
 GlaxoSmithKline	Document Name	Clinical Protocol 207587		
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	eldo_clinical_doc	2.0; Most-Recent; Effective; CURRENT	090032d580d16e68	24-Mar-2017 07:31:59
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Clinical Protocol

207587

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SUMMARY INFORMATION


Title:	A Clinical Study to Assess the Photosensitisation and Photoallergy Potential of a Cosmetic Facial Product in Healthy Subjects
Protocol Number:	207587
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
---	----------

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Principal Investigator:	Regina M. Doi, Dermatologist
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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.

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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 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:	
Investigator Signature:	PPD
Date of Signature/ Agreement:	




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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 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.

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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. ~~striketrough~~

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 errors in text to reflect the schedule of events and details in main sections; patch sites will be assessed 48 hours after patch removal and irradiations on Tuesdays in the Induction Phase.	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	SYNOPSIS: Brief Summary and Study Design 3.1 Study Design	Signature:
Protocol Version No.: 2.0	Substantial/ Major <input type="checkbox"/>	Clarify wording: AND ONCE FOR FINAL INDUCTION PHASE PATCH GRADING/ASSESSMENT ON THE FIRST DAY OF THE REST PHASE (VISIT 14/DAY 22) Clarify wording that if a		Study Design 3.1 Study Design 3.1 Study Design	Date:


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		subject develops a combined irritation score of 3 or greater during the Induction Phase, the site will not be irritated, a new patch will be applied to a naïve site, which will be irritated following removal 24 hours later and per the schedule of events.		3.4 Study Design and application Amount Justification 6.2.2 Patch Assessment 12.2 Appendix 2	
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:
Protocol Version No.:	Substantial/ Major <input type="checkbox"/>				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:
Protocol Version No.:	Substantial/ Major <input type="checkbox"/>				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:
Protocol Version No.:	Substantial/ Major <input type="checkbox"/>				Date:

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SCHEDULE OF EVENTS

Study Phase	Screening	Induction												Rest	Challenge				
Study Week	-	Week 1				Week 2				Week 3				Week 4-5	Week 6				
<div>Study Day</div> <div>Procedure/ Assessment</div>	VISIT 1 DAY -14 to DAY 0	VISIT 2 DAY 1	VISIT 3 DAY 2	VISIT 4 DAY 4	VISIT 5 DAY 5	VISIT 6 DAY 8	VISIT 7 DAY 9	VISIT 8 DAY 11	VISIT 9 DAY 12	VISIT 10 DAY 15	VISIT 11 DAY 16	VISIT 12 DAY 18	VISIT 13 DAY 19	VISIT 14 DAY 22	VISIT 15 DAY 36	VISIT 16 DAY 37	VISIT 17 DAY 38	VISIT 18 DAY 39	VISIT 19 DAY 40
Day of Week	-	Mon	Tue	Thu	Fri	Mon	Tue	Thu	Fri	Mon	Tue	Thu	Fri	Mon	Mon	Tue	Wed	Thu	Fri
Informed Consent	X																		
Demographics	X																		
Medical History	X																		
Current/Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
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	X	X	X	X
Randomisation		X																	
Patch Application		X ^b		X ^b		X ^b		X ^b		X ^b		X ^b			X ^c				
Patch Removal			X ^d		X ^d		X ^d		X ^d		X ^d		X ^e			X			
UVA Irradiation			X		X		X		X		X		X			X ^f			
Grading/Assessment of the patch sites		X ^g	X	X	X	X	X	X	X	X	X	X	X	X ^h	X ⁱ	X	X ^j	X ^j	X ^j
Adverse Events ^k		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Conclusion/ Exit from Study/																			X

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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 12 times during the Induction Phase - 6 patch application visits – patches will be applied Mondays and Thursdays. The patches will remain in place for 24 hours during the week.
- c. Challenge Phase Patch application (Visit 15/Day 36) - 2 patches will be applied to naïve (virgin) skin sites. The patches will remain in place on the naïve sites for 24 (± 2) hours and will be evaluated at 30 minutes (up to 1 hour) after patch removal and again at 24 (± 2), 48 (± 2) and 72 (± 2) hours after patch removal (e.g., apply the patches on Monday, remove the patches on Tuesday, and evaluate the sites on Wednesday, Thursday and Friday. (Challenge Phase)
- d. 30 minutes (up to 1 hour) after each removal of the patches, a trained blinded assessor will perform an assessment of all test sites for irritation symptoms using the scoring system detailed in Appendix 2
- e. Visit 13/Day 19 will be the final Induction Phase patch removal - Approximately 30 minutes (up to 1 hour) after removal of the patch, a trained blinded assessor will perform an assessment of all test sites for irritation symptoms using the scoring system detailed in Appendix 2
- f. UVA Irradiation during the Challenge Phase will only be on one of the two the naïve patch locations.
- g. Visit 2 (Day 1) Baseline grading/assessments of the patch sites will be performed prior to the patch application.
- h. Final Grading/assessment of irradiation from the Induction Phase will be carried out on Visit 14/Day 22 (first Day of the Rest Phase).
- i. Visit 15 (Day 36) Grading/assessments of each of the naïve challenge patch sites will be performed prior to application of the 2 Challenge patches.
- j. Further evaluations of the naïve patch sites (irradiated and non-irradiated) 24 (± 2), 48 (± 2) and 72 (± 2) hours after the challenge patches are removed.
- 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.

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Patch Schedule

	INDUCTION												REST	CHALLENGE				
	Week 1				Week 2				Week 3				Week 4-5	Week 6				
Activity	MON	TUE	THU	FRI	MON	TUE	THU	FRI	MON	TUE	THU	FRI		MON	TUE	WED	THU	FRI
Application of the 1 st patch	X																	
Removal of the 1 st patch / Assess/UVA Irradiation		X																
Assess 1 st patch/Application of the 2 nd patch			X															
Removal of the 2nd patch / Assess/UVA Irradiation				X														
Assess 2nd patch/Application of the 3rd patch					X													
Removal of the 3rd patch / Assess/UVA Irradiation						X												
Assess 3rd patch/Application of the 4h patch							X											
Removal of the 4th patch / Assess/UVA Irradiation								X										
Assess 4th patch/Application of the 5th patch									X									
Removal of the 5th patch/ Assess/UVA Irradiation										X								
Assess 5th patch/Application of the 6th patch											X							
Removal of the 6th patch/ Assess/UVA Irradiation												X						
Assess Challenge Patch naïve sites (<i>prior to Challenge patch application</i>)														X				
Application of the Challenge patches (2 patches)														X				
Removal of the Challenge patches/Assess/UVA Irradiation (<i>to one challenge patch location</i>)															X			
Evaluation after Irradiation																X	X	X
Dermatologist Assessment	X																	X

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SYNOPSIS FOR STUDY 207587

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).

Phototoxicity assessments aim to demonstrate the absence of irritation potential of a product when applied to the skin and exposed to ultra violet (UVA) radiation. Photosensitisation assessments aim to prove the absence of allergic potential of a product applied to the skin when exposed to UVA radiation.

In this three-phase phototoxicity-photosensitisation (PT-PA) study, the test material and a positive control of saline solution are applied under a semi-occlusive patch to the upper back of each subject. The first phase of the study is an Induction Phase; a controlled amount of the test product and control product is applied over a defined surface area of skin (amount per unit area), under a semi-occlusive patch. The patch will remain on the skin for 24 (± 2) hours during this phase. Following patch removal, the patch site will be exposed to ultraviolet – A (UVA) radiation and re-assessed **24 48** hours later prior to re-application of another semi-occlusive patch (with both the test and control product) to the same site. The Induction phase will last 3 weeks. After a subject completes the Induction Phase they will enter a Rest Phase of 2 weeks' duration, during which no patches will be applied. After the Rest Phase, subjects will return to the clinical site for the Challenge Phase. In the Challenge phase two test patches will be applied to virgin skin areas on each subject's upper back for 24 hours. Following removal of both patches, one of the Challenge patch test sites will be exposed to UVA radiation. Both Challenge patch test sites will be assessed up until 72 (± 2) hours later.

The objective of this clinical study is to assess the phototoxicity and photosensitisation potential of a cosmetic test product under exaggerated conditions of use with controlled product application and under supervision of a dermatologist.


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Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
To determine the photoirritation and photosensitisation 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 tolerance of a cosmetic facial skin product.	Assessment of frequency and severity of Adverse Events

Study Design

Overall Design
This is an assessor-blinded (single), test site randomised, intra-subject comparison, repeated insult patch test to evaluate the skin irritation and sensitisation potential of a cosmetic facial product, under exaggerated conditions of use with controlled product application and under supervision of a dermatologist.
Day -14 to 0 / Visit 1 - Screening Visit
NOTE: Visit 1 and Visit 2 could be combined
<p>The following assessments will be conducted:</p> <ol style="list-style-type: none"> 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 14 - Induction Phase (3 Weeks)
NOTE: Visit 1 and Visit 2 could be combined
<ol style="list-style-type: none"> 1. The following assessments will be conducted: 2. Continued eligibility check 3. Current/Concomitant Medications review 4. Inclusion/Exclusion criteria review (Inclusion criteria 3c (only) at Visit 2, if Visit 1 and 2 are not combined). 5. Dermatologist determination for continued eligibility to participate in the

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- study (Visit 2/Day 1 only - if visits not combined)
6. Test Site Designation and Randomisation (Visit 2/Day 1 only)
 7. Baseline grading/assessment of test sites (Per Appendix 2) (Visit 2/Day 1 only)
 8. Patch applications (6 patch applications every Monday and Thursday, for 3 consecutive weeks).
 9. Patch removal 24 (\pm 2) hours after application (Tuesday and Friday). Reaction grading/assessment performed by a qualified staff member (24 \pm 2 hours after application). Grading/assessments will be 30 minutes (up to 1 hour) after each patch removal (per Appendix 2)
 10. Application site exposed to UVA irradiation.
 11. ~~24~~ **48** (\pm 2) hours after each UVA irradiation (or 72 (\pm 2) hours, in case of irradiation on Fridays), the sites will be evaluated for signs of dermatological reactions, according to Appendix 2.
 12. Adverse event assessment

*NOTE: Subjects will report to the study site 12 times during the Induction Phase (6 patch applications and removals) **AND ONCE FOR FINAL INDUCTION PHASE PATCH GRADING/ASSESSMENT ON THE FIRST DAY OF THE REST PHASE (VISIT 14/DAY 22)**. No Patch Applications from Days 22 to 35 (Rest Phase).*


Days 22 - Day 35 / Visit 14 -Visit 15 – Rest Phase (2 Weeks)

No Patch Application

Days 36 to 39 / Visit 15-Visit 18 – Challenge Phase

The following assessments will be conducted:

1. Continued eligibility check
2. Current/Concomitant Medications review
3. Grading/assessment of naïve challenge patch sites performed by a qualified staff member (per Appendix 2) prior to Challenge patch application (Visit 15/Day 36).
4. Challenge Patch application, 2 patches to naïve sites (Visit 15/Day 36).
5. Patch removal 24 (\pm 2) hours later (Visit 16/Day 37).
6. Reaction grading/assessment performed by a qualified staff member 30 minutes (maximum 1 hour) after patch removal (Visit 16/Day 37).
7. One of the naïve patched sites will be exposed to 5 Joules per square centimeter (J/cm^2) UVA radiation.
8. Subjects will return for grading/assessment performed by a qualified staff member 24 (\pm 2) hours after UVA irradiation (Visit 17/Day 38). Both irradiated non non-irradiated sites will be assessed.

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<p>9. Subjects will return for grading/assessment performed by a qualified staff member 48 (\pm 2) hours after UVA irradiation (Visit 18/Day 39). Both irradiated non non-irradiated sites will be assessed.</p> <p>10. Adverse event assessment.</p>
Day 40 / Visit 19 – End of Study
<p>The following assessments will be conducted:</p> <ol style="list-style-type: none"> 1. Current/Concomitant Medications review 2. Adverse event assessment. 3. Subjects will return for grading/assessment performed by a qualified staff member 72 (\pm 2) hours after UVA irradiation (Visit 19/Day 40). Both irradiated non non-irradiated sites will be assessed. 4. Dermatologist final assessment 5. Subject discharge from the study site following completion of all study procedures.

Type and Planned Number of Subjects


Approximately 40 healthy subjects will be screened to randomise at least 30 subjects to ensure at least 25 evaluable subjects complete the entire study. This sample size is standard in clinical testing practices and is consistent with the ANVISA guidelines (ANVISA, 2012).

Diagnosis and Main Criteria for Inclusion

Healthy male and female volunteers aged 18 to 65 with no dermatological disorders, with a Fitzpatrick skin phototype II 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 [REDACTED]	N/A Site to supply
Product Format	200ml clear PET Bottle	N/A
Application Quantity	0.02 millilitres per square centimetre (ml/cm ²)	0.02 ml/cm ²
Route of Administration	Topical application via semi occlusive patch	

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Application Instructions	Applied on-site by technician
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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 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.

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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).

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

Several types of substances do not present an inherent irritant or allergenic potential, however, they may provoke skin reactions when exposed to sunlight, either because ultraviolet radiation converts them into other substances, or because they are photo activated to excited states capable of interacting with the skin. (Billhimer, 1990). Specifically, topically applied agents can cause contact dermatitis or interact with sunlight to cause phototoxic reactions. These reactions occur on first exposure to the

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product and usually resemble exaggerated sunburn and may be characterised by a sensation of prickling and burning.

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


Skin sensitisation is an immunological process in which the responsiveness to a specific chemical allergen is increased. By definition, skin sensitisation is induced when a susceptible individual is exposed to an inductive chemical allergen. This allergen causes a skin immune response that, at a certain range, will result in the development of contact sensitisation (Kimber *et al.*).

The phototoxicity test measures the potential of a test product to produce phototoxic reactions in human subjects upon exaggerated application. Evaluator comparison of cutaneous responses to test product alone, test product exposed to UVA radiation and an irradiated, control product site provides an assessment of the phototoxic potential of the test product.

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

The photoallergenicity test measures the potential of test products to produce allergic reactions in the presence of UVA radiation. This test consists of three phases: a 3-week Induction phase consisting of repeated 24 hour semi-occlusive patch applications on the backs of healthy subject and subsequent exposure to UVA radiation after each patch removal; a 2 week Rest phase; and a final Challenge phase, consisting of two parallel 24 hour semi-occlusive patch applications to naive sites, one of which is subsequently exposed to UVA radiation upon patch removal, and evaluation of cutaneous responses of both sites 24, 48 and 72 hours after patch removal.

The inclusion of evaluations at 24, 48 and 72 hours for the two challenge sites (with and without exposure to UVA radiation) provides simultaneous evaluation of the potential for contact irritation, phototoxicity, contact allergy and photoallergy.

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The objective of this clinical study is to assess the phototoxicity and photosensitisation potential of a cosmetic test product under exaggerated conditions of use with controlled product application and under supervision of a dermatologist.


2. OBJECTIVE(S) AND ENDPOINT(S)

Objective(s)	Endpoint(s)
Primary	
To determine the photoirritation and photosensitisation 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 tolerance of a cosmetic facial skin product.	Assessment of frequency and severity of Adverse Events

3. STUDY PLAN

3.1. Study Design

Overall Design
This is an assessor-blinded (single), test site randomised, intra-subject comparison, repeated insult patch test to evaluate the skin irritation and sensitisation potential of a cosmetic facial product, under exaggerated conditions of use with controlled product application and 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: <ol style="list-style-type: none"> 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 14 - Induction Phase (3 Weeks) NOTE: Visit 1 and Visit 2 could be combined

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1. The following assessments will be conducted:
2. Continued eligibility check
3. Current/Concomitant Medications review
4. Inclusion/Exclusion criteria review (Inclusion criteria 3c (only) at Visit 2, if Visit 1 and 2 are not combined).
5. Dermatologist determination for continued eligibility to participate in the study (Visit 2/Day 1 only - if visits not combined)
6. Test Site Designation and Randomisation (Visit 2/Day 1 only)
7. Baseline grading/assessment of test sites (Per Appendix 2) (Visit 2/Day 1 only)
8. Patch applications (6 patch applications every Monday and Thursday, for 3 consecutive weeks).
9. Patch removal 24 (\pm 2) hours after application (Tuesday and Friday). Reaction grading/assessment performed by a qualified staff member (24 \pm 2 hours after application). Grading/assessments will be 30 minutes (up to 1 hour) after each patch removal (per Appendix 2)
10. Application site exposed to UVA irradiation.
11. **24 48** (\pm 2) hours after each UVA irradiation (or 72 (\pm 2) hours, in case of irradiation on Fridays), the sites will be evaluated for signs of dermatological reactions, according to Appendix 2.
12. Adverse event assessment

*NOTE: Subjects will report to the study site 12 times during the Induction Phase (6 patch applications and removals) AND **ONCE FOR FINAL INDUCTION PHASE PATCH GRADING/ASSESSMENT ON THE FIRST DAY OF THE REST PHASE (VISIT 14/DAY 22)** No Patch Applications from Days 22 to 35 (Rest Phase).*


Days 22 - Day 35 / Visit 14 ~~Visit 15~~ – Rest Phase (2 Weeks)

No Patch Application

Days 36 to 39 / Visit 15-Visit 18 – Challenge Phase

The following assessments will be conducted:


1. Continued eligibility check
2. Current/Concomitant Medications review
3. Grading/assessment of naïve challenge patch sites performed by a qualified staff member (per Appendix 2) prior to Challenge patch application (Visit 15/Day 36).
4. Challenge Patch application, 2 patches to naïve sites (Visit 15/Day 36).
5. Patch removal 24 (\pm 2) hours later (Visit 16/Day 37).
6. Reaction grading/assessment performed by a qualified staff member 30

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<p>minutes (maximum 1 hour) after patch removal (Visit 16/Day 37).</p> <ol style="list-style-type: none"> One of the naïve patched sites will be exposed to 5 Joules per square centimeter (J /cm²) UVA radiation. Subjects will return for grading/assessment performed by a qualified staff member 24 (± 2) hours after UVA irradiation (Visit 17/Day 38). Both irradiated non non-irradiated sites will be assessed. Subjects will return for grading/assessment performed by a qualified staff member 48 (± 2) hours after UVA irradiation (Visit 18/Day 39). Both irradiated non non-irradiated sites will be assessed. Adverse event assessment.
Day 40 / Visit 19 – End of Study
<p>The following assessments will be conducted:</p> <ol style="list-style-type: none"> Current/Concomitant Medications review Adverse event assessment. Subjects will return for grading/assessment performed by a qualified staff member 72 (± 2) hours after UVA irradiation (Visit 19/Day 40). Both irradiated non non-irradiated sites will be assessed. Dermatologist final assessment Subject discharge from the study site following completion of all study procedures.

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"> Applying any other product, including cosmetics, moisturisers and other topical products to the test site (dorsum). Changing any cosmetic habits, including personal hygiene. Changing dietary habits. <ul style="list-style-type: none"> Getting the patches 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.


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5. Removing the patches.
6. Wearing tight or restrictive clothing that can remove the patch through friction or cause redness.
7. Exposure of the back to sunlight, artificial UV light or cosmetic procedures (includes tanning beds, Intense Pulsed Light, etc.).
8. Introduction of new personal care/household products including but not limited to; soap, laundry detergent, or fabric softener.
9. Engaging in activities that are expected to result in excessive sweating.
10. Missing the first day of application during the Induction Phase, or the day of application during the Challenge Phase.
11. Missing 2 or more consecutive visits or more than 2 alternative visits.

Medications and Treatments

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

1. Having any aesthetic or dermatological treatment performed on the body.
2. Changing hormone treatment.
3. Changing contraceptive method.
4. Not to not use 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

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3.3. Type and Planned Number of Subjects

Approximately 40 healthy subjects will be screened to randomise at least 30 subjects to ensure at least 25 evaluable subjects complete the entire study. This sample size is standard in clinical testing practices and is consistent with the ANVISA guidelines (ANVISA, 2012).

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

3.4. Study Design and Application Amount Justification

Study Design:

This will be a single-center, randomised, assessor (single) blind study in healthy subjects aged 18 to 65 years. Subjects will be exposed to repeated insult dermal semi-occlusive patch application of a topical cosmetic formulation 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 Fitzpatrick Phototype II 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 continued eligibility (if Visits 1 and 2 are not combined) as well as review of concomitant medications since screening. The test site will be designated above the waist between the left scapula and the spinal mid-line. The sites within the patch of test product and negative control application will be randomly assigned and baseline grading/assessment of each test site will be performed.

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During the induction phase, there will be 6 patch applications (a patch will contain both the test product and saline solution) over 3 consecutive weeks, with each patch applied on Mondays and Thursdays. Each patch will remain in place for 24 (\pm 2) hours and then be removed, the treated areas will be cleaned with saline solution. After 30 minutes (maximum of 1 hour) the sites will be graded/evaluated as per the scale in Appendix 2. The patch test site will then be exposed to 5 J/cm² UVA radiation. The patch application site will be assessed pre-irradiation, following patch removal. Irradiation time depends on the power output of the light source and distance from the subject, and will be determined by the study site prior to UVA exposure. Irradiation will occur on the same days as patch removal (Tuesday and Fridays). Assessment of the irradiated sites will occur 48 hours (or 72 hours if the irradiation occurred on a Friday) after UVA exposure, prior to new patch application to the same site.

Rest Phase:


After the last 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. Two naïve sites (previously un-patched, virgin areas) will be selected for the challenge patches both of these naïve areas will be graded/evaluated prior to any product application. Two patches, each with the test product and saline solution, will be randomly applied to each of the Challenge sites for 24 (\pm 2) hours, according to each subject's random assignment on Day 1 of the Induction phase. After 24 (\pm 2) hours, subjects will return for Challenge patch removal, the sites will be cleaned with saline solution and then graded/evaluated after 30 minutes (maximum of 1 hour). One of the Challenge patch sites will then be irradiated with 5 J/cm² of UVA radiation. Subjects will return 24 (\pm 2), 48 (\pm 2), and 72 (\pm 2) hours after patch removal for further grading/assessments of both the irradiated and non-irradiated Challenge sites.

End of Study:

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

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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 site will be conducted once at Baseline (Visit 2/Day 1) prior to any patch application and then a further 11 times post-baseline during the Induction Phase, once during the Rest Phase (for the final assessment of irradiated patch site), and 5 times during the Challenge Phase by a blinded assessor (a qualified staff member). Sites will be assessed prior to UVA exposure to allow responses to minimize the impact of UVA-induced erythema or pigmentation.


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, **IRRADIATION OF THE SITE WILL NOT BE PERFORMED**, 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

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(e.g., rash, hives) will be recorded as AEs. As each subject will be exposed to UVA radiation during the induction and challenge phases, it is expected that the sites become hyperpigmented and may exhibit erythema as a natural response to UVA exposure. These responses are expected and will be disregarded in evaluations, using the negative control (saline solution) as the standard for determining the expected degree of reaction.

Reactions observed after application of patches and before UVA exposure, or observed on the non-irradiated site during the challenge phase, will be used to evaluate the primary irritation potential of the product. These data will not be used to evaluate the photoirritation or photosensitisation potential of the formulation.

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 0.02 ml/cm².

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 with the saline solution control. 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.

Photoreactions to exogenous agents typically occur in response to UVA light (315-400 nanometers (nm)) rather than at the shorter wavelengths of UVB or UVC. The photoreactions can be divided into two types of responses; photoirritancy

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(phototoxicity) and photoallergy (Norbert, 2005). A 5 J/cm² dose of UVA radiation has been established as a sufficient for eliciting photo contact allergic test reactions (Hasan, 1996).

UVA Lamp:

Subject UVA irradiation will be performed with Newport 67005, serial 120 power supply model 69907 with filter adapter and xenon lamp of 150 Watts.

The solar simulator will be used to irradiate the test areas with the requested irradiation intensity on circular spots of approximately 1 cm².

Before UVA exposure of each test site, the UVA irradiance will be measured with a radiometer calibrated against a spectroradiometric measurement of the solar simulator output. A spectroradiometric measurement of the UV source of the solar simulator is performed at least every 18 months by an authorized expert.

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.

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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 II 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.

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- 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.
- d) History of abnormal reaction to sun exposure.

5. CLINICAL STUDY/ EXPERIMENTAL PRODUCT

- a) Participation in another clinical study (including cosmetic studies) or receipt

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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 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.

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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.

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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 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 continued eligibility (if Visits 1 and 2 are not combined) as well as review of concomitant medications since screening. The test site will be designated above the waist between the left scapula and the spinal mid-line. The sites within the patch of test product and negative control application will be randomly assigned and baseline grading/assessment of each site will be performed.

During the induction phase, there will be 6 patch applications of both the test product and saline solution over 3 consecutive weeks, each patch will be applied on Mondays and Thursdays. Each patch will remain in place for 24 (\pm 2) hours and then removed and the treated areas may be cleaned with saline solution. After 30 minutes (maximum of 1 hour) sites will be graded/evaluated as per the scale in Appendix 2. The patch test site will then be exposed to 5 J/cm² UVA radiation. The patch

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application site will be assessed pre-irradiation, following patch removal. Irradiation time depends on the power output of the light source and distance from the subject, and will be determined by the study site prior to UVA exposure. Irradiation will occur on the same days as patch removal (Tuesday and Fridays). Assessment of the irradiated sites will occur 48 hours (or 72 hours if the irradiation occurred on a Friday) after UVA exposure, prior to new patch application to the same site.

Rest Phase:

After the last 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. Two naïve sites (previously un-patched areas) will be selected for the challenge patches, these areas will be graded/evaluated prior to any product application. Two patches, each with both the test product and saline solution, will be randomly applied to each of the challenge sites for 24 (± 2) hours, according to each subject's random assignment on Day 1 of the Induction phase. After 24 (± 2) hours, subjects will return for Challenge patch removal, the sites will be cleaned with saline solution and then graded/evaluated after 30 minutes (maximum of 1 hour). One of the Challenge sites will then be irradiated with 5 J/cm² of UVA radiation. Subjects will return 24 (± 2), 48 (± 2), and 72 (± 2) hours after patch removal for further grading/assessments of both the irradiated and non-irradiated Challenge patch sites.

End of Study:

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

5.3. Product Assignment

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

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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 randomised 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.

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Care should be taken with the supplied product and 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.

5.4.1. 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.

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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 that the subject is free of any pre-existing dermatological pathology. Additionally, a final assessment at Visit19 by a qualified dermatologist will confirm whether it is medically appropriate to exit the subject from the study (Edward & Robillard, 2008).

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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 18

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/cm² 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 24 ± 2 hours, the sequence of the product application to the cells will be 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 continued eligibility (if Visits 1 and 2 are not combined) as well as review of concomitant medications since screening. The test site will be designated above the waist between the left scapula and the spinal mid-line. The sites of test product and negative control application will be randomly assigned and baseline grading/assessment of each test site will be performed.

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During the Induction phase, there will be 6 patch applications of both the test product and saline solution over 3 consecutive weeks, with each patch applied on Mondays and Thursdays. Each patch will remain in place for 24 (\pm 2) hours, then 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. The patch test site will then be exposed to 5 J/cm² UVA radiation. The patch application site will be assessed pre-irradiation, following patch removal. Irradiation time depends on the power output of the light source and distance from the subject, and will be determined by the study site prior to UVA exposure. Irradiation will occur on the same days as patch removal (Tuesday and Fridays). Assessment of the irradiated sites will occur 48 hours (or 72 hours if the irradiation occurred on a Friday) after UVA exposure, prior to new patch application to the same site.

Rest Phase:


After the last 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. Two naïve sites (previously un-patched areas) will be selected for the Challenge patches, these areas will be graded/evaluated prior to any product application. Two patches, each with both the test product and saline solution, will be randomly applied to each of the naïve challenge sites for 24 (\pm 2) hours, according to each subject's random assignment on Day 1 of the Induction phase. After 24 (\pm 2) hours, subjects will return for Challenge patch removal, sites will be cleaned with saline solution and then graded/evaluated after 30 minutes (maximum of 1 hour). One of the Challenge patch sites will then be irradiated with 5 J/cm² of UVA radiation. Subjects will return 24 (\pm 2), 48 (\pm 2), and 72 (\pm 2) hours after patch removal for further grading/assessments of both the irradiated and non-irradiated Challenge sites.

6.2.2 Patch Assessments

An experienced trained assessor (s) will assess all the 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 time point.

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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 13 for the Induction Phase (every 24 ± 2 hours following application, and 48 ± 2 (OR 72 ± 2 **IN CASE OF IRRADIATION ON FRIDAYS**) hours following patch site exposure to 5 J/cm^2 UVA radiation). After the last grading/evaluation in the Induction Phase at Visit 14, subjects will enter a Rest Phase of 2 weeks.

After completing the Rest Phase, subjects will return for the Challenge Phase (Visit 15). Each the naïve patch sites will be assessed prior to Challenge patch application. The 2 Challenge patches (with both the test and saline solution products) will be randomly applied to the Challenge site (previously untreated areas of skin) for 24 ± 2 hours. After Challenge patch removal at the study site (Visit 16), the patch site will be cleaned with saline solution and graded/evaluated after 30 minutes (maximum of 1 hour). One of challenge patch test site will then be exposed to 5 J/cm^2 UVA radiation. Subjects will return for further assessments after 24 ± 2 hours (Visit 17), 48 ± 2 hours (Visit 18) and 72 ± 2 hours (Visit 19) post patch removal for further grading/assessment of both the irradiated and non-irradiated Challenge sites.


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 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 assessor 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, **IRRADIATION OF THE SITE WILL NOT BE PERFORMED** 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

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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 19 - Last Subject Last Visit (LSLV)

At Visit 19 any current and concomitant therapy taken will be reviewed, and continued eligibility will be checked. Final challenge site assessment 72 ± 2 hours (Visit 19) post patch removal (per Section 6.2.2) will take place.

A final evaluation by a qualified dermatologist will take place before the subject completes 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.

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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.

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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. As each subject will be irradiated during the induction phase, it is expected that the sites become hyperpigmented and may exhibit erythema as a natural response to UVA exposure. Only in case of unusual reactions will these 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.

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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:

1. The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
2. The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.
3. 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.
4. 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).
5. AEs will be collected from the start of the product application and until 5 days

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following last administration of the study product.

6. 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.
7. 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.

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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

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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 (see section 8.3)
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 (Rafaela Ross):

Tel: PPD [REDACTED]

E-mail: PPD [REDACTED]

Pharmacovigilance (Brazil) Fax Number: PPD [REDACTED]

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.

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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

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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.

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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.

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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 (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 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 code the 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

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9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Approximately 40 healthy subjects will be screened to randomise at least 30 subjects to ensure at least 25 evaluable subjects complete the entire study. This sample size is standard in clinical testing practices and is consistent with the ANVISA guidelines (ANVISA, 2012).

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 study product. 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 phototoxicity and photosensitisation 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.

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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 across time points. 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 the 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.

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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) 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 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

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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.

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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

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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.

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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	Square Centimeter
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

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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
J	Joules
LSLV	Last Subject Last Visit
m ²	Square meter
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

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SIGNATURE PAGE

Clinical Protocol 207587

Date	Signed By
23-Mar-2017 11:04:34	PPD
Justification	Approved

Date	Signed By
23-Mar-2017 12:21:29	PPD
Justification	Clinical Operations Approval

Date	Signed By
23-Mar-2017 13:44:28	PPD
Justification	Biostatistics Approval

Date	Signed By
24-Mar-2017 07:31:50	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	