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CLINICAL PROTOCOL

A Clinical Study to Assess the Local Cutaneous and Ocular Tolerance of a Developmental Cosmetic Facial Serum Formulation in Healthy Females with Sensitive Skin

Protocol Number:	209442
Compound/Product Name:	Developmental Cosmetic Facial Serum
United States (US) Investigational New Drug (IND) Number:	Not Applicable
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Other Regulatory Agency Identified Number:	Not Applicable
Phase:	Not Applicable

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Research & Development Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	GlaxoSmithKline Consumer Healthcare (GSK CH) St George's Avenue, Weybridge, Surrey, KT13 0DE, UK

Document History

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

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

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

Background and Rationale

A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use. Thus, as a general requirement, the safety of a developmental formulation should be confirmed before it is marketed.

Acceptability 'in-use' studies are useful clinical models with which to determine the irritation potential (local tolerance) of a cosmetic formulation to provide confidence the finished product is suitable for general sale.

The objective of this clinical study is to determine the local cutaneous and ocular tolerance of a developmental cosmetic facial serum in healthy females with sensitive facial skin under normal conditions of use.

Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To determine the local cutaneous tolerance profile of the investigational product in healthy females with sensitive facial skin under normal conditions of use.	Change from baseline (prior to any product application) in dermatologist visual assessment scores of signs and symptoms of cutaneous irritation to 21 (+2) days of product use.
Secondary	
To determine the local ocular tolerance profile of the investigational product in healthy females with sensitive facial skin under normal conditions of use.	Change from baseline (prior to any product application) in ophthalmologist visual assessment scores of signs and symptoms of ocular irritation to 21 (+2) days of product use.
To determine the local cutaneous and ocular tolerance of the investigational product from the perspective of the subject in healthy females with sensitive facial skin under normal conditions of use.	Change from baseline in subject self-assessment scores of signs and symptoms of cutaneous and ocular irritation to 1-2 hours after first product application and following 21 (+2) days of use.
Safety	
To evaluate the general safety of two cosmetic facial serums.	Frequency and severity of Adverse Events.

Study Design

This is a randomized, evaluator-blind (dermatologist and ophthalmologist), 2-arm, parallel-group, single-center, non-comparative clinical 'in-use' study to determine the local cutaneous and ocular tolerance of a developmental cosmetic facial serum formulation in healthy female subjects aged 18 to 65 years (inclusive) with clinically evaluated sensitive skin, as determined by a positive response to a Lactic Acid Sting Test (LAST), with minimal signs or symptoms of cutaneous irritation and no signs or symptoms of ocular irritation. A reference product, proven to be suitable for use in a sensitive skin population, is included to enable the study to be conducted in a randomized and blinded manner, rather than as a single-arm or open-label study, to minimize bias and ensure a robust outcome.

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study.

At Visit 1 (screening), subjects who agree to participate in the study by signing the informed consent will be assessed by a qualified dermatologist for baseline clinical assessments of the signs and symptoms of cutaneous irritation and by a qualified ophthalmologist for baseline clinical assessments of the signs and symptoms of ocular irritation. Following these assessments, a LAST will be conducted in the nasolabial region to confirm whether the subject has sensitive skin. Subjects will only be considered eligible to continue in the study if they present a positive response to the LAST. Medical history, Fitzpatrick skin type, prior, current and concomitant medication will also be recorded at this visit. Subjects will be asked to self-assess baseline signs and symptoms of cutaneous and ocular irritation prior to the LAST and any product application.

Subjects will only be considered eligible to continue in the study if they have a dermatologist signs and symptoms cutaneous irritation score of greater than or equal to 0.5 (very slight) for erythema and a score of greater than or equal to 0.5 (very slight) for dryness, a score of 0 (none) or 0.5 (very slight) for scaling and 0 (none) or 0.5 (very slight) for edema. Any subject with a score of 3 (severe) in any cutaneous irritation attribute will exclude the subject from the study, as this does not reflect the target population for the product. Any ophthalmologist signs and symptoms attribute score of greater than 0 (none) will exclude the subject from the study.

For subjects who continue to be eligible to participate in the study, the first application of their assigned product will be at the investigational site, under the supervision of a trained technician. Subjects will be asked to complete further self-assessment questions of the signs and symptoms of cutaneous and ocular irritation they are experiencing, 1-2 hours after first application. Subjects will then be instructed to apply their assigned product at home again the same evening and twice-daily for 21 (+2) days as part of their normal skin care routine. A paper diary will be provided to each subject to record the number of daily applications of product, from first application at site to final application at home. The final application of product will be at home on the morning of the final visit (Visit 2).

At Visit 2 (final visit), the dermatologist and ophthalmologist will conduct final clinical assessments of the signs and symptoms of cutaneous and ocular irritation, respectively. Subjects will also be asked to conduct a final self-assessment of the signs and symptoms of cutaneous and ocular irritation. Subjects will return their completed diary and supplied product and will subsequently be discharged from the study.

Study Products

Subjects will be assigned to 1 of the 2 study products in accordance with the randomization schedule.

The investigational product is a developmental formulation intended to be used as a cosmetic facial serum by adult consumers with sensitive facial skin. The comparator product is a commercially marketed facial serum, also intended to be used by adult consumers with sensitive facial skin.

The instructions for use provided to subjects in this study are consistent with those intended to be communicated to consumers when the product is made freely available for purchase.

Type and Planned Number of Subjects

Healthy female subjects, aged 18 to 65 years with clinically assessed sensitive skin, and no ophthalmological conditions will be enrolled into this study. Female subjects with sensitive skin have been selected as they are the target consumers for the finished product with greater familiarization and habitual use of facial products.

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study. It is deemed that 30 subjects per arm are considered sufficient to assess the primary endpoint: dermatologist assessment of signs and symptoms of cutaneous irritation total score. The sample size for this study has been selected based on clinical considerations and to ensure compliance with the Agência Nacional de Vigilância Sanitária (ANVISA) Guideline for the Safety Evaluation of Cosmetic Products (ANVISA, 2012) which mandates an investigational product be tested on at least 30 subjects.

Schedule of Activities

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

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening/Baseline	Final Visit
	Visit 1 Day 1	Visit 2 Day 21 (+ 2)
Informed Consent (date and time captured)	X	
Demographics	X	
Medical History	X	
Medications Review	X	X
Inclusion/Exclusion Criteria	X	
Fitzpatrick Skin Type Assessment	X	
Subject Self-Assessment	X [a]	X
Clinical Assessment by Dermatologist	X	X
Clinical Assessment by Ophthalmologist	X	X
Lactic Acid Sting Test (LAST)	X	
Subject Eligibility for Enrollment	X	
Randomization	X	
Product and Diary Dispensing	X	
Supervised Product Application [b]	X	
Adverse Events (AEs) Review [c]	X	X
Product and Diary Return	X	X
Study Conclusion/Subject Exit from Study		X

a. Subject self-assessment on Visit 1 will occur twice; once prior to the LAST and product application and once 1-2 hours after first supervised product application.
b. Supervised product application should not occur until at least 30 minutes following the LAST.
c. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by completing the Informed Consent Form (ICF).

Footnotes:
The diary will be used to maintain and record compliance and to capture subject comments.
The diary will be reviewed by the Investigator or their designee at final visit.
First product application will be conducted at the site under the supervision of the investigator or their designee.

2 INTRODUCTION

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

A cosmetic product on the market must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking into account, in particular, the product's presentation, its labelling, and any instructions. (Cosmetics Europe, 2004)

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

Clinical studies to evaluate the irritation and sensitization potential of a product must consider a number of variables including the components used in the formulation, ingredient concentration, absorption, amount applied, skin condition, application directions and frequency, as well as the cumulative effect (Dooms-Goossens, 1993). The most common form of intolerance to cosmetics is characterized by irritation, burning sensation, redness, pruritus and erythema at the application site (Lumelsky *et al*., 2001).

Skin is characterized as ‘sensitive’ if it commonly presents a non-inflammatory response to application of topical products, as realized through subjective sensations such as stinging, burning and itching, often without any visible signs or symptoms. The absence of visible signs or symptoms of irritation presents a challenge in the objective diagnosis of sensitive skin. However, several substances are known to trigger an irritant response in people with sensitive skin, such as benzoic acid, cinnamic acid, non-ionic emulsifiers, sodium lauryl sulfate, lactic acid, propylene glycol, urea and sorbic acid (De Groot *et al*., 2010; Lundov *et al*., 2010). Therefore, a routine test to clinically diagnose sensitive skin is a lactic acid sting test (LAST), whereby an aqueous solution of lactic acid is applied to the nasolabial fold to attempt to trigger a sensorial response, often alongside a placebo such as saline. The stinging sensation to the irritant may be measured in a binary way (i.e. presence or absence) or with a magnitude scale (Farage *et al*., 2006). The LAST procedure allows for the clinical diagnosis and enrollment of subjects with sensitive skin into clinical trials to enable the local tolerance of an investigational product to be evaluate in this population.

2.1 Study Rationale

GSK CH has developed a new cosmetic facial serum intended to be suitable for use by adult consumers with sensitive facial skin. Clinical data are required to demonstrate that the developmental formulation has a favorable local tolerance profile in the target population under normal conditions of use, prior to commercialization.

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

2.2 Background

A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use. Thus, as a general requirement, the safety of a developmental formulation should be confirmed before it is marketed.

Acceptability 'in-use' studies are useful clinical models with which to determine the irritation potential (local tolerance) of a cosmetic formulation to provide confidence an investigational product is suitable for general sale in the target population. Such studies aim to provide a clinical and subjective characterisation of the signs and symptoms of irritation following regular application of a topical product and often involve dermatologist and ophthalmologist oversight.

The investigational product is a developmental formulation intended to be used as a cosmetic serum by healthy adult consumers with sensitive facial skin. The formulation has been designed to provide topical moisturization while minimizing the quantity of known irritants and allergens.

The objective of this clinical study is to determine the local cutaneous and ocular tolerance of a developmental facial serum product in healthy females with clinically confirmed sensitive facial skin under normal conditions of use.

2.3 Mechanism of Action/Indication

Cosmetic products are preparations applied to the body, especially the face, intended to be applied for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions. The investigational product is a cosmetic facial serum that is intended to be applied topically by healthy female subjects with sensitive skin, immediately after cleansing.

Serum is a skincare product applied directly to the skin after cleansing but before moisturizing with the intent of delivering ingredients directly onto the skin.

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

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To determine the local cutaneous tolerance profile of the investigational product in healthy females with sensitive facial skin under normal conditions of use.	Change from baseline (prior to any product application) in dermatologist visual assessment scores of signs and symptoms of cutaneous irritation to 21 (+2) days of product use.
Secondary	
To determine the local ocular tolerance profile of the investigational product in healthy females with sensitive facial skin under normal conditions of use.	Change from baseline (prior to any product application) in ophthalmologist visual assessment scores of signs and symptoms of ocular irritation to 21 (+2) days of product use.
To determine the local cutaneous and ocular tolerance of the investigational	Change from baseline in subject self-assessment scores of signs and symptoms

product from the perspective of the subject in healthy females with sensitive facial skin under normal conditions of use.	of cutaneous and ocular irritation to 1-2 hours after first product application and following 21 (+2) days of use.
Safety	
To evaluate the general safety of two cosmetic facial serums.	Frequency and severity of Adverse Events.

The objective of this clinical study is to determine the local tolerance profile of a developmental facial serum product in healthy females with sensitive facial skin under normal conditions of use, following 21 (+2) days twice daily application.

This study will be considered a success if at least 90% of completed subjects do not have a significant increase (i.e. a unit increase score of 1 in the total score) from baseline in dermatologist assessed signs and symptoms of cutaneous irritation following 21 (+2) days of investigational product use.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, evaluator-blind (dermatologist and ophthalmologist), 2-arm, parallel-group, single-center, non-comparative clinical 'in-use' study to determine the local cutaneous and ocular tolerance of a developmental cosmetic facial serum formulation in healthy female subjects aged 18 to 65 years (inclusive) with clinically evaluated sensitive skin, as determined by a positive response to a LAST, with minimal signs or symptoms of cutaneous irritation and no signs or symptoms of ocular irritation. A reference product, proven to be suitable for use in a sensitive skin population is included to enable the study to be conducted in a randomized and blinded manner, rather than as a single-arm or open-label study, to minimize bias and ensure a robust outcome.

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study.

At Visit 1 (screening), subjects who agree to participate in the study by signing the informed consent will be assessed by a qualified dermatologist for baseline clinical assessments of the signs and symptoms of cutaneous irritation and by a qualified ophthalmologist for baseline clinical assessments of the signs and symptoms of ocular irritation. Following these assessments, a LAST will be conducted in the nasolabial region to confirm whether the subject has sensitive skin. Subjects will only be considered eligible to continue in the study if they present a positive response to the LAST. Medical history, Fitzpatrick skin type assessment, prior, current and concomitant medication will also be recorded at this visit. Subjects will be asked to self-assess baseline signs and symptoms of cutaneous and ocular irritation prior to the LAST and any product application.

Subjects will only be considered eligible to continue in the study if they have a dermatologist signs and symptoms cutaneous irritation score of greater than or equal to 0.5 (very slight) for erythema and a score of greater than or equal to 0.5 (very slight) for dryness, a score of 0 (none) or 0.5 (very slight) for scaling and 0 (none) or 0.5 (very slight) for edema. Any subject with a score of 3 (severe) in any cutaneous irritation attribute will exclude the subject from the study, as this does not reflect the target population for the product. Any ophthalmologist signs and symptoms attribute score of greater than 0 (none) will exclude the subject from the study.

For subjects who continue to be eligible to participate in the study, the first application of their assigned product will be at the investigational site, under the supervision of a trained technician.

Subjects will be asked to answer further self-assessment questions of the signs and symptoms of cutaneous and ocular irritation they are experiencing, 1-2 hours after first application. Subjects will then be instructed to apply their assigned product at home again the same evening and twice-daily for 21 (+2) days as part of their normal skin care routine. A paper diary will be provided to each subject to record the number of daily applications of product, from first application at site to final application at home. The final application of product will be at home on the morning of the final visit (Visit 2).

At Visit 2 (final visit), the dermatologist and ophthalmologist will conduct final clinical assessments of the signs and symptoms of cutaneous and ocular irritation, respectively. Subjects will also be asked to conduct a final self-assessment of the signs and symptoms of cutaneous and ocular irritation. Subjects will return their completed diary and supplied product and will subsequently be discharged from the study.

4.2 Rationale for Study Design

Acceptability 'in use' studies aim to determine the irritation potential of topical products in the target population under the intended conditions of use, prior to commercialization.

The investigational product being evaluated is a developmental formulation intended to be used as a cosmetic facial serum by adult consumers with sensitive facial skin. The formulation has been designed to provide topical moisturization while minimizing the quantity of known irritants and allergens. A reference product, proven to be suitable for use in a sensitive skin population is included to enable the study to be conducted in a randomized and blinded manner, rather than as a single-arm or open-label study, to minimize bias and ensure a robust outcome.

Subjects will only be considered eligible to continue in the study if they have a dermatologist signs and symptoms cutaneous irritation score of greater than or to equal 0.5 (very slight) for erythema and a score of greater than or equal to 0.5 (very slight) for dryness, as this is representative of the target consumer for the finished product. Subjects presenting a score greater than 0.5 (very mild) for edema and scaling are excluded from the study as they do not represent the target population for the product.

Any subject with a score of 3 (severe) in any cutaneous irritation attribute will exclude the subject from the study, as this does not reflect the target population for the product.

Per ANVISA guidelines, acceptability studies are indicated to be conducted for a 3-week period of use, taking into account the normal conditions of use.

No formal statistical comparison between the reference product and investigational product is required in order to evaluate the local tolerance of the investigational product.

4.3 Justification for Dose

The first administration will be supervised by a trained technician when the subjects are at the site at for Screening/Visit 1.

Subjects will be instructed to use the product twice-daily (morning and evening) as part of their normal facial care regimen, post cleansing and prior to moisturization (if appropriate), in their usual manner. The instructions for use provided to subjects in this study are consistent with those intended to be communicated to consumer when the product is made freely available for purchase: "Apply twice daily to freshly cleansed skin in place of your current serum and before your moisturizer".

Subjects who already use a facial serum will be instructed to replace their current serum with the product they have been assigned to use for the duration of the study.

4.4 End of Study Definition

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

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Healthy female subjects, aged 18 to 65 years with clinically assessed sensitive skin and no ophthalmological conditions will be enrolled into this study. Female subjects with sensitive skin have been selected as they are the target consumers for the finished product with greater familiarization and habitual use of facial products.

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study. It is deemed that 30 subjects per arm are considered sufficient to assess the primary endpoint: dermatologist assessment of signs and symptoms of cutaneous irritation total score. The sample size for this study has been selected based on clinical considerations and to ensure compliance with the ANVISA Guideline for the Safety Evaluation of Cosmetic Products (ANVISA, 2012) which mandates an investigational product be tested on at least 30 subjects

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

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

Site personnel performing the subject inclusion and exclusion criteria and subject eligibility should be the investigator, a suitable Medically Qualified Person (MQP) or designee as appropriate. This should be documented in the site logs.

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is female who, at the time of screening, is between the ages of 18 and 65 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, the application schedule, the lifestyle guidelines, and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee (if the investigator is not suitably qualified), no clinically significant/relevant abnormalities in medical history or upon dermatologist and ophthalmologist examination, or condition, that would impact the subject's safety,

wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.

5. A subject with sensitive facial skin, defined as a positive response to a lactic acid sting test in the nasolabial area.
6. A subject with a dermatologist signs and symptoms of cutaneous irritation score of greater than or equal to 0.5 (very slight) for erythema.
7. A subject with a dermatologist signs and symptoms of cutaneous irritation score of greater than or equal to 0.5 (very slight) for dryness.
8. A subject with a dermatologist signs and symptoms of cutaneous irritation score of 0 (none) or 0.5 (very sight) for scaling.
9. A subject with a dermatologist signs and symptoms of cutaneous irritation score of 0 (none) or 0.5 (very sight) for edema.
10. A subject with an ophthalmologist total signs and symptoms of ocular irritation score of 0 (none).

5.3 Exclusion Criteria

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

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject who is pregnant (self-reported).
5. A subject who is breastfeeding.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
8. A subject unwilling or unable to comply with the Lifestyle Considerations required by this study, as described in this protocol.
9. A subject with current or recent (within last 6 months before the start of the study) history of atopic lesions and/or eczema
10. A subject with a history of allergic reactions to topical-use products, cosmetics or medications or their ingredients.

11. A subject with any history of significant diseases or medical conditions known to alter skin or eye 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.
12. A subject presenting open sores, pimples, or cysts at the application site (face).
13. A subject with an active dermatosis (local or disseminated) that might interfere with the results of the study.
14. A subject with a dermatologist signs and symptoms of cutaneous irritation score of 3 (severe) for erythema, edema, scaling or dryness.
15. A subject considered immune-compromised.
16. A subject currently using any medication which in the opinion of the investigator, may affect the evaluation of the investigational product, or place the subject at undue risk
17. A subject who has used any of the following topical or systemic medications up to two weeks before the screening visit: immuno-suppressants, antihistamines, non-steroidal anti-inflammatory drugs (NSAIDS), and/or corticosteroids.
18. A subject who has used oral or topical treatment with vitamin A acid and/or its derivatives up to 1 month before the screening visit.
19. A subject who has been vaccinated up to 1 month before the screening visit or who are intending to receive a vaccination during their participation in the study.
20. A subject with a recent history (within the last 5 years) of alcohol or other substance abuse.
21. A subject with any skin marks on the face that might interfere with the evaluation of possible skin reactions (e.g. pigmentation disorders, vascular malformations, scars, tattoos, excessive hair, numerous freckles).
22. Subjects with corneal ulcers, keratoconus, blepharitis, meibomitis, pterygium, chemosis, moderately or severe hyperemia or other active ocular diseases.
23. A subject who has previously been enrolled in this study.

5.4 Randomization Criteria

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

5.5 Lifestyle Considerations

Following consent to participate in the study by completing the ICF, subjects may be asked to remove any leave on cosmetics (including make-up) prior to the visit assessments.

During the entire study (Screening – Last Subjects Last Visit (LSLV)) the following must be avoided:

- Making a change to current facial care habits and practices, including the addition or removal of any new facial topical product to their current regimen and/or switching brands of facial topical products, other than as defined in this protocol.
- Introduction of new home care products which may come into contact with the skin, including laundry detergent, shower gel, shampoo, bath soap.
- Intentional exposure to artificial ultraviolet (UV) light or sunbathing.

- Undergoing any non-invasive, minimally-invasive or invasive cosmetic or surgical procedures on the face, e.g. waxing, bleaching etc.

Visit 2:

- Prior to the final visit (Visit 2), subjects must not apply any topical products (including leave-on cosmetics) to their face other than their assigned product.
- Subjects must cleanse their face with either tap water or their current cleanser in the morning prior to site visit and apply their assigned product for the final use, 2-4 hours prior to the visit.
- Subjects must refrain from drinking caffeinated drinks (e.g. coffee, tea, cola etc.) prior to Visit 2.

5.6 Screen Failures

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

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

5.7 Sponsor's Qualified Medical Personnel

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

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

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

5.8 Clinical Assessor Qualifications

All clinical assessments will be made by a single qualified dermatologist and a single qualified ophthalmologist for all subjects throughout the study. Each assessor will visually assess subjects for eligibility to continue in the trial and at the end of the 21 (+2) day product use period.

The intensity of any visual signs of dermal irritation will be recorded according to the grade of the reactions in the Dermatological Evaluation (Safety and Other Assessments). The dermatologist is responsible for grading the level of cutaneous irritation and their opinion on the correct classification of the irritation scores is final. The same dermatologist will be used to evaluate all subjects in the study.

The intensity of any visual signs of ocular irritation will be recorded according to the grade of the reactions in the Ophthalmological Evaluation (Safety and Other Assessments). The

ophthalmologist is responsible for grading the reactions, their opinion on the classification of the ocular irritation scores is final. The same ophthalmologist will be used to evaluate all subjects in the study.

Any observed cutaneous or ocular response that can be denoted according to the grade of the reactions will not be considered an adverse event. Only in the case of unusual reactions, in the opinion of the clinical expert, will these reactions and the consequences observed upon evaluation be documented as AEs.

6 INVESTIGATIONAL/STUDY PRODUCTS

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Investigational Product	Reference Product
Product Name	Developmental Serum	Physiogel Calming Relief Anti-Redness Serum (Korean market place product)
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]
Product Format	30 ml Bottle with piston pump	
Dispensing Details	A kit will be dispensed to each subject containing 2 bottles	
Application Quantity	To be used as per normal home use application	
Route of Administration	Topical dermal (facial) application	
Application Instructions	Apply twice daily to freshly cleansed skin in place of your current serum and before your moisturizer	
Return Requirements	All used/unused samples to be returned to the study site	

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

Other items to be supplied by the clinical investigational site:

- Aqueous Lactic Acid solution (10%) – For LAST
- Saline solution (0.9 Molar) – For LAST
- Cotton Buds - For LAST

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

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

6.1.1 Dosage Form and Packaging

Both the developmental serum and the comparator serum will be supplied to the clinical site as labelled packaged bottles for dispensing by the site staff. The commercial bottles will have the commercial labels removed.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, container number, directions for use and storage requirements.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

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

6.1.2 Preparation and Dispensing

Both the investigational product and the reference product will be dispensed by qualified unblinded site personnel according to the randomization schedule. These staff members will not be involved in any safety or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to. An additional site member of site staff, should ensure the dispensing procedures are completed accurately.

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

6.2 Administration

The first application of product will be under supervision at the study site at Visit 1 (Day1) following baseline subject self-assessment questions, dermatologist and ophthalmologist assessments and the LAST.

Subjects will be instructed to self-administer their assigned product per the usage instructions.

6.2.1 Dosing Errors

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

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Dosing errors occurring to a study subject are to be captured in the Case Report Form (CRF). In the event of a medication dosing error, the sponsor should be notified immediately.

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

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

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

6.3 Investigational/Study Product Storage

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

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

Site staff will instruct subjects on the proper storage requirements for all take-home products.

6.4 Investigational/Study Product Accountability

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

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

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

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

Subjects should return all products to the study site at the end of the study (LSLV) or before if a subject withdrawals/is withdrawn.

6.4.1 Destruction of Investigational/Study Product Supplies

At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the two study arms using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the site. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visit.

Returned study products should not be re-dispensed to any subject.

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

This study is described as examiner-blind (the clinical examiners (dermatologist, ophthalmologist) will be blinded to the product received). The study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation.

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

Subjects will be instructed not to remove study products from the opaque bags outside of the dispensing room, while at the study site. Dispensing staff will not be involved in any safety assessment procedures during the study.

6.6 Breaking the Blind

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

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

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

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

6.7 Subject Compliance

Study products will be administered under the supervision of investigator site personnel for the first application.

A paper diary will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety must be reviewed by the investigator (or suitably qualified designee) with the subjects, and transcribed to the CRF as appropriate.

The number of any missed or additional applications will be captured as protocol deviations and transcribed from the diary into the CRF. Subjects will be re-instructed in the correct usage requirements and diary completion as needed.

6.8 Concomitant Medication/Treatment(s)

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

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF.

7.2 Lost to Follow up

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

Final safety assessments should be carried out wherever possible when the subject returns to the study site, which will include the following:

- Dermatologist assessment of cutaneous irritation
- Ophthalmologist assessment of ocular irritation
- Subject self-assessment questions

Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and request that the subject return for a final visit, and follow-up with the subject regarding any unresolved adverse events (AEs), and follow-up assessments (dermatologist and ophthalmologist assessments and subject self-assessment questions).

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

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

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

8 STUDY PROCEDURES

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

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

8.1 Visit 1 (Day 1) Screening/Baseline

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

The following procedures will be completed:

8.1.1 Informed Consent

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

the study. Two copies of the informed consent form (ICF) signature page will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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

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

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

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

e-Consent is a tool that assists in the consent process by using multimedia components delivered by an electronic system (e.g. iPad/tablet). The multimedia components consist of video, audio, knowledge review, dictionary and electronic signature.

The site staff can use the system to consent the subject with the benefit of helping the subject understand the research they are taking part in and to control the consent process.

The system will allow for a copy of the consent to be printed and given to the subject and for consent documents to be retained by the site in PDF format.

A GSK CH approved vendor will be used to provide the system and training and a help desk will be provided as needed.

If the country and/or site does not have approval to use the e-Consent system, or the subject does not want to use the e-Consent system, then the conventional paper process will be followed. It is possible to use the e-Consent system to educate the subject while using paper to obtain signatures.

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

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race. Fitzpatrick skin type assessment (Appendix 2 - Fitzpatrick Skin Type Grading) will also be conducted by a trained evaluator and recorded on the CRF.

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

8.1.3 Medical History and Prior Medication/Treatment

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

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

8.1.4 Inclusion/Exclusion Criteria

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

8.1.5 Subject self-assessment

Subjects will be asked to answer the self-assessment questions as per section Safety and Other Assessments prior to the LAST, randomization and any product application (baseline).

The self-assessment questions will be asked again 1-2 hours following first supervised product use. Subject responses will be directly entered into the CRF by site staff.

8.1.6 Dermatologist Assessment

A qualified dermatologist will visually assess the subject at Visit 1 (baseline) prior to randomization to determine their eligibility to continue in the study. This will ensure the subject is free of any preexisting dermatological pathology prior to using the study products (Edward, 2008). For inclusion into the study each subject should have a dermatologist signs and symptoms cutaneous irritation score of equal to or greater than 0.5 (very slight) for erythema and a score of greater than or equal to 0.5 (very slight) for dryness, a score of 0 (none) or 0.5 (very slight) for scaling and 0 (none) or 0.5 (very slight) for edema. Any attribute score of 3 (severe) will exclude the subject from the study as this is not the intended population for the product.

The intensity of any visual signs of dermal irritation will be recorded according to the grade of the reactions according to the Dermatological Evaluation (Safety and Other Assessments). The dermatologist is responsible for grading the level of cutaneous irritation and their opinion on the correct classification of the irritation scores is final. Scores will be directly entered into the CRF.

Any observed cutaneous response that can be denoted according to the grade of the reactions will not be considered an adverse event. Only in the case of unusual reactions will these reactions and the consequences observed upon evaluation be documented as AE's.

Any subject with a score of 3 (severe) in any attribute will exclude the subject from the study, as this does not reflect the target population for the product.

8.1.7 Ophthalmologist Assessment

A qualified ophthalmologist will assess the subject at Visit 1 (baseline) prior to randomization to determine their eligibility to continue in the study. This will ensure the subject is free of any preexisting ophthalmological pathology prior to using the study products. (Edward, 2008). For inclusion into the study each subject should have a total ocular irritation score of 0 (none).

The intensity of any visual signs of ocular irritation will be recorded according to the grade of the reactions according to the Ophthalmological Evaluation (Safety and Other Assessments). The ophthalmologist is responsible for grading the reactions, their opinion on the classification of the ocular irritation scores is final. Scores will be directly entered into the CRF.

Any observed ocular response that can be denoted according to the grade of the reactions will not be considered an adverse event. Only in the case of unusual reactions will these reactions and the consequences observed upon evaluation be documented as AE's.

8.1.8 Lactic Acid Stinging Test (LAST)

Subjects will be instructed to wash their face with room-temperature tap water and to pat dry with paper towels provided by the investigational site. This will ensure a clean surface with which to conduct the LAST. Approximately 30 minutes after washing, a trained technician will apply an aqueous solution of 10% lactic acid to one nasolabial fold and a saline solution (0.9 Molar) to the other nasolabial fold in the following manner:

The test substances (10% lactic acid or 0.9M NaCl) will be applied concurrently to either the right or the left nasolabial fold and corresponding infraorbital cheek of the subject, according to a randomization scheme provided by the Sponsor, using a cotton-tipped swab. After dipping the swab into each of the test substances, each will be applied to the upper end of the nasolabial fold, about 3 cm under the inner corner of the eye, and moved in a rotating motion of the swab across the infraorbital part of the cheek to about 3 cm under the outer corner of the eye and back along the fold of the nostrils and back, and along the nasolabial fold to the side of the corner of the mouth and back, ending at the point where the application started. The complete movement will be repeated once more. The applied test substances should not extend beyond this area. For each application a fresh swab will be used.

The Sponsor will provide a randomization schedule for the left and right side of the face to have a balanced randomization of the two solutions over the screened subjects.

Subjects will be asked to report any sensations of discomfort 2-3 minutes and 5-6 minutes after application on a 4-point scale (Christensen *et al*., 1995; Table 8-1). Scores will be entered into the CRF by a technician. The test will be suspended after 6 minutes if no local sensation is reported, or immediately upon any reported score of 3.

At this time or after 6 minutes, the subject will be instructed to remove the solution by thoroughly washing with room-temperature tap water and drying their face with a paper towel.

The sum of the 2-3 and 5-6-minute subject self-assessment scores will be calculated in the CRF for the lactic acid and saline-treated nasolabial folds. Subjects who report a total score greater than or equal to 2 in the difference between lactic acid and saline will be considered to have had a positive response to the LAST. Otherwise, subjects will be considered to have had a negative response to the LAST. Only subjects with a positive response to the LAST will be enrolled into the study.

Table 8-1 Lactic Acid Sting Test Score

Score	Description
0	No discomfort/sensation
1	Mild discomfort/stinging
2	Moderate discomfort/stinging
3	Severe discomfort/stinging

Sensations of discomfort may or may not appear. In instances where sensations of discomfort do appear, they may go unnoticed for 1-2 minutes to start but should intensify up to 5-6 minutes. The test will be suspended after 6 minutes if no local sensation is reported, or immediately upon any subject reported score of 3. At this time, or after 6 minutes, the subject will be instructed to remove the solution by thoroughly washing with water and drying their face with a paper towel.

Any observed response that can be denoted according to the score of the reactions (per Table 8-1) will not be considered an adverse event. Only in the case of unusual reactions, in the

opinion of the qualified dermatologist, will these reactions and the consequences observed upon evaluation be documented as AE's.

The subject will not be informed which nasolabial fold received the lactic acid solution and which nasolabial fold received saline solution.

8.1.9 Subject Eligibility

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

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

8.1.10 Randomization

Each eligible subject will be randomized to one of the two serum products under investigation and given instructions on how to apply the product.

8.1.11 Supervised Product Application

Sufficient product will be provided to last the complete study period. Subjects will use the product at home, twice a day during the study period of 21 (+ 2) days, including the morning of the final visit and will be instructed to contact the study site if they have any reactions.

Subjects will be dispensed a paper diary alongside their assigned product to be completed at home to record product use.

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

8.2 Visit 2/Day 21 (Final Visit)

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

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

8.2.1 Dermatologist Assessment

A final assessment by the same dermatologist, will be completed at the end of the 21 (+2) day product use period (Visit 2).

The intensity of any visual signs of dermal irritation will be recorded according to the grade of the reactions according to the Dermatological Evaluation (Safety and Other Assessments). The dermatologist is responsible for grading the level of cutaneous irritation and their opinion on the correct classification of the irritation scores is final.

Any observed cutaneous response that can be denoted according to the grade of the reactions will not be considered an adverse event. Only in the case of unusual reactions, in the opinion of the qualified dermatologist, will these reactions and the consequences observed upon evaluation be documented as AE's.

8.2.2 Ophthalmologist Assessment

A final assessment by the same ophthalmologist, will be completed at the end of the 21 (+2) day product use period (Visit 2).

The intensity of any visual signs of ocular irritation will be recorded according to the grade of the reactions according to the Objective Ophthalmological Evaluation (Safety and Other Assessments). The ophthalmologist is responsible for grading the reactions, their opinion on the classification of the ocular irritation scores is final.

Any observed ocular response that can be denoted according to the grade of the reactions will not be considered an adverse event. Only in the case of unusual reactions, in the opinion of the qualified ophthalmologist, will these reactions and the consequences observed upon evaluation be documented as AE's.

8.2.3 Subject self-assessment

Subjects will be asked to answer the self-assessment questions as per section Safety and Other Assessments at the end of the 21 (+2) day product use period. Subject responses will be directly entered into the CRF by site staff.

8.3 Diary Review

The diary will be reviewed by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in Adverse Event and Serious Adverse Events.

Any additional comments relating to medications/treatments provided in the diary will be reviewed by the investigator or medically qualified designee with the subject and entered into the CRF as appropriate.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log of the CRF.

8.4 Study Conclusion

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

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

8.5 Follow-up Visit

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

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

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

9.2 Safety and Other Assessments

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

9.2.1 Dermatologist Assessment of Signs and Symptoms of Cutaneous Irritation

A qualified dermatologist will visually assess the signs and symptoms of cutaneous irritation based on erythema, dryness, scaling and edema. The following grades and their respective numerical equivalent scores will be used to record the response observed at the time of clinical examination.

Table 9-1 Dermatological Evaluation

Attribute	Description (Score)				
Erythema	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Dryness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Scaling	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Edema	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

Dermal responses that can be accurately described by a dermal response score will not be considered adverse events. Only in the case of unusual reactions in the opinion of the dermatologist will these reactions and the consequences observed upon evaluation be documented as AE's.

Any subject with a score of 3 (severe) in any attribute at the Screening visit (Visit 1) will exclude the subject from the study, as this does not reflect the target population for the product.

9.2.2 Ophthalmologist Assessment of Signs and Symptoms of Ocular Irritation

A qualified ophthalmologist will visually assess the signs and symptoms of ocular irritation. The following grades and their respective numerical equivalent scores will be used to record the response observed at the time of examination.

Table 9-2 Ophthalmological Evaluation

Attribute	Description (Score)				
Eczema of the eyelid	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Conjunctivitis	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Follicles	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Chemosis conjunctivae	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

Ocular responses that can be accurately described by an ocular irritation score will not be considered adverse events. Only in the case of unusual reactions in the opinion of the ophthalmologist will these reactions and the consequences observed upon evaluation be documented as AE's.

9.2.3 Subject Self-Assessment of Signs and Symptoms of Cutaneous and Ocular Irritation

Subjects will be instructed to self-assess any sensations of cutaneous or ocular discomfort that they are currently experiencing per the below scales.

Table 9-3 Subject Self-Assessment Scale for Signs and Symptoms of Cutaneous Irritation

Attribute		Description (Score)			
Redness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Dryness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Stinging/Burning	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Itching	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Tightness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

Table 9-4 Subject Self-Assessment Scale for Signs and Symptoms of Ocular Irritation

Attribute		Description (Score)			
Redness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Dryness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Stinging/Burning	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Itching	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

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

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

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Any observed response to the LAST that can be denoted according to the score of the reactions (per Table 8-1) will not be considered an adverse event. Only in the case of unusual reactions, in the opinion of the qualified dermatologist, will these reactions and the consequences observed upon evaluation be documented as AE's.

10.2 Definition of a Serious Adverse Event (SAE)

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

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

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

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

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

10.4 Reporting Procedures

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

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

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

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

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

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

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

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

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

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

investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

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

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

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

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

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

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

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

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

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

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

10.6 Follow-up of Adverse Events

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

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

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

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

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

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

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

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

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

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

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

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

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

10.8.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box (PPD) within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox (PPD). Original pregnancy information forms will be retained in the investigator study master file.

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

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

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

11 DATA MANAGEMENT

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

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

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

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, dispensing records, subject files and records, etc.) which contain the source of data recorded in the CRF should be specified.

The CRF can be used as a source document at the discretion of data management.

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

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

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

11.2.1 Data Queries

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

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

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

11.3 Processing Patient Reported Outcomes

Paper based patient reported outcome (PRO) data may be collected from a diary, questionnaires, or other specified document, etc. and entered into the data management system (DMS).

Electronic Patient reported outcome (ePRO) data may be collected using electronic devices and transferred electronically to GSKCH or third-party DM vendor.

All PRO source data should be reviewed by the Study Staff and the Study Monitor in order to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or GSK CH as required.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO that will be forwarded to GSK CH or third-party Vendor.

In this study subjects will be provided with a diary card to complete during the home use period, following first supervised product use and diary completion. Subject self-assessment responses will be collected directly in the CRF.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study. It is deemed that 30 subjects per arm are considered sufficient to assess the primary endpoint of the dermatologist assessment of signs and symptoms of cutaneous irritation total score. The sample size for this study has been selected based on clinical considerations and to ensure compliance with the ANVISA Guideline for the Safety Evaluation of Cosmetic Products which mandates an investigational product be tested on at least 30 subjects.

12.2 Statistical Methods and Analytical Plan

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

12.2.1 Definition of Analysis Populations

The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject actually received.

All assessments of safety will be based on the safety population.

12.2.2 Exclusion of Data from Analysis

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

12.2.3 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 for the safety population.

12.2.4 Study Drug/Product Compliance

Compliance to the study product use will be tabulated and summarized for the safety population.

12.2.5 Prior and Concomitant Medications

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

12.2.6 Primary Analysis(es)

The primary endpoint will be the change from baseline (prior to any product application) in dermatologist signs and symptoms of cutaneous irritation total score following 21 (+2) days of product use. The primary analysis will be performed using the Safety population.

The dermatologist assessment of signs and symptoms of cutaneous irritation total score will be calculated as the sum of the individual dermal response attributes (erythema, dryness, scaling, and edema). The change from baseline in the total score will be summarised by number and percentage of subjects by visit for each treatment group. No formal statistical inference will be performed.

In addition, the individual attribute responses and the total score will be listed for each subject by visit and by treatment group.

12.2.7 Secondary Analysis(es)

The key secondary endpoint will be the change from baseline (prior to any product application) in the ophthalmologist signs and symptoms of ocular irritation total score following 21 (+2) days of product use.

The ophthalmologist assessment of signs and symptoms of ocular irritation total score will be calculated as the sum of the individual ocular response scores (eczema of the eyelid, conjunctivitis, follicles, chemosis conjunctivae). The change from baseline in the total score will be summarised by number and percentage of subjects by visit for each treatment group. No formal statistical inference will be performed.

In addition, the individual attribute responses and the total score will be listed for each subject by visit and by treatment group.

Further secondary endpoints are change from baseline (prior to any product application) in the total subject self-assessment scores for signs and symptoms of cutaneous irritation and ocular irritation at 1-2 hours and 21 (+2) days of product use.

All secondary analyses will be performed using the Safety population.

12.2.8 Safety Analysis(es)

Adverse events 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 presented for each of the test products.

12.2.9 Other Analysis(es)

No other analyses will be performed for this study.

12.2.10 Handling of Dropouts and Missing Data

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

12.2.11 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

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

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

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

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016)**,** guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

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

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

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

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK CH processes.

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

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

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

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

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

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

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

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of developmental cosmetic facial serum at any time.

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

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

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

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15 APPENDICES

15.1 APPENDIX 1 - ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANVISA	Agência Nacional de Vigilância Sanitária
BDM	Biostatistics and data management
CRF	case report form
CSA	clinical study agreement
DMS	Data Management Services
EC	ethics committee
EC	European Commission
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FSFV	First subject first visit
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRC	internal review committee
IRT	Interactive Response Technology
LAST	Lactic acid sting test
LSLV	last subject last visit
M	Molar
MedDRA	medical Dictionary for Regulatory Activities
MQP	Medically qualified person
N/A	not applicable
NSAID	Non-steroidal anti-inflammatory drug
PI	principal investigator
PI	Personal information
PRO	Patient Reported Outcomes
QC	quality control
RAP	Reporting and analysis plan
SAE	serious adverse event
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
UK	United Kingdom
UV	Ultraviolet

15.2 APPENDIX 2 – FITZPATRICK SKIN TYPE GRADING

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

Table 15-2 FITZPATRICK SKIN TYPE GRADING

Skin Type	Sunburn and Tanning History

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