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Clinical Protocol

207235

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SUMMARY INFORMATION

Title:	A Human Subject 24 Hour Patch Test to Assess the Irritation Potential of Four Skin Serum Products
Protocol Number:	207235
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) Rua Hungria, 1240 4º andar, Jardim Europa São Paulo/SP – Brazil, CEP 01455-000 Tel: PPD [REDACTED]
Product Name:	Experimental Daily Defense Serum
Development Phase:	N/A


Expert Advice Outside of Normal Working Hours:	Tel: PPD [REDACTED] (US)
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	Martina - Valinhos – São Paulo – Brazil.
Study Site Telephone Number:	PPD
Study Examiner(s):	Patch assessors will be assigned according to the site schedule (before First Subject First Visit) and documented in the site file.

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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 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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




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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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IRB/ IEC 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.

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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. ~~striketthrough~~

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.: 1	Non-Substantial/Minor <input checked="" type="checkbox"/>	Correction to site telephone number.	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Summary Information	Signature: PPD
Protocol Version No.: 2.0	Substantial/ Major <input type="checkbox"/>	Update to clarify recording of dermal response scores. Clarify the wording for success criteria.		6.3 Patch Assessments 7.1.1 Events NOT meeting definition of an AE include: Summary/Statistical methods 9.2.3. Criteria for Evaluation	Date: PPD

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Amendment No.: 2	Non-Substantial/Minor <input checked="" type="checkbox"/>	A new formulation code for one of the test products. Clarification of wording	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Product Information 5.1 Study Product 5.5 Packaging and labelling 4.3 Screening/Baseline Failures 6.1.2 Informed Consent	Signature: PPD
Protocol Version No.: 3.0	Substantial/ Major <input type="checkbox"/>				Date: PPD
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 <input type="checkbox"/>		Informed Consent <input type="checkbox"/> Yes <input type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input type="checkbox"/> No CRF <input type="checkbox"/> Yes <input type="checkbox"/> No		Signature: PPD
Protocol Version No.:	Substantial/ Major <input type="checkbox"/>				Date: PPD
Amendment No.:	Non-Substantial/Minor <input type="checkbox"/>		Informed Consent <input type="checkbox"/> Yes <input type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input type="checkbox"/> No CRF <input type="checkbox"/> Yes <input type="checkbox"/> No		Signature: PPD
Protocol Version No.:	Substantial/ Major <input type="checkbox"/>				Date: PPD

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SCHEDULE OF EVENTS

Procedures	Visit 1 Screen	Visit 2 Day 1	Visit 3 Day 2	Visit 4 Day 3	Visit 5 Day 4
Informed consent	X				
Demographics	X				
Medical History	X				
Current/Concomitant Medications reviewed	X	X	X	X	X
Inclusion and Exclusion criteria	X				
Eligibility to participate determined by Investigator (dermatologist)	X				
Continued eligibility		X	X	X	X
Randomisation		X			
Application of patches to test sites		X			
Removal of patches at study site 24 (± 2hrs) after application			X		
Assessment of test sites 15-30 minutes following patch removal at study centre ^a			X		
Assessment of test sites 24 (± 2hrs) following patch removal at study centre ^a				X	
Final assessment of test sites 48 (± 2hrs) following patch removal at study centre ^a					X
Adverse event assessment ^b		X	X	X	X
Study Conclusion					X

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

b. 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.

NOTE: Visit 1 and visit 2 could occur on the same day, but Visit 2 must be within 7 days of Visit 1.

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PROTOCOL SYNOPSIS FOR STUDY 207235

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. For this reason, the raw materials used in a product formulation must be raw materials with proven safety and tolerability. As a general requirement the safety and tolerability of a final formulation must be confirmed before it is marketed. (Guideline for the Safety Evaluation of Cosmetic Products; Agência Nacional de Vigilância Sanitária (ANVISA) 2012).


Cutaneous compatibility studies such as patch tests are designed to confirm the absence of irritation and/or sensitization during single or repeated topical application of a cosmetic product to human subjects.

Among the numerous cutaneous methods, patch tests are a well-recognized diagnostic tool (Lachapelle, 2012). This methodology involves occlusive or semi-occlusive application of test product to the skin, ensuring a higher contact between the components of the product formula and the skin.

The objective of this clinical study is to assess the cutaneous irritation potential of four test products under maximized conditions with dermatologist supervision.

Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
To assess the irritation potential of four prototype daily defense serum formulations after 24 (\pm 2) hours under semi-occlusive patch application to the skin of healthy volunteers	Trained evaluator assessment of product tolerability through visual assessment of cutaneous irritation 15-30 minutes, 24 \pm 2 and 48 \pm 2 hours after patch removal
Secondary	
To evaluate the general safety of four prototype daily defense serum formulations	Frequency and severity of Adverse Events

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Study Design

This is an evaluator (single) blind, test site randomized and intra-subject comparison patch test study to evaluate the cutaneous irritation potential of four experimental daily defense serum formulations, including a saline solution as a negative control.

Subjects will be exposed to 24 hour semi-occlusive patch applications of the test products and negative control.

Type and Planned Number of Subjects


Sufficient subjects will be screened such that approximately 40 subjects will be randomized to ensure approximately 30 evaluable subjects complete the entire study.

Diagnosis and Main Criteria for Inclusion

Healthy male and female volunteers aged 18 to 65 with no active dermatological conditions will be enrolled into this study.

Product Information

	Test Product 1	Test Product 2	Test Product 3	Test Product 4	Reference Product 1
Product Name	Experimental Daily Defense Serum A	Experimental Daily Defense Serum C	Experimental Daily Defense Serum G	Experimental Daily Defense Serum N	Saline Solution Sodium Chloride (NaCl; 0.9% _{aq})
Product Formulation Code (MFC)	CCI [REDACTED]	CCI [REDACTED]	CCI [REDACTED]	CCI [REDACTED]	N/A Site to Supply
Dose	0.02ml/cm ²	0.02ml/cm ²	0.02ml/cm ²	0.02ml/cm ²	0.02ml/cm ²
Route of Administration	Topical application via semi occlusive patch	Topical application via semi occlusive patch	Topical application via semi occlusive patch	Topical application via semi occlusive patch	Topical application via semi occlusive patch

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Statistical Methods


The primary evaluation will be the irritation scores after patch removal for each of the four test formulations.

The study will be considered a success if no irritation is observed which is attributable to the test product at any time point, or if any observed irritation for the test product is not clinically differentiable from the saline solution

~~The primary outcome for success is that there will be no evidence of irritation observed in the test products at any time point attributable to the product.~~

No formal statistical inference will be performed. Summary statistics will be presented by product group for skin irritation scores at 15-30 mins, 24 and 48 hours after patch removal. These will include mean irritation scores (if any subjects have reported irritation) and the number and percentage of subjects recording each category of skin irritation scores.

Adverse Events (AE) will be tabulated by the sponsor 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 product group/test site.

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1. INTRODUCTION

In recent years the cosmetic industry has grown considerably, along with its concern for the development of safe and effective products. This heightened industry awareness, combined with consumer and regulatory agency requirements have led cosmetic manufacturers to adopt procedures that provide them with a better understanding of the safety and compatibility of their products. This includes the conduct of clinical tests to assess the safety and efficacy of products under supervision of a dermatologist prior to marketing.


A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use (Guideline for the Safety Evaluation of Cosmetic Products; ANVISA, 2012). The raw materials used in the product formulation must be of proven safety with established use in the cosmetic industry, safety and compatibility of the final formulation must also be confirmed before it is marketed.

Skin contact with topical products such as cosmetics may trigger different types of reactions including eczematous, contact dermatitis, urticaria, acne and spots. Contact dermatitis can arise from two mechanisms: primary irritation, through the action of irritant substances; or sensitization, in the presence of an allergenic ingredient (Birmingham, 1965)

Tests to evaluate the irritation and sensitization potential of a product must take into account a number of variables including the components used in the formulation concentration, absorption, amount applied, skin condition, application directions and frequency, as well as any cumulative effects (Dooms-Goossens, 1993).

Primary irritation results from a direct chemical attack on the skin and is characteristically a rapid response, occurring on first contact with the skin. The effect may be limited to the stratum corneum and may result in symptoms such as dryness, flaking, or cracking. Primary irritation may involve deeper penetration, through the epidermis and into the dermis, where the classic inflammatory response takes place with erythema (reddening) and possibly edema (swelling), vesiculation (blistering) or exudation (weeping).

The human patch test is a well-established industry test for assessing primary skin irritation potential. The products are applied via an occlusive or semi-occlusive patch.

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This occlusion provides a higher contact between the components of the product formula and the skin.

This clinical study is being performed to assess the primary irritation potential of the four study products. A standard saline solution will also be included as a negative control.

All test products will be applied via semi-occlusive patches onto the dorsum (scapular region) skin of healthy subjects for a 24 hour period. Subjects will leave the patches in place until they return to the site where the patches will be removed and the skin assessed for any signs of irritation. Visual evaluations of dermal irritancy will be performed by (where ever possible) the same trained assessor 15 to 30 minutes after patch removal, and again at 24 (\pm 2) and 48 (\pm 2) hours after the patch removal. The scores will be analyzed to establish the irritation potential of each test product.

2. OBJECTIVE(S) AND ENDPOINT(S)


Objective(s)	Endpoint(s)
Primary	
To assess the irritation potential of four prototype daily defense serum formulations after 24 (\pm 2) hours under semi-occlusive patch application to the skin of healthy volunteers	Trained evaluator assessment of product tolerability through visual assessment of cutaneous irritation 15-30 minutes, 24 +/- 2 and 48 +/-2 hours after patch removal
Secondary	
To evaluate the general safety of four prototype daily defense serum formulations	Frequency and severity of Adverse Events

3. STUDY PLAN

3.1. Study Design

This is an evaluator (single) blind, single site, randomized and intra-subject comparison patch test study to evaluate the cutaneous irritation potential of four experimental daily defense serum formulations, including a saline solution as a negative control.


Subjects will be exposed to 24 hour semi-occlusive patch applications of the test products and negative control. At all study visits, subjects will be asked by a trained

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technician if there have been any feelings of discomfort since the last visit, and also if any medication has been taken during this period.

3.2. Subject Restrictions

Lifestyle/ Dietary
<p>During the entire study (Screening – Last Subject Last Visit (LSLV) the following should be avoided:</p> <ol style="list-style-type: none"> 1. Applying any other product to the test site. 2. Changing any cosmetic habits, including personal hygiene. 3. Changing dietary habits. 4. Getting the patch test site wet: during showers or bathing, in pools or lakes/ocean, sauna (study site to provide instructions on how to shower/bathe throughout the study). 5. Activities that cause excessive sweating. 6. Removing the patches. 7. Wearing tight or restrictive clothing that can remove the patch through friction or cause redness. 8. Exposure to excessive prolonged sunlight and not to undergo artificial tanning or use tanning beds 9. Introducing new products during the study including soap, laundry detergent, or fabric softener.
Medications and Treatments
<p>During the entire study (Screening – LSLV) the following medications and treatments should be avoided:</p> <ol style="list-style-type: none"> 1. Subjects will be instructed to avoid cosmetics, moisturizers, and other topical product application on the dorsum (back) area for the duration of their time in the study. 2. Having any body aesthetic or dermatological treatments performed. 3. Changing hormone treatment. 4. Changing contraceptive method. 5. Subjects will be instructed to not use the following medications: <ol style="list-style-type: none"> a) Systemic or topical corticosteroids b) Systemic or topical immunosuppressive drugs c) Systemic or topical antihistamines d) Vitamin A acid and its derivatives e) Non-steroidal anti-inflammatory drugs 6. Concomitant topical treatment at test sites

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3.3. Type and Planned Number of Subjects

Healthy male and female volunteers aged 18 to 65 with no dermatological disorders will be enrolled into this study. Subjects with a Fitzpatrick phototype I to IV (Appendix 3) will be recruited to ensure any reactions are clearly visible on subject's skin. A sufficient number of subjects will be screened such that approximately 40 subjects will be randomized to ensure at least 30 evaluable subjects complete the study.

The sample size has been selected to provide descriptive information on the tolerability and safety of the products.

Subjects will be recruited from the site's database.

3.4. Dose 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/cm².

This is a single-dose study; subjects will have a semi-occlusive patch (adhesive tape) measuring 65cm², containing paper discs of 1.2cm² onto which 0.02ml/cm² (Lee, 2007) each of the four experimental daily defense serum formulations and negative control; saline solution (sodium chloride (NaCl_{aq}) 0.9%) will be applied by trained personnel, once, according to the randomisation schedule for 24 (± 2) hours on the dorsum (scapular) region.

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.

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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.) Subjects must have intact skin on the proposed application site; dorsum (scapular region).
4. Skin Type
Fitzpatrick phototype I to IV
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


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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 vaccination within 3 weeks of the screening visit.
- k. Currently receiving allergy injections, or due to receive an 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. Known or suspected intolerance or hypersensitivity to any of the study materials (or closely related compounds) or any of their stated ingredients,

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including any component of the patches.

- c. History of sensitization 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

- a. 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, 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

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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, behavioral 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:

- a) The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- b) 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.
- c) 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.
- d) 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-randomization will not be replaced.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study.

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

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5. PRODUCT INFORMATION

5.1. Study Product

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


	Test Product 1	Test Product 2	Test Product 3	Test Product 4	Reference Product 1
Product Name	Experimental Daily Defense Serum A	Experimental Daily Defense Serum C	Experimental Daily Defense Serum G	Experimental Daily Defense Serum N	Saline Solution Sodium Chloride (NaCl _{aq} ; 0.9%)
Product Formulation Code (MFC)	CCI	CCI	CCI	CCI	N/A Site to supply
Dose	0.02ml/cm ²	0.02ml/cm ²	0.02ml/cm ²	0.02ml/cm ²	0.02ml/cm ²
Route of Administration	Topical application via semi occlusive patch	Topical application via semi occlusive patch	Topical application via semi occlusive patch	Topical application via semi occlusive patch	Topical application via semi occlusive patch

5.2. Dose Schedule

Subjects will be exposed to a 24 ± 2 hour dermal application of the four experimental daily defense serum formulations and negative control. Patches will be applied by trained staff at the study site.

Subjects will be instructed to keep the patches dry and in place for 24 ± 2 hours. The subjects will be asked to return to the clinic where the patches will be removed and discarded. Upon removal of the patches, the subjects will be asked to wait in the clinic for assessments to be made 15-30 minutes post patch removal. Subjects will then return to the clinic for two additional assessments at 24 ± 2 and 48 ± 2 hours after patch removal.

The study products will be applied to discs (or cells) of the patch test adhesive tape. The number of cells available on the patch test tape is 6 (but only 5 cells will be used).

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5.3. Overdose

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

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

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

5.4. Product Assignment


Each subject will have all 4 test products 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 randomization schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.4.1 Randomization

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 randomization schedule. Randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible. The randomization number will be associated with the random location assignment of product to test site.

5.4.2 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.

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5.4.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know where each product was applied on a subject 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.

5.5. 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 Experimental daily defence serums (CCI [REDACTED]) will be supplied in pump packs with 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 1) 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 products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study.

5.5.1. Accountability of Product

All products supplied are for use only in this clinical study and should not be used for any other purpose. Products are only to be used and applied by the study site technician.

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current and will contain the following information:

- The identification of the subject to whom the study product was dispensed.

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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 should not be destroyed without prior written authorization by the Sponsor. When destruction of the study products takes place a dated certificate of, or receipt for destruction, will be provided to the Sponsor.

5.5.2. 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/Visit. 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. Subjects who successfully complete the telephone screening will be scheduled for the Screening Visit. At the Screening Visit, the following procedures will be completed:

6.1.2 Informed Consent

The investigator, or designee, must obtain ~~written~~ (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 ~~written~~ **SIGNED AND DATED** consent will be provided by the investigator or by GSKCH. The investigator, or designee, should

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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: Fitzpatrick skin type scale, year of birth, gender and race.


6.1.4 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 (Day 1), Visit 3 (Day 2) and Visit 4 (Day 3)

Visit 2 may be combined with Visit 1 (Screening) but should be no more than 7 days following Visit 1.

At Visit 2 any concomitant therapy taken will be reviewed, and continued eligibility will be checked before product application (and randomisation of product application ordering). This will be reviewed again before each subsequent visit.

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6.2.1 Application of patches

Test products and control (0.02ml/cm² of each product) will be applied to a 1.2cm² paper disc (or cell) contained within an adhesive patch (measuring 65cm²). The number of cells available on the patch test tape is 6 (but only 5 cells will be used). The patch is then applied onto the dorsum (scapula region) of each subject for a period of 24 ± 2 hours, the sequence of the product application to the cells will be according to the randomization schedule.

Patch assessments will be performed at Visit 3, 4 and 5 per section 6.3.

6.3 Patch Assessments


Experienced trained assessor (s) will assess all patch sites for the duration of the study according to the scoring scale in Appendix 2. Where ever possible the same experienced trained assessor will perform all skin assessments for a given subject at each time point; 15-30 minutes post patch removal (Visit 3, Day 2) in addition to 24 ± 2 (Visit 4, Day 3) and 48 ± 2 hours (Visit 5, Day 4) post patch removal. Patch sites will be graded using a magnifying glass with a fluorescent daylight lamp. The assessor will be blinded to the treatment allocation.

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 (Scale 1) and other features indicative of irritation (Scale 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.

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.

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

6.4 Visit 5 (Day 4) Study Conclusion

Final review of any concomitant therapy taken adverse events experienced since the last visit and continued eligibility will be performed before final patch assessment (48 ± 2 hours) as per Section 6.3.

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:

Any abnormal laboratory test results (if applicable) or other safety assessments,

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including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.

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

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

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

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:

Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.


The disease/disorder/ 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..

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

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


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

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.

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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.

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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:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort

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and not interfering with everyday activities.

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

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

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 Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator **must** document in the medical notes (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

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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 dose) (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

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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 SAE Coordinator as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The SAE Coordinator should be notified of the situation by telephone or email.

Brazil SAE Coordinator (Rafaela Ross):

Tel: PPD [REDACTED]
E-mail: PPD [REDACTED]

Brazil backup contact (Ricardo Vila):

Tel: PPD [REDACTED]

The SAE Coordinator 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.

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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 AE or 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/IEC 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 or IEC, 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 investigational product.

Information on pregnancy identified during the screening phase and prior to

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investigational 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 investigational 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

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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 printed 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 (day and month)) 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 by the sponsor using MedDRA 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 (InFormTM).

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

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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.


Protocol deviations are any changes or discrepancies from the protocol that have not been approved by IRB. Protocol procedures should be fully followed, taking appropriate action to prevent any deviations from protocol. However, in case of intercurrents, it is up to the Investigator to analyze the occurrence, as well as the measures that should be taken for the incident.

Any deviation from the plan of this protocol should be described and justified in the final report and submitted to the IRB

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 code the terms (Adverse Events and Drugs) and report 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.

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9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Sample Size Determination

The primary evaluation will be irritation scores after patch removal for each test product at each assessment

No statistical analyses will be performed in this study. The number of subjects to be assessed (N=30 completing the study) was based on clinical considerations.

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.

Since this is a study to evaluate safety and tolerability, 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 of the test 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 objective will be to assess the skin irritation potential of the test formulations, based on the irritancy score after patch removal. ~~The study will be considered a success if no irritation is observed which is attributable to the test product at any time point.~~ **The study will be considered a success if no irritation is observed which is attributable to the test product at any time point, or if any observed irritation for the test product is not clinically differentiable from the saline solution**

Safety and tolerability will be evaluated by adverse events assessments.

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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 / analysis (as appropriate).

9.3.1. Demographic and Baseline Characteristics

Age will be summarized descriptively using 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 scores assessed using the dermal scale described in Scale 1 of Appendix 2. No formal statistical inference will be performed. Summary statistics will be presented by product group for skin irritation scores at 15-30 mins, 24 and 48 hours after patch removal. This will include mean irritation scores (if any subjects have reported/developed irritation) and the number and percentage of subjects recording each category of skin irritation scores.

9.3.3. Secondary Analysis(es)

Other skin effects, if manifest, will be assessed using the scale described in Scale 2 of Appendix 2. These effects will be summarized descriptively as the number and percent of subjects reporting each category of score. A combined dermal and other effects score will also be derived as the sum of these 2 scores. This combined score will also be summarized descriptively as the number and percent of subjects reporting/developing each category of score.

9.3.4. 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

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completed. For treatment-related AEs, these will also be presented by product group/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 (Resolution n° 466 de 12 December 2012), and with GSK policy.

The study will also be conducted in accordance with ICH GCP and all applicable subject privacy requirements. 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/IEC 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/IEC)
4. GSK will provide full details of the above procedures, either verbally, in writing, or both.

The informed consent will also contain the following: As with any other product, this product may cause unexpected reactions, such as “redness”, “swelling”, “itching”, and “burning sensation” in the application site. However, all adverse reactions caused by the test product will be followed by a dermatologist until their resolution and appropriate medication will be provided if necessary. As A benefit for participating in

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the study, subjects will be examined before the beginning of the study by an expert physician and, if any problem is identified in the relevant site, they will be notified and advised. Subjects may also learn about their correct skin tone/type (phototype) based on the procedures followed.

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.

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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/IEC, and should provide the sponsor and the IRB/IEC 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/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
3. If the IRB/IEC 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

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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

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provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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

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

11. REFERENCES

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Dooms-Goossens, A, Corticosteroid contact allergy: an EECDRG Multicenter study <i>Contact Dermatitis</i> , 1996, 0105-1873, 35(1):40
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Lee E, An S, Choi D, Moon S, Chang I. Comparison of objective and sensory skin irritations of several cosmetic preservatives. <i>Contact Derm</i> 2007; 56 : 131-6.
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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ANVISA	Agência Nacional de Vigilância Sanitária
aq	Aqueous
CD	Compact Disc
CRF	Case Report Form
EDC	Electronic Data Capture
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ICF	Informed Consent Form
IRB	Institutional Review Board
ITT	Intention to Treat
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

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12.2. Appendix 2 – Skin Irritation Scoring System

Scale 1: Dermal Response

Score	Skin Appearance
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site


Effects on superficial layers of the skin should be recorded as follows:

Scale 2: Other Effects

Score (Numeric equivalent)	Observation
A (0)	Slight glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudate covering all or portion of the patch site
H (3)	Small petechial erosions and/or scabs

When an “Other Effects” score is observed, each score should be reported as a number and letter combination score and also as a numerical total (i.e. numerical “Dermal Response” score + numeric equivalent for the “Other Effects” lettered score).


A “Strong” reaction to the test patch is defined as a ‘dermal response’ score of 3-7 or any dermal score combined with ‘other effects’ rating of 4.

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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).

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

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SIGNATURE PAGE

207235 Clinical Protocol

Date	Signed By
06-Mar-2017 10:58:05	PPD
Justification	Approved

Date	Signed By
07-Mar-2017 03:12:13	PPD
Justification	Approved

Date	Signed By
07-Mar-2017 06:38:57	PPD
Justification	Clinical Operations Approval

Date	Signed By
07-Mar-2017 08:35:16	PPD
Justification	Biostatistics Approval

Date	Signed By
Justification	

Date	Signed By
Justification	