of the Solar Simulator Output

A multiport solar simulator utilizing a 300 W xenon arc lamp fitted with 6 liquid light guides 8 mm in diameter and two filters (Schott WG 320/1 mm dichroic mirror and UG 11/1mm) will be used for this study.

The accuracy of the SPF measured is dependent on the absorbance characteristics of the sunscreen filtering system to be tested in conjunction with the source spectrum. Therefore, it is important to define the source by the spectral distribution of its erythemal efficacy as well as its overall spectral irradiance characteristics.

Thus, the source spectra specification is described in terms of cumulative erythemal effectiveness by successive wavelength bands from < 290 nm up to 400 nm. The erythemal

effectiveness of each wavelength band is expressed as the percentage relative cumulative erythemal effectiveness (% RCEE) and will fall within the limits defined in Table 1.

The spectral output of the solar simulator will have been confirmed within the past 18 months or after 3000 hours of lamp running time, whichever is sooner, or after changing any significant physical component of the solar simulator, by calibrated spectroradiometric measurement. The spectroradiometer used to measure the spectral output of the solar simulator will be fitted with a double monochromator and its resolution bandwidth will be $\leq$ 2 nm with measurements made in steps not exceeding the bandwidth. The spectroradiometer will have been calibrated within the past 18 months against standard light sources for its response to spectral irradiances, for its wavelength accuracy and for linearity of signal responses at all wavelengths over an irradiance range covering the actual source measurement range.

The total irradiance of the solar simulator will also be measured and must not exceed 1600 W/m^2.

The total radiometric proportion of the UVA II (320 nm to 340 nm) irradiance of the simulator will be $\geq$ 20% of the total UV (290 nm to 400 nm) irradiance. Additionally, the UVA I region (340 nm to 400 nm) irradiance will be $\geq$ 60 % of the total UV irradiance.

Table 15-3 - % RCEE acceptance limits for the UV solar simulator output

Spectral Range nm	**Measured % RCEE**	
	Lower Limit	Upper Limit
< 290	-	<0.1
290 to 300	1.0	8.0
290 to 310	49.0	65.0
290 to 320	85.0	90.0
290 to 330	91.5	95.5
290 to 340	94.0	97.0
290 to 400	99.9	100.0