Clinical Protocol

207585

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Human Repeat Insult Patch Test (HRIPT) in Healthy Subjects to Assess the Cutaneous Irritation and Sensitisation Potential of a Cosmetic Facial Product.
Protocol Number:	207585
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) Rua Hungria, 1240 4º andar, Jardim Europa São Paulo/SP – Brazil, CEP 01455-000 Tel: PPD
Product Name:	Facial micellar cleanser
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD (US)

Key Protocol Authors:	
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Study Site Telephone Number:	PPD
Study Examiner(s):	Study examiner (s) will be assigned according to the site schedule (before First Subject First Visit) and documented in the site file.
Dermatologist:	Study Dermatologist will be assigned according to the site schedule (before First Subject First Visit) and documented in the site file.

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current 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.

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

Table of Content

PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IRB in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IRB as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:

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Protocol Version No.:	Substantial/ Major ☐				Date:

SCHEDULE OF EVENTS

Study Phase	Screening	Induction									Rest	Challenge			
Study Week	-	Week 1			Week 2			Week 3			Week 4-5	Week 6			
Study Day / Procedure/ Assessment	VISIT 1 DAY -14 to DAY 0	VISIT 2 DAY 1	VISIT 3 DAY 3	VISIT 4 DAY 5	VISIT 5 DAY 8	VISIT 6 DAY 10	VISIT 7 DAY 12	VISIT 8 DAY 15	VISIT 9 DAY 17	VISIT 10 DAY 19	VISIT 11 DAY 22	VISIT 12 DAY 36	VISIT 13 DAY 38	VISIT 14 DAY 39	VISIT 15 DAY 40
Day of Week	-	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Mon	Wed	Thu	Fri
Informed Consent	X														
Demographics	X														
Medical History	X														
Current/Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fitzpatrick Skin Type Assessment	X														
Inclusion/Exclusion Criteria	X	X [a]													
Dermatologist Assessment [a]	X	X													X
Subject Eligibility	X	X													
Continued Eligibility		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X													
Patch Application [b]		X	X	X	X	X	X	X	X	X		X [f]			
Patch Removal [c]			X	X	X	X	X	X	X	X	X [e]		X [i]		
Grading/Assessment of the patch sites [d]		X [g]	X	X	X	X	X	X	X	X	X	X [h]	X [i]	X [j]	X [j]
Adverse Events [k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Conclusion/Discharge from Study/															X

Note: Visit 1 and Visit 2 could occur on the same day but Visit 2 must be within 14 days of Visit 1.

a. Performed by a qualified dermatologist (Inclusion criteria 3c)

b. Subjects will report to the study site 10 times during the Induction Phase (9 patch applications). The patches will remain in place for 48 (±2) hours during the week. Patches applied on Friday will remain in place for approximately 72 (±2) hours until Monday.

c. 30 minutes (up to 1 hour) after each patch removal, a trained blinded assessor will perform an assessment of all test sites for irritation symptoms using the scoring system detailed in Appendix 2.

d. A trained (by a dermatologist) blinded assessor will perform assessments of all test sites for symptoms of irritation using the scoring system detailed in Appendix 2.

e. Visit 11 (Day 22) will be the final Induction Phase patch removal and grading/assessment.

f. Challenge Phase patch application (after 2 week Rest Phase), Visit 12 (Day 36). The challenge patch will be applied to a naïve site and remain in place for 48 (±2) hours.

g. Visit 2 (Day 1) Baseline assessments of the patch sites will be performed prior to the patch application.

h. Visit 12 (Day 36) assessments of the naïve challenge patch site will be performed prior to the challenge patch application.

i. 30 minutes (up to 1 hour) following Challenge patch removal a trained blinded assessor will perform an assessment of the Challenge test site for irritation symptoms using the scoring system detailed in Appendix 2.

j. Further evaluations of naïve patch removal site will take place 24 (±2) and 48 (±2) hours after patch removal (e.g., apply the patch on Monday, remove the challenge patch on Wednesday, and evaluate the sites on Wednesday, Thursday and Friday).

k. Subjects are asked to report any adverse events from Visit 2 (or Visit 1 if patch application occurs at Visit 1) and the use of any concomitant medications throughout the study.

PROTOCOL SYNOPSIS FOR STUDY 207585

Brief Summary

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).

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).

The human repeated insult patch test (HRIPT) is a long standing, standard method to determine whether a defined exposure to a product will elicit a dermal irritant or allergic response under exaggerated conditions of exposure. It is also routinely used and accepted as an appropriate methodology to establish the sensitisation potential of topical products (e.g. by the FDA in the U.S.). The HRIPT requires approximately six weeks per a subject and involves three phases: Induction, Rest and Challenge, and is based on the modified Draize test. (Draize, 1944)

In this study the test material and the positive control of saline solution are applied under a semi-occlusive patch to a subject's upper back. The first phase of the study is an Induction Phase; a known amount of product is applied over a defined surface area of skin (amount per unit area) under a semi-occlusive patch. Each patch will remain on the skin for 48 (±2) hours (weekdays) or 72 (±2) hours (including inclusive weekends) during this phase. The patch will be removed and the site will be assessed then a new patch will be applied to the same site. After the Induction Phase, subjects will enter a Rest Phase of 2 weeks duration, during which no patches are applied. After the Rest Phase, subjects will return to the clinical site for the Challenge Phase. In this phase a challenge patch of both the test product and control is applied to virgin skin for 48 (±2) hours then assessed 30 minutes (maximum 1 hour) 24 (± 2) hours and 48 (±2) hours after patch removal.

The objective of this clinical study is to assess the irritation and sensitisation potential of a cosmetic test product after repeated patch applications to healthy human subjects by following a conventional HRIPT methodology under supervision of a dermatologist.

Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
To determine the irritation and contact sensitisation potential of a cosmetic facial skin product after repeated patch applications to the skin of healthy subjects.	Trained assessor assessment of local tolerance through visual assessment of cutaneous irritation via the combined *dermal response* and *other effects* scores over the induction and challenge phase.
Secondary	
To evaluate the general safety of a cosmetic facial skin product.	Assessment of frequency and severity of Adverse Events

Study Design

Overall Design
Test site randomized, assessor-blinded, single-center, Human Repeated Insult Patch Test (HRIPT) in healthy subjects to assess the cutaneous irritation and sensitisation potential of a cosmetic facial product, by following a conventional HRIPT methodology under supervision of a dermatologist.
Day -14 to 0 / Visit 1 - Screening Visit **NOTE: Visit 1 and Visit 2 could be combined**
The following assessments will be conducted: 1. Subject Informed Consent taken 2. Subject demographics collected 3. Medical history details 4. Details of current and concomitant medication collected 5. Fitzpatrick Skin Type Assessment (Appendix 3) 6. Inclusion/Exclusion criteria 7. Dermatologist determination for eligibility to participate in the study (including visual examination of the dorsum scapular region) 8. Subject Eligibility
Days 1 to 22 / Visit 2 - Visit 11 - Induction Phase (3 Weeks) **NOTE: Visit 1 and Visit 2 could be combined**
The following assessments will be conducted: 1. Continued eligibility check 2. Current/Concomitant Medications review 3. Inclusion/Exclusion criteria review (3c only at Visit 2 if Visit 1 and 2 are not combined).

4. Dermatologist determination for continued eligibility to participate in the study (Visit 2/Day 1 only - if visits not combined).
5. Test Site Designation and Randomisation (Visit 2/Day 1 only).
6. Baseline grading/assessment of test sites (Visit 2/Day 1 only) as per Appendix 2.
7. Patch applications (9 patch applications to the same test site, over 3 consecutive weeks with patches applied on alternate weekdays).
8. Patch removal after 48 (± 2) hours or 72 (± 2) hours over inclusive weekends.
9. Reaction grading/assessment performed by a qualified staff member, as per Appendix 2.
10. Adverse event assessment

Note: 30 minutes (maximum of 1 hour) after patch removal, sites will be graded/evaluated, then patches will be reapplied to the same sites.

Day 22- Day 36 / Visit 11 – Visit 12 - Rest Phase (2 Weeks)
No Patch Application

Days 36 to 39 / Visit 12 to Visit 14 - Challenge Phase

The following assessments will be conducted:

1. Continued eligibility check
2. Current/Concomitant Medications review
3. Grading/assessment of naïve challenge patch site performed by a qualified staff member. (As per Appendix 2). Prior to Challenge patch application. (Visit 12/Day 36).
4. Challenge Phase patch application to naïve site (Visit 12/Day 36).
5. Patch removal 48 (± 2) or 72 (± 2) hours over inclusive weekends after application. (Visit 13/Day 38).
6. Reaction grading/assessment performed by a qualified staff member at approximately 30 minutes (maximum 1 hour) after patch removal.
7. 24 (± 2) hours after patch removal (Visit 14/Day 39) subjects will return for assessment performed by a qualified staff member.
8. Adverse event assessment.

Day 40 / Visit 15 – End of Study

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Adverse event assessment.
3. 48 (± 2) hours after patch removal (Visit 15/Day 40) final challenge patch site assessment performed by a qualified staff member.
4. Dermatologist final assessment.
5. Subject discharge from the study site following completion of all study

procedures.

Type and Planned Number of Subjects

Approximately 280 healthy subjects will be screened to randomize at least 240 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is observed in 200 subjects, there is a 95% certainty that the actual rate of reaction in the wider population is <1.8%.

Diagnosis and Main Criteria for Inclusion

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

Product Information

	Test Product	Reference Product
Product Name	Facial micellar cleanser	Saline Solution: Sodium Chloride (NaCl; 0.9%)
Product Formulation Code (MFC)	CCI	N/A Site to supply
Product Format	200ml clear PET Bottle	N/A
Application Quantity	0.02 millilitres/square centimetre (ml/cm^2)	0.02 ml/cm^2
Route of Administration	Topical dermal application via semi occlusive patch	
Application Instructions	Applied on-site by technician	

Statistical Methods

The focus of the statistical analysis will be the evaluation of the frequency and level of irritation and sensitisation responses of the investigational product. All subjects with any product applied will be included in the analysis population.

Individual observations will be assessed based on Appendix 2 and a narrative description of all skin responses, both in the induction and challenge phases, will be provided. A frequency tabulation of the number of subjects with any skin response versus those without any skin response will be presented by treatment group for both the induction and challenge phases of the study. If there are subjects with non-zero dermal response or superficial irritation scores, a combined dermal and others effects

score will be determined across all time points over the induction and challenges phases as well as at each assessment time point and summarised using descriptive statistics.

No interim or subgroup analyses are planned.

Adverse Events (AE) will be tabulated according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Frequencies and percentages will be presented overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related AEs, AEs leading to discontinuation, and serious AEs will be completed. For treatment-related AEs, these will also be presented by treatment/test site.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained and signed off prior to study unblinding.

1. 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).

The objective of such compatibility studies, performed by applying materials to the skin under a patch, is to evaluate potential untoward effects during exaggerated application to the skin to provide assurance that the product is well tolerated and safe for use. A common method to assess the potential of topically applied product to cause irritation or sensitisation involved repeated patch applications of a product to the skin (Basketter, 2008).

The objective of this clinical study is to assess the irritation and sensitisation potential of a cosmetic test product after repeated semi-occlusive patch applications to healthy human subjects by following a conventional HRIPT methodology under supervision of a dermatologist.

2. OBJECTIVE(S) AND ENDPOINT(S)

Objective(s)	Endpoint(s)
Primary	
To determine the irritation and contact sensitisation potential of a cosmetic facial skin product after repeated patch applications to the skin of healthy subjects.	Trained assessor assessment of local tolerance through visual assessment of cutaneous irritation via the combined *dermal response* and *other effects* scores over the induction and challenge phase.
Secondary	
To evaluate the general safety of a cosmetic facial skin product.	Assessment of frequency and severity of Adverse Events

3. STUDY PLAN

3.1. Study Design

Overall Design
Test site randomized, assessor-blinded, single-center, Human Repeated Insult Patch Test (HRIPT) in healthy subjects to assess the cutaneous irritation and sensitisation potential of a cosmetic facial product, by following a conventional HRIPT methodology under supervision of a dermatologist.
Day -14 to 0 / Visit 1 - Screening Visit **NOTE: Visit 1 and Visit 2 could be combined**
The following assessments will be conducted: 1. Subject Informed Consent taken 2. Subject demographics collected 3. Medical history details 4. Details of current and concomitant medication collected 5. Fitzpatrick Skin Type Assessment (Appendix 3) 6. Inclusion/Exclusion criteria 7. Dermatologist determination for eligibility to participate in the study (including visual examination of the dorsum scapular region) 8. Subject Eligibility
Days 1 to 22 / Visit 2 - Visit 11 - Induction Phase (3 Weeks) **NOTE: Visit 1 and Visit 2 could be combined**
The following assessments will be conducted: 1. Continued eligibility check

2. Current/Concomitant Medications review
3. Inclusion/Exclusion criteria review (3c only at Visit 2 if Visit 1 and 2 are not combined).
4. Dermatologist determination for continued eligibility to participate in the study (Visit 2/Day 1 only - if visits not combined).
5. Test Site Designation and Randomisation (Visit 2/Day 1 only).
6. Baseline grading/assessment of test sites (Visit 2/Day 1 only) as per Appendix 2.
7. Patch applications (9 patch applications to the same test site, over 3 consecutive weeks with patches applied on alternate weekdays).
8. Patch removal after 48 (± 2) hours or 72 (± 2) hours over inclusive weekends.
9. Reaction grading/assessment performed by a qualified staff member, as per Appendix 2.
10. Adverse event assessment

Note: 30 minutes (maximum of 1 hour) after patch removal, sites will be graded/evaluated, then patches will be reapplied to the same sites.

Day 22- Day 36 / Visit 11 – Visit 12 - Rest Phase (2 Weeks)
No Patch Application

Days 36 to 39 / Visit 12 to Visit 14 - Challenge Phase

The following assessments will be conducted:

1. Continued eligibility check
2. Current/Concomitant Medications review
3. Grading/assessment of naïve challenge patch site performed by a qualified staff member. (As per Appendix 2). Prior to Challenge patch application. (Visit 12/Day 36).
4. Challenge Phase patch application to naïve site (Visit 12/Day 36).
5. Patch removal 48 (± 2) or 72 (± 2) hours over inclusive weekends after application. (Visit 13/Day 38).
6. Reaction grading/assessment performed by a qualified staff member at approximately 30 minutes (maximum 1 hour) after patch removal.
7. 24 (± 2) hours after patch removal (Visit 14/Day 39) subjects will return for assessment performed by a qualified staff member.
8. Adverse event assessment.

Day 40 / Visit 15 – End of Study

The following assessments will be conducted:

6. Current/Concomitant Medications review
7. Adverse event assessment.
8. 48 (± 2) hours after patch removal (Visit 15/Day 40) final challenge patch site

assessment performed by a qualified staff member.
9. Dermatologist final assessment.
10. Subject discharge from the study site following completion of all study procedures.

3.2. Subject Restrictions

Lifestyle/ Dietary

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

1. Applying any other product to the test site (dorsum).
2. Use of cosmetics, moisturisers, and other topical products on the back area.
3. Changing any cosmetic habits, including personal hygiene.
4. Changing dietary habits.
5. Getting the patch test site wet: during showers or bathing, in pools or lakes/ocean, sauna or activities that cause excessive sweating. The study site will provide instructions on how to shower or bathe throughout the study.
6. Removing the patches.
7. Wearing tight or restrictive clothing that can remove the patch through friction or cause redness.
8. 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.
9. Introduction of new products during the study including but not limited to soap, laundry detergent, or fabric softener.
10. Engaging in activities that result in excessive sweating.
11. Missing the first day of application during the Induction Phase, or the day of application during the Challenge Phase.

12. Missing 2 or more consecutive visits or more than 2 alternate visits.

Medications and Treatments

During the entire study (Screening – LSLV) the following medications and treatments should be avoided:

1. Having any body aesthetic or dermatological treatments performed.
2. Changing hormone treatment.
3. Changing contraceptive method.
4. Use of the following medications:
    a. Systemic or topical corticosteroids
    b. Systemic or topical immunosuppressive drugs
    c. Systemic or topical antihistamines, Vitamin A acid and its derivatives, or non-steroidal anti-inflammatory drugs
    d. Concomitant topical treatment at test sites

3.3. Type and Planned Number of Subjects

Approximately 280 healthy subjects will be screened to randomize at least 240 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is observed in 200 subjects, there is a 95% certainty that the actual rate of reaction in the wider population is <1.8%.

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

3.4. Study Design and Application Amount Justification

Study Design:

This will be a single-center, randomised, assessor blind study in healthy subjects aged 18 to 65 years. Subjects will be exposed to repeated insult dermal semi-occlusive patch application of a cosmetic facial skin product and negative control (saline

solution).

Screening:

During screening subjects will sign an informed consent document and then a dermatological assessment will be conducted to ensure subjects have no dermatological conditions on their dorsum (backs) that might impact subject safety or study results and to ensure subjects have a Fitzpatrick Phototype I to IV.

Each subject's medical history and medication history will be reviewed, as well as inclusion/exclusion criteria. After which, site staff will review lifestyle guidelines and directions with eligible subjects.

Induction Phase:

Visit 2/Day 1 of the induction phase could be combined with Visit 1.

On Day 1 of the Induction Phase, eligible subjects will return to the study site and another dermatological assessment will be conducted to ensure subject continued eligibility (if Visits 1 and 2 are not combined), as well as a review of concomitant medications since screening. Test sites will be designated above the waist between the left scapula and waistline and away from the spinal mid-line. The site of application of the products will then be randomly assigned. Baseline grading/assessment of the test sites will then be performed.

There will be a total of 9 patch applications, over 3 consecutive weeks during the induction phase, with patches applied on alternate weekdays each week (Monday, Wednesday, and Friday). Each patch will contain the test product and saline solution. Each patch will remain in place for 48 (± 2) hours on weekdays and 72 hours on weekends. The patch will be removed and the area will be cleaned with saline solution. After 30 minutes (maximum of 1 hour) the site will be graded/evaluated as per the scale in Appendix 2. A new patch of both test product and saline solution will then be reapplied to the same site.

Rest Phase:

After the last patch removal and grading/evaluation of the Induction Phase, subjects will enter a Rest Phase of 2 weeks. During this time there will be no product patch applications.

Challenge Phase:

After completing the Rest Phase, subjects will return for the Challenge Phase. A naïve site (previously un-patched area) will be selected for the Challenge patch, this area will be graded/evaluated prior to any patch application. A patch with the test product and saline solution will then be randomly applied to the selected previously untreated areas of skin according to the subject's random assignment as determined on Day 1 of the Induction phase. After 48 (± 2) hours, each subject will return for Challenge patch removal, the site will be cleaned with saline solution and graded/evaluated after 30 minutes (maximum of 1 hour). Subjects will return after 24 (± 2) hours and 48 (± 2) hours post patch removal for further grading/assessment.

End of Study:

After the 48-(± 2) hour grading/assessment, a final clinical assessment by a qualified dermatologist will be performed to confirm it is medically appropriate to exit the subject from the study. After all study assessments are completed, subjects will be discharged from the study site.

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

Patch Assessments:

The results of the patch site assessments (Appendix 2) will be presented as individual responses to each test product and the negative control (saline solution) at each assessment time point. All responses will be reviewed in context of the grading scale.

Assessment of the patch sites will be conducted once at Baseline (Visit 2/Day 1) prior to any patch applications and then a further 8 times post-baseline during the Induction Phase, once during the Rest Phase (for the final Induction Phase patch removal), and four times during the Challenge Phase (prior to Challenge patch application and post) by a blinded assessor (a qualified staff member).

Any skin response at a patched site will be clinically assessed using the criteria recommended by the US Department of health and Human Services Food and Drug Administration (FDA), 1999.

Each of the scores represents an effect that is localised in a representative portion of the patch area, defined as 25% or more of the patch test site. Individual observations will be recorded in tables and a narrative description of all skin responses (any

score>0) will be provided. Superficial irritation scores are only provided if there is a dermal response score >0.

Each Superficial Irritation Score should be reported as a letter. The combined score will equal the sum of the dermal response score plus the numerical equivalent of the superficial irritation score (e.g. dermal response score=3 and superficial irritation score="C" implies a combined score of 3 + 2 = 5).

If a subject develops a combined score of 3 or greater at any point during the Induction phase, the patch will be applied to an adjacent naïve site for the next application. If a combined score of 3 or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will however, receive patches on naïve test sites during the challenge phase of the study unless, in the opinion of the Investigator, it would be unwise to do so.

Dermal irritation or sensitisation reactions within the patch area (i.e., irritation reactions outlined in Appendix 2) will not be recorded as AEs during the study. Reactions to the patch itself will also not be recorded as AEs. Unexpected reactions (e.g., rash, hives) will be recorded as AEs. These responses are expected in these study conditions and will be disregarded in evaluations, using the negative control (saline solution) as the standard for determining the expected degree of reaction.

Application Amount Justification:

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 $0.02ml/cm^2$.

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 negative control and will also be applied to the back through semi-occlusive application.

The semi-occlusive patches are made of a hypoallergenic material with round chambers (or cells) of an absorbent material. Standardized amounts will be applied in these cells, approximately 0.02 ml (if application with a pipette is possible) or 20 mg (if application with a pipette is not possible, in this study, only products of the sponsor, GlaxoSmithKline will be tested. One of the patch cells will contain the

control and, therefore, will be filled in with saline solution, and one of the other cells will be filled with the test product.

The study will be conducted under the supervision of a qualified dermatologist. Prospective subjects will be assessed by the qualified staff member as a prerequisite to enrollment, and again at study end.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Safety Statement.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

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

1. CONSENT
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form.

2. AGE
Aged between 18 and 65 years inclusive.

3. GENERAL HEALTH
a.) Good general and mental health with, in the opinion of the investigator or medically qualified designee no clinically significant and relevant abnormalities in medical history or upon physical examination. b.) Healthy, intact skin at the proposed application site; dorsum (scapular region). c.) Clinical assessment for eligibility (at Visit 1 and Visit 2 – if not combined) by

a dermatologist to ensure subject is free of clinically relevant dermatological conditions.

4. SKIN TYPE
Fitzpatrick phototype I to IV (see Appendix 3).

5. COMPLIANCE
Agreement to comply with the procedures and requirements of the study and to attend the scheduled assessment visits.

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. PREGNANCY
Women who are known to be pregnant or who are intending to become pregnant over the duration of the study.

2. BREAST-FEEDING
Women who are breast-feeding

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
a) Any history of significant dermatological diseases or conditions 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. b) Presence of open sores, pimples, or cysts at the application site. c) Active dermatosis (local or disseminated) that might interfere with the results of the study. d) Considered immune compromised. e) History of diseases aggravated or triggered by ultraviolet radiation. f) Participants with dermatographism. g) Currently using any medication which in the opinion of the investigator, may

affect the evaluation of the study product, or place the subject at undue risk.

h) Use of the following topical or systemic medications: immunosuppressants, antihistamines, non-hormonal anti-inflammatory drugs, and corticosteroids up to 2 weeks before screening visit.

i) Oral or topical treatment with vitamin A acid and/or its derivatives up to 1 month before the screening visit.

j) Intention of being vaccinated during the study period or has been vaccinated within 3 weeks of the screening visit.

k) Currently receiving allergy injections, or received an allergy injection within 7 days prior to Visit 1, or expects to begin injections during study participation

4. ALLERGY/ INTOLERANCE

a) Previous history of atopy, allergic reactions, irritation or intense discomfort feelings to topical-use products, cosmetics or medication.

b) Study subjects with a history of allergy to the study material/product, hypoallergenic tape, or to the cotton patches.

c) History of sensitisation in a previous patch study.

5. CLINICAL STUDY/ EXPERIMENTAL PRODUCT

a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days of the screening visit.

b) Previous participation in this study.

6. SUBSTANCE ABUSE
Recent history (within the last 5 years) of alcohol or other substance abuse.

7. DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

a) Intense sunlight exposure or sun tanning sessions up to 30 days before the Screening evaluation.

b) Intention of bathing (in the sea or a pool), sauna, water sports, or activities that

lead to intense sweating.

c) Any Subject who, in the judgment of the Investigator, should not participate in the study.

d) Any skin marks on the test site that might interfere with the evaluation of possible skin reactions (e.g. pigmentation disorders, vascular malformations, scars, tattoos, excessive hair, numerous freckles).

e) Prisoner or involuntary incarcerated subject.

f) Subject from an indigenous tribe.

8. PERSONNEL
An employee of the sponsor or the study site or members of their immediate family.

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening of subjects considered previous screen failures will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

1. The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
2. The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
3. In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject's record.
4. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.5. Subject Replacement

Subjects who withdraw from the study post-randomisation will not be replaced.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

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

5. PRODUCT INFORMATION

5.1. Study Product

The following study product will be supplied by the Clinical Supplies Department, GSKCH:

	Test Product	Reference Product
Product Name	Facial micellar cleanser	Saline Solution: Sodium Chloride (NaCl; 0.9%)
Product Formulation Code (MFC)	CCI [redacted]	N/A Site to supply
Product Format	200ml clear PET Bottle	N/A

Application Quantity	0.02 ml/cm^2	0.02 ml/cm^2
Route of Administration	Topical dermal application via semi occlusive patch	
Application Instructions	Applied on-site by technician	

5.2. Application Schedule

Induction Phase:

Visit 2/Day 1 of the induction phase could be combined with Visit 1.

On Day 1 of the Induction Phase, eligible subjects will return to the study site and another dermatological assessment will be conducted to ensure subject continued eligibility (if Visits 1 and 2 are not combined), as well as a review of concomitant medications since screening. The test site will be designated above the waist between the left scapula and waistline and away from the spinal mid-line. The site of application of the products will then be randomly assigned. Baseline grading/assessment of the test sites will then be performed.

There will be 9 patch applications to the same test site with the test product and saline solution over 3 consecutive weeks during the Induction phase, with patches applied on alternate weekdays each week (Monday, Wednesday, and Friday). Each patch will remain in place for 48 (± 2) hours on weekdays and 72 (± 2) hours on weekends. The patches will be removed and the treated areas will be cleaned with saline solution. After 30 minutes (maximum of 1 hour) the site will be graded/evaluated, new patches will be applied to the same site.

If a subject develops a combined score of 3 or greater at any point during the Induction phase, the patch will be applied to an adjacent naïve site for the next application. If a combined score of 3 or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will however, receive patches on naïve test sites during the challenge phase of the study unless, in the opinion of the Investigator, it would be unwise to do so.

Rest Phase:

After the last patch removal and grading/evaluation of the Induction Phase, subjects will enter a Rest Phase of 2 weeks. During this time there will be no patch applications.

Challenge Phase:

After completing the Rest Phase, subjects will return for the Challenge Phase. The naïve sites for the Challenge patch will be graded/evaluated prior to any patch application. The Challenge Patch with both the test product and saline solution will be randomly applied to the selected previously untreated area of skin on the back according to the subject's random assignment on Day 1 of the Induction phase for 48 (± 2) hours. After on-site patch removal, the site will be cleaned with saline solution and graded/evaluated after 30 minutes (maximum of 1 hour). Subjects will return after 24 (± 2) hours and 48 (± 2) hours post patch removal for further grading/assessments of the Challenge site.

End of Study:

After the 48 (± 2) hour grading/assessment, a final clinical assessment by a qualified dermatologist will be performed to confirm it is medically appropriate to exit the subject from the study. After all study assessments are completed, subjects will be discharged from the study site.

5.3. Product Assignment

Each subject will have the test product and the negative control applied to their backs (dorsum region). The location for each study product application for each subject will be assigned in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.3.1 Randomisation

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomized according to the randomisation schedule. Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible. The randomisation number will be associated with the random location assignment of product to test site.

5.3.2 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation/test site location. Investigators

dispensing the product will be aware of each product's location and must not divulge information to the study staff or assessors. The assessor performing the assessment of irritation will be blinded to the product allocation.

5.3.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Wherever possible the Investigator (or designee) must contact the Sponsor prior to breaking the blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

The study blind must be returned to GSKCH at the end of the study.

5.4. Packaging and Labelling

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

The facial micellar cleanser CCI will be supplied in 200 ml bottles and will have a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number, product code letter and directions for storage.

The investigator or designee will supply the saline solution (Reference Product) with a study label affixed. Each study label will contain the information according to the site specific internal requirements.

Care should be taken with the supplied product and its label so that it is maintained in good condition. It is important that all labels remain intact and legible for the duration of the study.

5.4.1. Accountability of Product

The test product supplied is for use only in this clinical study and should not be used for any other purpose.

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current.

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.4.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Events section.

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

6.1. Visit 1 - Screening Visit

6.1.1 Telephone 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.

6.1.2. Informed Consent

The investigator, or designee, must obtain signed and dated (by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

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 the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly after the subject has signed. The subject will be provided with a copy of their signed and dated consent form and any other written information which they are be instructed to retain.

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. Subjects should be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

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

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, Fitzpatrick skin type (skin phototype classification, according to the Fitzpatrick classification, per Appendix 3), gender and race.

6.1.4 Dermatologist Assessment

For products with specific safety appeals, the study must be followed up by a specialist (ANVISA, 2012). A qualified dermatologist will assess the overall subject eligibility at the Screening Visit and continued eligibility in the study at Visit 2 (if not combined) to ensure the subject is free of any pre-existing dermatological pathology. Additionally a final assessment at Visit 15 by a qualified dermatologist will confirm it is medically appropriate to exit the subject from the study at the final visit. (Edward & Robillard, 2008).

6.1.5. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.2. Visit 2 - Baseline Visit To Visit 14

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

At Visit 2 any current and concomitant therapy taken will be reviewed, and continued eligibility will be checked before any patch application (and randomisation of product application ordering). 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).

6.2.1 Application of patches

The test product and saline solution (0.02 ml/cm^2 of each product) will be applied to a paper disc (or cell) contained within an adhesive patch. The number of cells available on the patch test tape can vary but in this study one will be used for test product and one for the reference; saline solution). The patch is then applied onto the dorsum (scapula region) of each subject for a period of 48 ± 2 hours, the sequence of the product application to the cells will be randomly assigned to each subject according to the randomisation schedule.

Induction Phase:

Visit 2/Day 1 of the induction phase could be combined with Visit 1.

On Day 1 of the Induction Phase, eligible subjects will return to the study site and another dermatological assessment will be conducted to ensure subject continued eligibility (if Visits 1 and 2 are not combined), as well as a review of concomitant medications since screening. The test site will be designated above the waist between the left scapula and waistline and away from the spinal mid-line. The site of application of the products will then be randomly assigned. Baseline grading/assessment of the test sites will then be performed.

There will be 9 patch applications to the same test site of both the test product and saline solution over 3 consecutive weeks during the induction phase, with a patch applied on alternate weekdays each week (Monday, Wednesday, and Friday). Each patch will remain in place for 48± 2 hours on weekdays and 72 ± 2 hours on weekends. The patch will be removed and the treated areas will be cleaned with saline solution. After 30 minutes (maximum of 1 hour) the site will be graded/evaluated as per the scale in Appendix 2. A new patch will then be reapplied to the same site.

Rest Phase:

After the last patch removal and grading/evaluation of the Induction Phase, subjects will enter a Rest Phase of 2 weeks. During this time there will be no product patch applications.

Challenge Phase:

After completing the Rest Phase, subjects will return for the Challenge Phase. A naïve site (previously un-patched area) will be selected for the Challenge patch, this area will be graded/evaluated prior to any patch application (according to Appendix 2). A Challenge patch with both the test product and saline solution will be randomly applied to this previously untreated area of skin according to each subject's random assignment as determined on Day 1 of the Induction phase. After 48 (± 2) hours, each subject will return for Challenge patch removal, the site will be cleaned with saline solution and graded/evaluated after 30 minutes (maximum of 1 hour). Subjects will return after 24 (± 2) hours and 48 (± 2) hours post Challenge patch removal for further grading/assessment.

End of Study:

After the 48-(± 2) hour grading/assessment, a final clinical assessment by a qualified dermatologist will be performed to confirm it is medically appropriate to exit the subject from the study. After all study assessments are completed, subjects will be discharged from the study site.

6.2.2 Patch Assessments

An experienced trained assessor (s) will assess all patch sites for the duration of the study according to the scoring scale in Appendix 2. Each patch will be removed and the treated areas will be cleaned with saline solution before visual assessment. Where ever possible the same experienced trained assessor will perform all skin assessments for a given subject at each assessment time point.

A Baseline patch site assessment will be carried out at Visit 2 (or Visit 1 if visits combined) prior to any patch application. Patch assessments will then be performed at Visits 3 to 11 for the Induction Phase (every 48 ± 2 hours following application). After the last grading/evaluation of the Induction Phase at Visit 11, subjects will enter a Rest Phase of 2 weeks.

After completing the Rest Phase, subjects will return for the Challenge Phase (Visit 12). Prior to the Challenge patch application the naïve patch sites will be assessed. The challenge patch will be randomly applied to previously untreated areas of skin for 48 ± 2 hours. After on-site patch removal (Visit 13), the patch site will be cleaned with saline solution and graded/evaluated after 30 minutes (maximum of 1 hour). Subjects will return for further assessments after 24 ± 2 hours (Visit 14) and 48 ± 2 hours (Visit 15) post patch removal for further grading/assessment.

Patch sites will be graded using a magnifying glass with a fluorescent daylight lamp. The assessor will be blinded to the treatment allocation location.

The results will be presented as individual responses to each test product at each assessment time point.

In any case of a positive reaction a dermatologist will be available to perform secondary assessments and grade the response with any further action as needed. This should occur the same day as the initial assessment performed by the trained assessor.

The intensity of any visual signs of irritation will be recorded by the trained examiner, according to the quantity and grade of the reactions (Appendix 2) according to the skin appearance (Table 1) and other features indicative of irritation (Table 2) observed. The trained examiner is responsible for grading the reactions, and the trained examiner's opinion on the interpretation of the results is final.

If a subject develops a combined score of 3 or greater at any point during the Induction phase, the patch will be applied to an adjacent naïve site for the next application. If a combined score of 3 or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will however, receive patches on naïve test sites during the challenge phase of the study unless, in the opinion of the Investigator, it would be unwise to do so.

Any observed response which can be denoted using the irritation criteria summarized in Appendix 2, will not be considered an adverse event. In addition any tape-related irritation will also not be noted as an AE. Only in case of unusual reactions, these reactions and the consequences upon the evaluation of the respective test areas will be documented as AE's.

All responses will be reviewed in context of the grading scale in this protocol (Appendix 2).

6.3. Visit 15 - Last Subject Last Visit (LSLV)

At Visit 15 any current and concomitant therapy taken will be reviewed, and continued eligibility will be checked. Final challenge site assessment 48 ± 2 hours (Visit 15) post patch removal (per Section 6.2.2) will take place.

A final evaluation by a qualified dermatologist will take place before the subject exits from the study (per Section 6.1.4).

6.3.1. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the CRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent
6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

Adverse Event Definition:
An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout product. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational or washout product.

Events meeting AE definition include:

1. Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.

2. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

3. New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study.

4. Signs, symptoms, or the clinical sequelae of a suspected interaction.

5. 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).

Events NOT meeting definition of an AE include:

1. 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.

2. The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition..

3. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

4. Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

5. Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

6. Any observed response which can be denoted using the irritation criteria summarized in Appendix 2, will not be considered an adverse event. In addition any tape-related irritation will also not be noted as an AE. Only in

case of unusual reactions, these reactions and the consequences upon the evaluation of the respective test areas will be documented as AE's.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

A. Results in death

B. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

C. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

E. Is a congenital anomaly/birth defect

F. Other Situations

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above

definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

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

The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.

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

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs will be collected from the start of the product application and until 5 days following last administration of the study product.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

1. **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2. **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities

3. **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

The investigator will also consult the Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**

The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

AEs will be recorded in the AE section of the CRF.

Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in the subject's medical history.

AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last application) (since the last session)?"***

The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.

After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.
It is essential to enter the following information:

1. Protocol and subject identifiers
2. Subject's demography

3. Description of events, with diagnosis if available
4. Investigator opinion of relationship to study product
5. Criterion for seriousness.

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

1. Date of onset of AE
2. Date AE stopped, if relevant
3. Study product start date
4. Study product end date if relevant
5. Action taken on study product
6. Outcome if known

The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Serious Adverse Events to:
Brazil Clinical Study Manager (PPD**):**
Tel: PPD
E-mail: PPD
Pharmacovigilance (Brazil) Fax Number: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

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

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

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/SAEs 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 to

elucidate as fully as possible the nature and/or causality of the AE or SAE.

Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.

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

Regulatory and ethics reporting requirements for SAEs:

The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH 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 GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB and investigators.

Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

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

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:
Pregnancy information will be collected on all pregnancies reported following administration of any test product. Information on a pregnancy identified during the screening phase and prior to test product administration does not need to be collected.

7.6.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the test product. The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. 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 to GSKCH. 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, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK. While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting. If the subject becomes pregnant during the study they should be withdrawn from the study and this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or 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 in the Source Document Designation Form. In some cases the CRF can be used as a source document.

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

8.2. Electronic Case Report Form

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

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded in the CRF or as part of the query text.

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

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm™).

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.

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. 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.

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, 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 ensure the code terms (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and 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. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Approximately 280 healthy subjects will be screened to randomize at least 240 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is

observed in 200 subjects, there is a 95% certainty that the actual rate of reactions in the wider population is <1.8%.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

The 'Intent to treat' (ITT) population includes all subjects who are randomised into the study and have skin irritation scores from at least one of the test sites available.

A separate Per Protocol (PP) analysis will not be performed. Protocol deviations will however be listed for review.

The Safety population includes all subjects who received any application of the study products. All safety analyses will be performed using the Safety population.

9.2.2. Exclusion of Data from Analysis

No data will be excluded from any analysis.

9.2.3. Criteria for Evaluation

The primary evaluation will be to assess the cutaneous irritation and sensitisation potential of the test and control product, based on the irritation (dermal response) and superficial irritation (other effects) score/grade after patch removal during the induction and challenge phase using the ITT population.

Safety and tolerability will be evaluated by adverse events assessments using the Safety population.

9.2.4. 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.

9.3. Statistical Methods and Analytical Plan

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

9.3.1. Demographic and Baseline Characteristics

Age will be summarized using descriptive statistics such as means, medians and standard deviations. Gender, race and Fitzpatrick skin type will be summarized using frequency counts and percentages.

9.3.2. Primary Analysis(es)

The primary analysis will be based on the irritation (dermal response) and superficial irritation (other effects) scores/grades assessed using the scales described in Tables 1 and 2 of Appendix 2. Individual observations will be assessed based on these scales and a narrative description of all skin responses, both in the induction and challenge phases, will be provided.

No formal statistical inference will be performed.

The number and percentage of subjects recording each category of score/grade, as well as any skin response versus those without any skin response will be presented by treatment group at each assessment time point and over the induction and challenge phases using the maximum grade/score. If there are subjects with non-zero dermal response or other effects scores, then the dermal response, other effects and a combined dermal and others effects score will be summarised using descriptive statistics at each assessment time point and over the induction and challenges phases using a total score across time points.

9.3.3. Safety Analysis(es)

Adverse Events (AE) will be tabulated according to the current version of the MedDRA. Frequencies and percentages will be presented overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related AEs, AEs leading to discontinuation, and serious AEs will be completed. For treatment-related or treatment skin site related AEs, these will also be presented by product/test site.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

1. Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.

2. Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable).

3. Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB).

4. GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK 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 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 or designee will monitor the study and site activity to verify that the:

1. Data are authentic, accurate, and complete.
2. Safety and rights of subjects are being protected.
3. 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 GSKCH. 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.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

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

10.5. Conditions for Terminating the Study

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

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/ follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority (ies).

In addition:

1. If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
2. If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
3. If the IRB terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. 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 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 GSKCH, 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 GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

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

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

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

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

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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
aq	Aqueous
AUC	Area under Curve
CD	Compact Disc
cm^2	Centimetre squared
CRF	Case Report Form
DVD	Digital Versatile Disc
EDC	Electronic Data Capture
EEMCO	European Group for Efficacy Measurements on Cosmetics and Other Topical Products
FSFV	First Subject First Visit
g	Gram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
hr	Hour(s)
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat

LSLV	Last Subject Last Visit
m^2	Square metre
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
min	Minute
ml	Milliliters
nm	Nanometers
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

12.2. Appendix 2 –Dermal Response Score

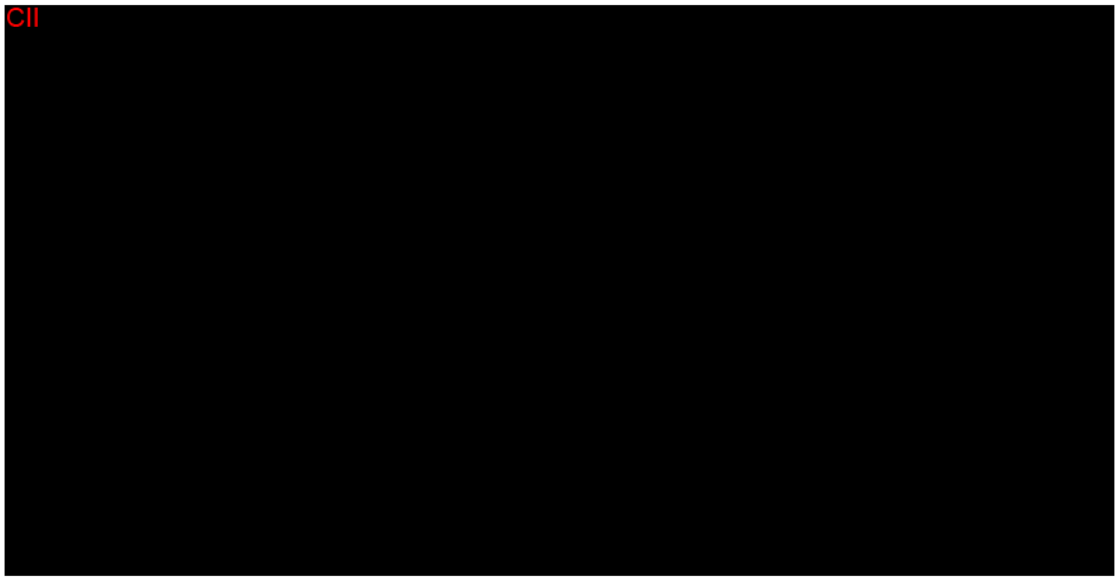
Any skin response at a patched site will be clinically assessed using the criteria recommended by the US Department of Health and Human Services Food and Drug Administration (FDA), 1999.

Any localised response to the patch application and removal that's typical to the procedure, won't be captured as an AE, unless more severe than expected in which case will be captured as an AE.

The following grades and their respective numerical equivalent scores will be used to express the response observed at the time of examination:

Table 1. Skin Irritation Scoring System

Table 2. Superficial Irritation Score (Symbols and Numerical Equivalents)



The results will be presented as individual responses to each test product and the negative control (saline solution) at each assessment time point. All responses will be reviewed in context of the grading scale.

Each of the scores represents an effect that is localised in a representative portion of the patch area, defined as 25% or more of the patch test site. Individual observations will be recorded in tables and a narrative description of all skin responses (any score >0) will be provided. Superficial irritation scores are only provided if there is a dermal response score >0.

Each Superficial Irritation Score should be reported as a letter. The combined score will equal the sum of the dermal response score plus the numerical equivalent of the superficial irritation score (e.g. dermal response score=3 and superficial irritation letter =”C” implies a combined score of 3 + 2 = 5).

If a subject develops a combined score of 3 or greater at any point during the Induction phase, the patch will be applied to an adjacent naïve site for the next application. If a combined score of 3 or greater occurs at the naïve site, no further patch applications will be made. Such reactive subjects will, however, receive patches on naïve test sites during the challenge phase of the study unless, in the opinion of the Investigator, it would be unwise to do so.

Dermal irritation or sensitisation reactions within the patch area (i.e., irritation reactions outlined in Table 1 and Table 2 above) will not be recorded as AEs during

the study. Reactions to the patch itself will also not be recorded as AEs. Unexpected reactions (e.g., rash, hives) will be recorded as AEs.

12.3. 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).

SIGNATURE PAGE

Clinical Protocol 207585

Date	Signed By
31-Jan-2017 05:39:05	PPD
Justification	Approved

Date	Signed By
31-Jan-2017 09:36:33	PPD
Justification	Approved

Date	Signed By
31-Jan-2017 13:03:14	PPD
Justification	Biostatistics Approval

Date	Signed By
31-Jan-2017 14:19:56	PPD
Justification	Clinical Operations Approval

Date	Signed By
Justification	

Date	Signed By
Justification	