Clinical Protocol

207782

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Clinical Study to Assess the Cutaneous and Ocular Local Tolerance of Two Cosmetic Facial Cleansers in Healthy Females with Sensitive Skin Under Normal Conditions of Use.
Protocol Number:	207782
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) Rua Hungria, 1240 4º andar, Jardim Europa São Paulo/SP – Brazil, CEP 01455-000 Tel: PPD
Product Name:	Micellar Cleanser Micellar Foaming Cleanser
Development Phase:	N/A

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

Key Protocol Authors:	
PRIMARY CONTACT **Clinical Study Manager:**	PPD, MSc GlaxoSmithKline Consumer Healthcare (GSKCH) St. Georges Avenue, Weybridge, Surrey, KT13 0DE. UK Tel. PPD
PRIMARY CONTACT **Clinical Study Manager:**	PPD Consumer Healthcare (GSKCH) Rua Hungria, 1240 4º andar, Jardim Europa São Paulo/SP – Brazil, CEP 01455-000 Tel: PPD
Biostatistician:	PPD, MSc
Other Protocol Authors:	
Clinical Supplies:	PPD
Data Manager:	PPD
Medical Expert:	PPD, MD, Ph.D

Principal Investigator:	Mariane Martins Mosca - Biologist
Study Site Name & Address:	ALLERGISA Pesquisa Dermato-Cosmética Ltda , Av. Dr. Romeu Tórtima, 452/466 – Barão Geraldo – Campinas – SP – Zipcode: 13084-791
Study Site Telephone Number:	PPD
Ophthalmologist:	Study Ophthalmologist will be assigned according to the site schedule (before Baseline Visit) and documented in the site file.
Dermatologist:	Study Dermatologist will be assigned according to the site schedule (before Baseline Visit) and documented in the site file.

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.

I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/ Agreement:	

Table of Content

PROCESS FOR AMENDING THE PROTOCOL

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

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

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

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

PROTOCOL AMENDMENT PAGE

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

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1 **Protocol Version No.:**	Non-Substantial/Minor ☒ Substantial/ Major ☐	Clarification to Inclusion and Exclusion criteria to be assessed Visit 2 by appropriately qualified members of staff. Removal of duplication of assessment at Visit 3 Clarification to detail: a	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	Schedule of Events Synopsis – Study Design 3.1 Study Design 4.1 Inclusion Criteria 4.2 Exclusion Criteria 6.1.5 Inclusion/Exclusion Criteria (Visit 1) 6.2.1 Inclusion/Exclusion Criteria (Visit 2) Synopsis – Study Design 3.1 Study Design 3.4 Study Design and	Signature: PPD Date: PPD

		combined score of at least 2 for the lactic Acid Stinging test outcome is needed. Additional text to clarify the 4 randomisation strata to be used. Correction to which visit the Subject Self-Assessment Questions will be asked.		Application Amount Justification 6.1.7 Lactic Acid Stinging Test 5.3.1 Randomization 12.5 Appendix 5	
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:

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

SCHEDULE OF EVENTS

Procedures	Visit 1 Screening	Visit 2 Baseline	Visit 3 (21(+ 2) Days)
Informed consent	X		
Demographics	X		
Medical History	X		
Current/Concomitant Medications reviewed	X	X	X
Inclusion and Exclusion criteria	X	X [a]	
Fitzpatrick Skin Type Assessment		X	
Contact Lens Wearer Status Assessment	X		
Skin Type Assessment by Dermatologist (Dry or Normal/Combination)		X	
Clinical Assessment by Dermatologist [b]		X	X
Clinical Assessment by Ophthalmologist [c]		X	X
Clinical Diagnosis of Sensitive Skin Confirmed by Lactic Acid Stinging Test	X		
Subject Self-Assessment Questions		X [d]	X
Subject Eligibility	X		
Continued Eligibility		X	X
Randomization & Stratification		X	
Product Dispensing (including Diary Card and Instructions for Use)		X	
Supervised First Product Application		X	
Return Product and Diary Card and Instructions for Use			X
Adverse Event Assessment [e]	X	X	X
Study Conclusion and Exit			X

NOTE: Visit 2 should be scheduled within 7 days of the Screening visit (Visit 1).

a. Inclusion Criteria **5A**, 5c, 5d and 5e and Exclusion Criteria **7B** and 7f will be assessed at Visit 2.

b. A qualified dermatologist will perform assessments for subject eligibility to participate in the study prior to any product application at Visit 2, in addition to assessments 1-hour (± 20 minutes) post first supervised product application and at Visit 3 following 3 weeks of product home use, using the scoring system detailed in Appendix 3.

c. A qualified ophthalmologist will perform assessments for subject eligibility to participate in the study prior to product application at Visit 2, in addition to assessments 1-hour (± 20 minutes) post first supervised product application and at Visit 3 following 3 weeks of product home use, using the scoring system in Appendix 4.

d. Subject Self-Assessment questions (Appendix 5) will be asked at Visit 2, BEFORE first product application and 1-hour (± 20 minutes) post supervised product application.

e. Adverse events will be captured following the lactic acid stinging test procedure.

PROTOCOL SYNOPSIS FOR STUDY 207782

Brief Summary

As a general requirement, the safety and compatibility of a new formulation should be confirmed before it is commercialised (Guideline for the Safety Evaluation of Cosmetic Products; Agência Nacional de Vigilância Sanitária, ANVISA, 2012).

Acceptability studies seek to prove in real conditions of use the absence of primary and/or accumulated irritation in normal conditions of use (ANVISA, 2012).

The objective of this clinical study is to assess the cutaneous and ocular local tolerance of two cosmetic facial cleansers in healthy females with sensitive skin under normal conditions of use.

Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
Assessment of the cutaneous and ocular tolerance of two cosmetic facial cleansers after 21 (+ 2) days of product use per the intended instructions in healthy female subjects with clinically assessed sensitive skin.	Dermatologist and ophthalmologist visual assessment of cutaneous and ocular irritation after 21 (+ 2) days of test product use.
Secondary	
Assessment of the cutaneous and ocular tolerance of two cosmetic facial cleansers after 21 (+ 2) days of product use per the intended instructions in healthy female subjects with clinically assessed sensitive skin.	Subject self-assessment question responses (redness, dryness, burning, itching and stinging) with regards to product use experience on the face and around the eyes after 21 (+ 2) days of test product use.
To evaluate the general safety of two cosmetic facial cleansers	Frequency and severity of Adverse Events

Study Design

Overall Design
This is an assessor blind (dermatologist and ophthalmologist) clinical in use study to determine the local cutaneous and ocular tolerance of two cosmetic facial cleanser products when used as per the intended instructions for use in a population of healthy female

subjects with clinically assessed sensitive skin.

Subjects who have sensitive skin as classified by a positive reaction to a lactic acid Stinging Test will be asked to use one of two cleansing products as part of their normal skin care routine for 3 weeks.

Both test products are the same formulation but are differentiated by the dispensing pack; to either a micellar cleanser or a foaming cleanser.

Subjects will be instructed to cleanse their face with one of the two test products at home twice-daily, for 21 (+ 2) days, including a supervised first application at the study site (Visit 2) and a final application at home on the morning of the final visit (Visit 3), as per the intended instructions for use.

A qualified dermatologist and a qualified ophthalmologist will assess the baseline cutaneous an ocular irritation of prospective subjects at Visit 2. For a subject to be considered eligible to participate in the study, all dermatologist and ophthalmologist assessment scores must be zero. Further dermatologist and ophthalmologist assessments will be completed 1-hour (± 20 minutes) post supervised first product use and at the final visit (Visit 3) at the end of the 21 (+2) day product use period. The intensity of any visual signs of cutaneous and ocular irritation will be recorded by the dermatologist and ophthalmologist, according to the assessment scales detailed in Appendix 3 and 4.

The dermatologist will also determine each subject's facial skin type as dry, oily or normal/combination skin. Any subject classified as having oily skin will not be considered eligible for participation in the study as they do not represent the target population for the product.

Subjects will be asked to complete self-assessment questions at Visit 2 prior to any study product use. In addition, randomized subjects will be asked to complete the self-assessment questions 1 hour (± 20 minutes) post supervised first product use and at the end of the 21 (+2) day product use period.

The objective of this clinical study is to assess the cutaneous and ocular local tolerance of two cosmetic facial cleansers in healthy females with sensitive skin under normal conditions of use.

Visit 1 – Screening Visit

The following assessments will be conducted:

1. Subject Informed Consent taken

2. Subject demographics collected
3. Medical history details collected
4. Details of current and concomitant medication collected
5. Inclusion/Exclusion criteria
6. Contact lens wearer status assessment (Yes or No)
7. Clinical diagnosis of sensitive skin confirmed by Lactic Acid sting test
8. Determination of subject eligibility to participate in the study
9. Adverse events will be reported following the Lactic Acid stinging test procedure

Visit 2 – Baseline Visit
Within 7 days of the Screening Visit

The following assessments will be conducted:

1. Current/Concomitant medications review
2. **INCLUSION/EXCLUSION CRITERIA**
3. Fitzpatrick skin type assessment (Appendix 2)
4. Dermatologist assessment of skin type status (dry, oily or normal/combination) Inclusion criteria 5e and Exclusion criteria 7f
5. Clinical dermatologist assessment for eligibility to participate in the study (including visual examinations) (Appendix 3). Inclusion criteria 5c
   Note: subject must have a total score of zero for inclusion into the study
6. Clinical ophthalmologist assessment for eligibility to participate in the study (including visual examinations) (Appendix 4). Inclusion criteria 5d
   Note: subject must have a total score of zero for inclusion into the study.
7. Subject self-assessment questions (Appendix 5). Prior to product use.
8. Continued eligibility check
9. Randomization and stratification
10. Dispense assigned study product and diary card/instructions for use
11. Supervised first use of assigned product
12. Dermatologist (Appendix 3) and ophthalmologist (Appendix 4) assessments 1 hour (± 20 minutes) post supervised first product application
13. Subject self-assessment questions (Appendix 5) 1 hour (± 20 minutes) post first supervised use
14. Adverse events assessment

Visit 3 - Week 3 / Exit from Study (21 (+ 2) Days)

The following assessments will be conducted:

1. Current/Concomitant medications review
2. Continued eligibility check
3. Return study product and diary card/instructions for use
4. Diary card check to confirm compliant product use
5. Dermatologist final assessment of tolerance (Appendix 3)

6. Ophthalmologist final assessment of tolerance (Appendix 4)
7. Subject final self-assessment questions (Appendix 5)
8. ~~Return assigned cleanser and Diary Card/Instructions for use~~
9. Adverse event assessment
10. Subject discharge from the study site following completion of all study procedures

Type and Planned Number of Subjects

Healthy female subjects, aged 18 to 65 years with sensitive skin and no dermatological or ophthalmological disorders 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 cleanser products. Prospective subjects shall be frequent users of make-up, including eye make-up.

Subjects with sensitive skin as determined by a positive response to the lactic acid Stinging Test will be considered eligible to participate in the study. Subjects with a Fitzpatrick phototype I to IV will be recruited to ensure any reactions are clearly visible on subject's skin. In addition to subjects who have a positive response to the lactic acid Stinging test, eligible subjects will have skin type assessed by a qualified dermatologist, and only subjects with dry or normal/combination skin will be considered eligible to participate in the study. Subjects with oily skin will not be enrolled as they do not represent the target population for the test products.

A sufficient number of subjects will be screened (up to 170) to randomize at least 92 subjects (46 per treatment group) to ensure that at least 40 subjects in each treatment group complete the study (80 subjects in total).

Randomization will be stratified by both contact lens wearer status (yes or no) and skin type (dry or normal/combination) to ensure that an equal population of contact lens wearers and skin type (dry or normal/combination) is randomized to each treatment.

The sample size is based on clinical considerations to provide descriptive information on the local tolerance and safety of the test products and is consistent with ANVISA guidelines (ANVISA, 2012).

Diagnosis and Main Criteria for Inclusion

Healthy female subjects aged 18 to 65 years with dry or normal/combination dermatologist assessed skin, no dermatological or ophthalmological disorders, Fitzpatrick skin phototype

I to IV and a positive response to a lactic acid Stinging Test will be considered eligible to participate in this study.

Product Information

	Test Product 1	Test Product 2
Product Name	Micellar Cleanser	Micellar Foaming Cleanser
Product Formulation Code (MFC)	CCI [redacted]	
Product Format	200ml Clear plastic bottle	150ml Plastic pump pack
Application Quantity	To be used as per normal home use application	
Route of Administration	Topical dermal application	
Application Instructions	Use morning and evening. Apply to a cotton pad and wipe over the entire face and closed eyes to gently cleanse. No need to rub or rinse. Cotton pads will be supplied. *	Use morning and evening. Massage gently onto wet skin on the face using fingertips, rinse thoroughly and pat skin dry.

**Cotton pads will additionally be supplied by the study site*

Statistical Methods

The focus of the statistical analysis will be the evaluation of the frequency of cutaneous and ocular reaction responses with each test product.

For the primary endpoints, individual observations will be assessed based on Appendix 3 and Appendix 4 and a narrative description of all cutaneous and ocular responses will be provided. A frequency tabulation of the number of subjects with any cutaneous and ocular response versus those without any cutaneous and ocular response for each assessment will be presented at each time point for each of the test products. If there are subjects with non-zero response scores, a combined skin (sum of dermal and superficial irritation) score, and a combined ocular (sum of conjunctiva and lacrimal) score at each time-point and for the sum across time points following product use (sum of Baseline (Visit 2) and Visit 3) will be determined and summarised using descriptive statistics.

For the secondary endpoints, each subject assessment (redness, dryness, burning, itching and stinging, as per Appendix 5) and combined score (summed across these 5 assessments)

will be similarly presented at each time point and for the sum across time points following product use (sum of Baseline (Visit 2) and Visit 3) for each of the test products.

Data will also be presented by sub-groups, contact lens wearer status (yes, no) and skin type (dry, normal/combined) at baseline.

No interim analyses are planned.

Adverse Events (AE) will be tabulated according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Frequencies and percentages will be presented overall, for each system organ class, and for each preferred term for each of the test products. Summaries of treatment-emergent AE's, treatment-related AE's, and AE's leading to discontinuation, and serious AE's will be presented.

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

1. INTRODUCTION

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

A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use (ANVISA, 2012). Thus, the raw materials used in the product formulation must be of proven safety and with established use in the cosmetic industry. As a general requirement, the safety of the final formulation must also be confirmed before it is marketed.

Cleansers are designed to remove dirt, sweat, sebum and oils from the skin. This is achieved through the use of surfactants that aid in the uplifting of dirt and solubilisation of oils. However, the interaction of cleansers and the stratum corneum can be detrimental to the skin, causing tightness and dryness as well as barrier damage, erythema, irritation and itch (Wihelm, 1994).

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

Clinical studies to evaluate the irritation and sensitisation potential of a product must take into account 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).

Acceptability studies aim to determine the irritation potential of cosmetic products under normal conditions of use, to provide data to support the local tolerance profile in the target population prior to commercialization.

Sensitive skin is regarded as a non-inflammatory response to products applied on the skin, and it is characterized by a sensorial reaction such as stinging, burning or itching, but with no visible irritation-related skin changes and with no immune response. This reaction often occurs on the face and may also be referred to as sensorial or subjective contact dermatitis or cosmetic intolerance syndrome, and is defined as elevated intolerance to topically applied substances, such as cosmetics and products for skin treatment. It has been verified that people with sensitive skin are prone to developing irritant or allergic contact dermatitis (Farage *et al*., 2006).

Some substances may trigger an irritant response in sensitive skin, such as benzoic acid, cinnamic acid, non-ionic emulsifiers, sodium lauryl sulfate, bronopol, lactic acid, propylene glycol, urea and sorbic acid (De Groot *et al*., 2010; Lundov *et al*., 2010). A widely used reactivity test to determine sensitivity to irritation is a stinging test, where lactic acid is applied to the nasolabial fold in order to induce a sensorial response. 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).

In general, facial skin types are classified into three types according to a subjective judgment, as: oily, normal, or dry. Relatively recently, another facial skin type has been added to these skin types, the combination skin type, which means that the individual shows regional differences in type (Youn 2005).

Subjects with a dermatologist assessed skin type of dry or normal/combination will be considered eligible to participate in this study. Dry skin is skin that produces less sebum than normal skin and as a result lacks lipids to maintain a healthy moisture barrier, it has a course feel and roughness which looks dull in appearance. Normal/combination skin is a term to described balanced skin, fine pores, good blood circulation, soft, smooth texture, and no blemishes or skin with a combination of skin types across the face from oily in the '*T-zone*' (forehead, chin and nose) to normal to dry on the cheeks, enlarged pores in some areas, with some impurities.

The objective of this clinical study is to assess the cutaneous and ocular local tolerance of two cosmetic facial cleansers in healthy females with sensitive skin under normal conditions of use.

2. OBJECTIVE(S) AND ENDPOINT(S)

Objective(s)	Endpoint(s)
Primary	
Assessment of the cutaneous and ocular tolerance of two cosmetic facial cleansers after 21 (+ 2) days of product use per the intended instructions in healthy female subjects with clinically assessed sensitive skin.	Dermatologist and ophthalmologist visual assessment of cutaneous and ocular irritation after 21 (+ 2) days of test product use.
Secondary	
Assessment of the cutaneous and ocular tolerance of two cosmetic facial cleansers after 21 (+ 2) days of product use per the intended instructions in healthy female subjects with clinically assessed sensitive skin.	Subject self-assessment question responses (redness, dryness, burning, itching and stinging) with regards to product use experience on the face and around the eyes after 21 (+ 2) days of test product use.
To evaluate the general safety of two cosmetic facial cleansers.	Frequency and severity of Adverse Events

3. STUDY PLAN

3.1. Study Design

Overall Design
This is an assessor blind (dermatologist and ophthalmologist) clinical in use study to determine the local cutaneous and ocular tolerance of two cosmetic facial cleanser products when used as per the intended instructions for use in a population of healthy female subjects with clinically assessed sensitive skin. Subjects who have sensitive skin as classified by a positive reaction to a lactic acid Stinging Test will be asked to use one of two cleansing products as part of their normal skin care routine for 3 weeks. Both test products are the same formulation but are differentiated by the dispensing pack; to either a micellar cleanser or a foaming cleanser. Subjects will be instructed to cleanse their face with one of the two test products at home twice-daily, for 21 (+ 2) days, including a supervised first application at the study site (Visit 2) and a final application at home on the morning of the final visit (Visit 3), as per the intended instructions for use.

A qualified dermatologist and a qualified ophthalmologist will assess the baseline cutaneous an ocular irritation of prospective subjects at Visit 2. For a subject to be considered eligible to participate in the study, all dermatologist and ophthalmologist assessment scores must be zero. Further dermatologist and ophthalmologist assessments will be completed 1-hour (± 20 minutes) post supervised first product use and at the final visit (Visit 3) at the end of the 21 (+2) day product use period. The intensity of any visual signs of cutaneous and ocular irritation will be recorded by the dermatologist and ophthalmologist, according to the assessment scales detailed in Appendix 3 and 4.

The dermatologist will also determine each subject's facial skin type as dry, oily or normal/combination skin. Any subject classified as having oily skin will not be considered eligible for participation in the study as they do not represent the target population for the product.

Subjects will be asked to complete self-assessment questions at Visit 2 prior to any study product use. In addition, randomized subjects will be asked to complete the self-assessment questions 1 hour (± 20 minutes) post supervised first product use and at the end of the 21 (+2) day product use period.

The objective of this clinical study is to assess the cutaneous and ocular local tolerance of two cosmetic facial cleansers in healthy females with sensitive skin under normal conditions of use.

Visit 1 – Screening Visit

The following assessments will be conducted:

1. Subject Informed Consent taken
2. Subject demographics collected
3. Medical history details collected
4. Details of current and concomitant medication collected
5. Inclusion/Exclusion criteria
6. Contact lens wearer status assessment (Yes or No)
7. Clinical diagnosis of sensitive skin confirmed by Lactic Acid sting test
8. Determination of subject eligibility to participate in the study
9. Adverse events will be reported following the Lactic Acid stinging test procedure

Visit 2 – Baseline Visit

Within 7 days of the Screening Visit

The following assessments will be conducted:

1. Current/Concomitant medications review
2. **INCLUSION/EXCLUSION CRITERIA**

3. Fitzpatrick skin type assessment (Appendix 2)
4. Dermatologist assessment of skin type status (dry, oily or normal/combination) Inclusion criteria 5e and Exclusion criteria 7f
5. Clinical dermatologist assessment for eligibility to participate in the study (including visual examinations) (Appendix 3). Inclusion criteria 5c
   Note: subject must have a total score of zero for inclusion into the study
6. Clinical ophthalmologist assessment for eligibility to participate in the study (including visual examinations) (Appendix 4). Inclusion criteria 5d
   Note: subject must have a total score of zero for inclusion into the study.
7. Subject self-assessment questions (Appendix 5). Prior to product use.
8. Continued eligibility check
9. Randomization and stratification
10. Dispense assigned study product and diary card/instructions for use
11. Supervised first use of assigned product
12. Dermatologist (Appendix 3) and ophthalmologist (Appendix 4) assessments 1 hour (± 20 minutes) post supervised first product application
13. Subject self-assessment questions (Appendix 5) 1 hour (± 20 minutes) post first supervised use
14. Adverse events assessment.

Visit 3 - Week 3 / Exit from Study (21 (+ 2) Days)

The following assessments will be conducted:

1. Current/Concomitant medications review
2. Continued eligibility check
3. Return study product and diary card/instructions for use
4. Diary card check to confirm compliant product use
5. Dermatologist final assessment of tolerance (Appendix 3)
6. Ophthalmologist final assessment of tolerance (Appendix 4)
7. Subject final self-assessment questions (Appendix 5)
8. ~~Return assigned cleanser and Diary Card/Instructions for use~~
9. Adverse event assessment
10. Subject discharge from the study site following completion of all study procedures

3.2. Subject Restrictions

Lifestyle/ Dietary

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

1. Changing any cosmetic habits, including personal hygiene.
2. Addition of any new cosmetic product to their current regimen or switching brands of facial cosmetic products.
3. Changing dietary habits.
4. Exposure to artificial ultraviolet (UV) light or cosmetic procedures (includes tanning beds, Intense Pulsed Light, etc.) on the face for the duration of the study.
5. Introduction of new products during the study, including but not limited to soap, laundry detergent, or fabric softener.
6. If subject is a contact lens wearer, contact lenses should be removed prior to product application.

Baseline Visit (Visit 2):

1. Application of any leave-on cosmetics (e.g. creams, lotions, foundation, mascara, eyeliner and concealer) to the face prior to the Baseline Visit (Visit 2) should be avoided on the day of the visit.

Final Visit (Visit 3):

2. Application of any leave-on cosmetics (e.g. creams, lotions, foundation, mascara, eyeliner and concealer) to the face should be avoided on the day of the visit.
3. Application of any detergents (e.g. soaps, shampoos, and bath and shower products) to the face, other than the dispensed test product should be avoided on the day of the visit.

Medications and Treatments

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

1. Aesthetic, cosmetic or dermatological treatment of the face and/or eyes
2. Change in hormone treatment or contraception

3. Use of the following medications:

    a. Systemic or topical corticosteroids

    b. Systemic or topical immunosuppressive drugs

    c. Systemic or topical antihistamines, Vitamin A acid and its derivatives, or non-steroidal anti-inflammatory drugs

    d. Concomitant topical treatment of the face and or eyes

3.3. Type and Planned Number of Subjects

Healthy female subjects, aged 18 to 65 years with sensitive skin and no dermatological or ophthalmological disorders 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 cleanser products. Prospective subjects shall be frequent users of make-up, including eye make-up.

Subjects with sensitive skin as determined by a positive response to the lactic acid Stinging Test will be considered eligible to participate into the study. Subjects with a Fitzpatrick phototype I to IV will be recruited to ensure any reactions are clearly visible on subject's skin. In addition to subjects who have a positive response to the lactic acid Stinging test, eligible subjects will have skin type assessed by a qualified dermatologist, and only subjects with dry or normal/combination skin will be considered eligible to participate in the study. Subjects with oily skin will not be enrolled as they do not represent the target population for the test products.

A sufficient number of subjects will be screened (up to 170) to randomize at least 92 subjects (46 per treatment group) to ensure that at least 40 subjects in each treatment group complete the study (80 subjects in total).

Randomization will be stratified by both contact lens wearer status (yes or no) and skin type (dry or normal/combination) to ensure that an equal population of contact lens wearers and skin type (dry or normal/combination) randomized to each treatment.

The sample size is based on clinical considerations to provide descriptive information on the local tolerance and safety of the test products and is consistent with ANVISA guidelines (ANVISA, 2012).

3.4. Study Design and Application Amount Justification

This is a single center, 2-arm, parallel group, non-comparative, assessor (dermatologist and ophthalmologist) blinded study in healthy female subjects with clinically assessed sensitive skin, conducted under the supervision of a dermatologist and ophthalmologist, to assess the cutaneous and ocular local tolerance of two cosmetic facial cleansers when used for a period of 21 (+2) days as per the intended instructions for use.

A lactic acid stinging test will be used to confirm whether a subject has sensitive skin (see 6.1.7). A subject must have a lactic acid stinging response **COMBINED** score of at least 2 (combined from each time point assessment) to be considered to have sensitive skin and therefore be eligible to participate in the study. A trained technician will conduct the lactic acid Stinging Test on subjects to ascertain whether a subject has sensitive skin.

Eligible subjects will be randomized and stratified, based on contact lens wearing status and skin type, to receive one of the two facial cleansing products under investigation and given instructions on how to correctly apply the product. Sufficient product will be provided so that the product can be used twice daily for the complete duration of study period.

The first use of the assigned test product will be performed at the study site, under study site staff supervision. One hour (±20 minutes) after the first product application subjects will have further dermatologist and ophthalmological evaluations and the subject self-assessment questions will be asked a second time. Subjects will receive a diary card to record twice daily product use over the duration of the study. Subjects will be instructed to use the test product twice daily at home during the study period of 21 (+2) days and will be instructed to contact the study site if they have any reactions.

At the end of the study period, final dermatological and ophthalmological assessments will be performed on all subjects. Subjects will also be asked the self-assessment questions based on their experience of product use.

Subjects will return their completed diary and all of the product packages, whether empty or not. The diary will be verified for adequate completion.

Assessments:

A qualified dermatologist and a qualified ophthalmologist will assess subjects at Visit 2 to determine eligibility prior to any study product use, and 1 hour (± 20 minutes) following first supervised test product use. This is to ensure that the subject is free of any preexisting dermatological and ophthalmological pathology prior to using the study products (Edward,

2008). Additionally, a final assessment at Visit 3 will be completed at the end of the 21 (+2) day product use period.

The intensity of any visual signs of cutaneous or ocular irritation will be recorded by the dermatologist and ophthalmologist, according to the severity of the reactions (Appendix 3 and 4). The dermatologist and ophthalmologist are responsible for grading the reactions, and their opinion on the classification of the irritation scores is final.

Female subjects with a Fitzpatrick phototype I to IV will be recruited to ensure any reactions are clearly visible on their skin.

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

A dermatologist will characterize each subject's skin and subjects with dry or normal/combination skin type who are meet all other inclusion and exclusion will be included in the study. Subjects with oily skin will be excluded from the study.

Subjects will be asked to answer a series of self-assessment questions prior to any product application (Appendix 5).

Any skin irritation will be assessed by a dermatologist in the product application area and periocular area using the criteria recommended by the US Department of Health and Human Services Food and Drug Administration (FDA), 1999. The intensity of the reactions will be classified according to the scores obtained in the applied scale, according to Appendix 3.

Any ocular irritation will be assessed by an ophthalmologist, through the observation of the presence of two factors: Lacrimation Intensity and Conjunctiva Involvement, according to Appendix 4. For the initial pre-treatment assessment, the 1 hour after the first application assessment, and for the final day 21 (+2) day assessment, each response will be graded as per the ocular reaction intensity classification scale (Appendix 4).

Application Quantity:

The application quantity of the study products has been selected based on the assumption that, typically, 4ml of a cleansing product will be applied to a facial area of approximately 400cm^2, as consistent with the average amount of non-lathering cleanser reported in the literature (Loretz, 2008).

Both test products are the same formulation but are differentiated by the dispensing pack; to either a micellar cleanser or a foaming cleanser.

Micellar Cleanser instructions for use: Use morning and evening. Apply to a cotton pad and wipe over the entire face and closed eyes to gently cleanse. No need to rub or rinse. Cotton pads will be supplied.

Micellar Foaming Cleanser instructions for use: Use morning and evening. Massage gently onto wet skin on the face using fingertips, rinse thoroughly and pat skin dry.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

4.1. Inclusion Criteria

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

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

2. AGE
Aged between 18 and 65 years inclusive.

3. GENDER
Subject is female.

4. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee no clinically significant and relevant abnormalities in medical history or upon physical (dermatologist or ophthalmologist) examination.

5. SKIN TYPE
a) Fitzpatrick phototype I to IV (see Appendix 1) – **VISIT 2** b) Sensitive Skin (as determined by the lactic acid Stinging test) c) Dermatologist score of zero (Appendix 2) - **VISIT 2** d) Ophthalmologist score of zero (Appendix 3) - **VISIT 2** e) Dermatologist assessed Dry or Normal/Combination Skin - **VISIT 2**

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

7. OTHER CRITERIA
Frequent use of facial cosmetic make-up, including eye-make-up (5 out of 7 days per week).

4.2. Exclusion Criteria

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

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

2. BREAST-FEEDING
Women who are breast-feeding

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
a) Any history of significant dermatological diseases or conditions or medical conditions known to alter skin appearance or physiologic response (e.g. diabetes,) which could, in the opinion of the Investigator, preclude topical application of the investigational products and/or interfere with the evaluation of the test site reaction. b) Presence of open sores, pimples, or cysts at the application site. c) Active dermatosis (local or disseminated) that might interfere with the results of the

study.

d) Considered immune compromised.

e) Participants with dermatographism.

f) Currently using any medication which in the opinion of the investigator, may affect the evaluation of the study product, or place the subject at undue risk

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

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

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

j) Currently receiving allergy injections, or received an allergy injection within 7 days prior to Screening visit, or expects to begin injections during study participation

4. ALLERGY/ INTOLERANCE

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

b) Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients

5. CLINICAL STUDY/ EXPERMENTAL PRODUCT

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

b) Previous participation in this study.

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

7. DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
a) Any Subject who, in the judgment of the Investigator, should not participate in the study. b) Any subject with corneal ulcers, keratoconus, blepharitis, meibomitis, pterygium, chemosis, moderately or severe hyperemia or other active ocular diseases. **VISIT 2** c) 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). d) Prisoner or involuntary incarcerated subject. e) Subject from an indigenous tribe. f) Subjects with a qualified dermatologist assessment of oily skin. **VISIT 2**

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

4.3. Screening/ Baseline Failures

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

4.4. Withdrawal/ Stopping Criteria

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

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

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

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

4.5. Subject Replacement

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

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study. The end of the study is defined as the date of the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

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

	Test Product 1	Test Product 2
Product Name	Micellar Cleanser	Micellar Foaming Cleanser
Product Formulation Code (MFC)	CCI [redacted]	
Product Format	200ml Clear plastic bottle	150ml Plastic pump pack
Application Quantity	To be used as per normal home use application	
Route of Administration	Topical dermal application	
Application Instructions	Use morning and evening. Apply to a cotton pad and wipe over the entire face	Use morning and evening. Massage gently onto wet

	and closed eyes to gently cleanse. No need to rub or rinse. Cotton pads will be supplied. *	skin on the face using fingertips, rinse thoroughly and pat skin dry.

**Cotton pads will additionally be supplied by the study site*

Other items to be supplied by the clinical study site:

1. 10% Aqueous Lactic Acid solution – For lactic acid stinging test
2. Saline solution – For lactic acid stinging test
3. Cotton Buds - For lactic acid stinging test
4. Cotton pads for use with micellar cleanser treatment arm

5.2. Application Schedule

Each eligible subject will receive one of the two cleansing products under investigation and given instructions on how to correctly apply the product. Sufficient product will be provided for the complete duration of the study period. Subjects will also receive a diary card with their assigned product to be completed at home to record each product use.

The first use of the assigned product will be performed at the study site, under study site staff supervision and recorded on the provided diary card. Subjects will then be instructed to use their assigned product at home again that evening and continue to use at home twice daily during the study period of 21 (+ 2) days per the instructions of use, including the morning of their final visit, recording each use on the diary card.

If subject is a contact lens wearer, contact lenses should be removed prior to any product application.

Subjects will return their completed diary and all of the product packages, whether empty or not. The diary will be verified for adequate completion and product use compliance.

As the usage of the product is indicated as twice daily, for a minimum of 21 days and a maximum of 23 days, a minimum of 42 applications and a maximum of 46 applications will be expected.

5.3. Product Assignment

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

5.3.1 Randomization

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomized according to the randomization schedule, which will be prepared (stratified) to achieve balance between contact lens wearer (Yes or No) and cosmetic skin type (dry or normal/combination).

THERE WILL BE A TOTAL OF 4 STRATA:

- **CONTACT LENS WEARER + DRY SKIN**
- **CONTACT LENS WEARER + NORMAL/COMBINATION SKIN**
- **NON CONTACT LENS WEARER + DRY SKIN**
- **NON CONTACT LENS WEARER + NORMAL/COMBINATION SKIN**

Randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible within each strata specific list.

The study site will receive two versions of the randomization schedule, each in a sealed envelope and clearly marked as either "For Dispensing" or "Emergency Use Only". The "For Dispensing" schedule will contain the list of randomization numbers and the test product code, a letter code A, or B will be used to determine which product is to dispensed.

To maintain the blinding of the study as much as possible, all treatment allocations for all randomization numbers on this randomization schedule will be masked with scratch-off panels. Only the panels required for the emergency unblinding the particular subject should be removed

The 'Emergency Use Only' randomization schedule will only be removed from the sealed envelope in an emergency situation. This schedule will have a randomization number

followed by the letter. The schedule will have a footnote with a key for the letters identifying the treatments.

5.3.2 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects.

Site staff dispensing and carrying out the first supervised product application will be aware of each subject's test product and must not divulge information to other study staff or the qualified dermatologist and/or qualified ophthalmologist who will be blinded to subject product assignment.

5.3.3 Code Breaks

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

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

5.4. Packaging and Labelling

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

The facial micellar cleanser (CCI [redacted] will be supplied in 200 ml bottles and the micellar foaming cleanser (CCI [redacted] will be supplied in 150ml pump packs. Both products will have a study label affixed by the Sponsor to the outer packaging. Each study label will contain, but not be limited to, protocol number, product code letter, directions for use and storage requirements.

Both test products are the same formulation but are differentiated by the dispensing pack; to either a micellar cleanser or a foaming cleanser.

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.

5.4.1. Accountability of Product

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

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

a) The identification of the subject to whom the study product was dispensed.
b) The date(s) and quantity of the study product dispensed to the subject.
c) The date(s) and quantity of the study product returned by the subject (if applicable).

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

5.4.2. Storage of Product

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

6. STUDY ASSESSMENTS AND PROCEDURES

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

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

6.1. Visit 1 - Screening Visit

6.1.1 Telephone Screening

Prior to the screening visit, telephone screening of interested subjects may be conducted using a telephone script. This will be conducted by the site recruitment staff or designee.

6.1.2. Informed Consent

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

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly after the subject has signed. The subject will be provided with a copy of their signed and dated consent form and any other written information which they are be instructed to retain.

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

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

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender and race.

6.1.4. Contact Lens Wearer Status Assessment

The following demographic parameter will be captured by the Investigator or designee and recorded on the CRF: Contact Lens Wearer (Yes/No).

6.1.5. Inclusion / Exclusion Criteria

Inclusion/exclusion criteria (excluding inclusion criteria **5A**, 5c, 5d, and 5e and exclusion criteria **7B** and 7f) will be assessed by the Investigator or designee and recorded on the CRF.

6.1.6. Medical History and Concomitant Medication

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

6.1.7. Lactic Acid Stinging Test

Subjects will be instructed to wash their face with warm (room temperature) water and dry it with paper towels. After 30 minutes the stinging test will be performed by a trained technician.

A 10% aqueous lactic acid solution (at room temperature) will be applied to one nasolabial fold and a saline solution (at room temperature) will be applied to the other nasolabial fold. The location of the application will be randomised by the study site. The solutions will be applied by fully saturating a cotton bud, then using several sweeps of the saturated cotton bud along each of the nasolabial folds (Right and Left).

At 2 minutes 30 seconds and 5 minutes after application, subjects will be asked to assess their feelings of discomfort (Christensen *et al*., 1995), according to the following scale:

The reaction may take 1 to 2 minutes to start, potentially intensifying up to 5 minutes. The test will be suspended after 5 minutes, if no local sensation is reported, or immediately after subject assessment of severe intensity (score of 3). At this time or after 5 minutes, the subject will be instructed to remove the solutions by washing with water and to dry their face with a paper towel.

Subjects who report a combined score (i.e. sum of the 2 minute 30 seconds and 5 minute assessments) of ~~greater than~~ **AT LEAST** 2 for the lactic acid treated site compared to the saline solution treated site will be considered eligible for further participation in the study.

Any negative response will exclude the subject from further participation in the study.

Any observed response that can be denoted according to the score of the reactions (per table above) 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.

6.1.8. Subject Eligibility

Subject eligibility will be assessed by the Investigator or medically qualified designee and recorded on the CRF.

6.2 Visit 2 – Baseline Visit

6.2.1. Inclusion / Exclusion Criteria

Inclusion criteria **5A**, 5c, 5d, and 5e and Exclusion criteria **7B** and 7f will be assessed by the Investigator or designee and recorded on the CRF.

6.2.2. Medical History and Concomitant Medication

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

6.2.3. Fitzpatrick Skin Type Assessment

Fitzpatrick skin type assessment (Appendix 2) will be conducted by a trained evaluator and recorded on the CRF.

6.2.4. Skin Type Assessment

A dermatologist will assess subjects skin type as dry, normal/combination or oily and the classification will be recorded on the CRF.

6.2.5. Dermatologist Assessment

A qualified dermatologist will visually assess the subject at Visit 2 to determine eligibility, prior to any study product use and 1 hour (± 20 minutes) following first supervised test product use. This assures that 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 total cutaneous irritation score of zero at Visit 2 prior to any

product application. Additionally, a final assessment at Visit 3 will be completed at the end of the 21 (+2) day product use period.

The intensity of any visual signs of irritation will be recorded according to the grade of the reactions (Appendix 3) according to the skin dermal response (Table 1) and other features indicative of irritation (Table 2) observed. 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 in Appendix 3 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.

6.2.6. Ophthalmologist Assessment

A qualified ophthalmologist will assess the subject at Visit 2 to determine eligibility, prior to any study product use, and 1 hour (± 20 minutes) following first supervised test product use. This assures that 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 zero at Visit 2 prior to any product application. Additionally, a final assessment at Visit 3 will be completed at the end of the 21 (+2) day product use period.

Ocular irritation will be assessed through the observation of the presence of two factors: Lacrimation Intensity and Conjunctiva Involvement, according to Appendix 4. For the initial pre-treatment assessment, the 1 hour after the first application assessment, and for the final day 21 (+2) day assessment, each response will be graded as per the ocular reaction intensity classification scale (Appendix 4). 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 in Appendix 4 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.

6.2.7. Subject self-assessment

Subjects will be asked to answer the self-assessment question as per Appendix 5 prior to any product use.

The self-assessment questions will be asked again 1 hour (± 20 minutes) following first supervised test product use. Additionally, a final assessment at Visit 3 will be completed at the end of the 21 (+2) day product use period.

6.2.8. Subject Eligibility

Subject eligibility for randomisation into the study will be assessed by the Investigator or medically qualified designee and recorded on the CRF.

6.2.9. Supervised Product Application

Each eligible subject will be randomised to a strata based on contact lens wearer status (Yes or No) and cosmetic skin type (dry or Normal/Combination) to receive one of the two cleansing products under investigation and given instructions on how to apply the product. Sufficient product will be provided so that the product can be used for the complete study period.

The first use of the assigned product will be performed at the study site, under study site staff supervision. One hour (+20 minutes) after the first product application subjects will undergo further dermatologist (per section 6.2.5) and ophthalmologist (per section 6.2.6) assessments and be asked to respond to the subject self-assessment questions (Appendix 5).

If subject is a contact lens wearer, contact lenses should be removed prior to any product application.

Subjects will receive a diary card with their assigned product to be completed at home to record product use. Subjects will use the product at home, twice a day during the study period of 21 (+ 2) days, and will be instructed to contact the study site if they have any reactions.

6.3. Visit 3 - Last Subject Last Visit (LSLV) and Study Conclusion

Subjects will return to the study site after 21 (+ 2) days of twice daily product use. Subjects will return their test products and diary card. The diary card will be reviewed to check compliance and evaluate subject comments. The total number of product applications and total number of missed product applications will be recorded in the CRF.

Final dermatologist (per section 6.2.5) and ophthalmologist (per section 6.2.6) assessments will be completed and the subject will answer the self-assessment questions (Appendix 5) based on their experience of using the product.

6.3.1. Diary Review

Any subject comment captured in the diary card which is considered an adverse event will be reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarised in Section 7.

Subjects who apply the product more or less frequently than twice a day will be considered to have deviated from the protocol. Additional and missed applications will be recorded on the Deviations Log.

6.3.2. Study Conclusion

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

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

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

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

procedure).

Events meeting AE definition include:

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

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

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

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

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

Events NOT meeting definition of an AE include:

a) 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.

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

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

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

e) 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.

f) Any observed response that can be denoted according to the grade of the reactions for the Lactic Acid Stinging test. Only in the case of unusual reactions will these reactions and the consequences observed upon evaluation be documented as AE's.

g) Any observed response that can be denoted according to the grade of the reactions

in Appendix 3 for cutaneous response and Appendix 4 for ocular response, 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.

7.1.2. Serious Adverse Events

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

A. Results in death

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

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

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

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

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

E. Is a congenital anomaly/birth defect

F. Other Situations

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

b) Examples of such events are invasive or malignant cancers, intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:
a) The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. b) The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF. c) There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK. d) The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose). e) AEs will be collected following the conduct of the lactic acid stinging procedure and until 5 days following last administration of the study product. f) SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject provides consent to participate in the study up to and including any follow-up contact. g) Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:
The investigator or designee will make an assessment of intensity for each AE and SAE

reported during the study and will assign it to one of the following categories:

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

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

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

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

Assessment of Causality:

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

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

c) The investigator will use clinical judgment to determine the relationship.

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

e) The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

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

g) 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.**

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

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

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

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

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

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

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

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

SAE Reporting to GSKCH:

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

a) Protocol and subject identifiers
b) Subject's demography
c) Description of events, with diagnosis if available
d) Investigator opinion of relationship to study product (see section 8.3)
e) Criterion for seriousness.

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

a) Date of onset of AE
b) Date AE stopped, if relevant
c) Study product start date

d) Study product end date if relevant
e) Action taken on study product
f) Outcome if known

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

~~Fax~~ EMAIL Serious Adverse Events to:
Brazil Clinical Study Manager PPD
Telephone PPD
E-mail: PPD

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

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

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

Follow-up of AEs and SAEs:

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

b) All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

c) The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.

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

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

Regulatory and ethics reporting requirements for SAEs:
a) The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. b) GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB and investigators. c) Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation. d) An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IRB, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

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

7.6.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
a) The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant

medications taken by the mother during the pregnancy) will be forwarded to GSKCH. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

b) While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.

c) A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK.

d) While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

e) If the subject becomes pregnant during the study they should be withdrawn from the study and this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

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

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in the Source Document Designation Form. In some cases, the CRF can be used as a source document.

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

8.2. Electronic Case Report Form

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

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

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

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

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

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

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

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

8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

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

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

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc., and entered into the sponsor's clinical data management system (DMS) by the study site representative. In instances where the PRO data is entered into the DMS by GSKCH, the PROs will be anonymized, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to the GSKCH approved vendor.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSKCH or approved vendor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

A sufficient number of subjects will be screened (up to 170) to randomize approximately 92 subjects (46 per treatment group) to ensure that at least 40 subjects in each treatment group complete the study (80 subjects in total).

Randomization will be stratified by both contact lens wearer status (yes or no) and skin type (dry or normal/combination). The aim is to ensure balance of strata effects between treatment groups.

The sample size is based on clinical considerations to provide descriptive information on the tolerability and safety of the products, and is consistent with ANVISA guidelines (ANVISA, 2012).

9.2. General Considerations

9.2.1. Definition of Analysis Populations

The 'Intent to treat' (ITT) population includes all subjects who are randomized into the study and have at least one cutaneous or ocular assessment following study product application.

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

The Safety population includes all subjects from the point of the lactic acid stinging test procedure until completion of the study.

9.2.2. Exclusion of Data from Analysis

No data will be excluded from any analysis.

9.2.3. Criteria for Evaluation of Local Tolerance

The primary evaluation will be dermatologist and ophthalmologist visual assessments of local tolerance after 21 (+2) days of twice-daily study product application using the ITT population.

This study will be considered a success if the majority (i.e. >50%) of subjects per treatment arm complete the study with combined dermatologist and ophthalmologist scores of zero at day 21 (+ 2).

9.2.4. Criteria for Assessing Safety

Safety will be evaluated via adverse events assessments using the Safety population.

9.2.5. Handling of Dropouts and Missing Data

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

9.3. Statistical Methods and Analytical Plan

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

9.3.1. Demographic and Baseline Characteristics

Age will be summarized using descriptive statistics such as means, medians and standard deviations. Gender, race, Fitzpatrick skin type, contact leans wearer status and cosmetic facial skin type assessment by dermatologist will be summarized using frequency counts and percentages,

9.3.2. Primary Analysis(es)

The primary endpoints will be the dermatologist and ophthalmologist assessments of local tolerance through visual assessment of cutaneous (dermal response and superficial irritation) and ocular (conjunctiva involvement and lacrimal intensity) irritation scores/grades using the scales described in Appendix 2 and 3.

Individual observations will be assessed based on these scales and a narrative description of all responses will be provided.

No formal statistical inference will be performed.

The number and percentage of subjects recording each category of score/grade, as well as any response versus those without any response will be presented for each assessment at each time point for each of the study test products. If there are subjects with non-zero response scores, a combined skin (sum of dermal and superficial irritation) score, and a combined ocular (sum of conjunctiva and lacrimal) score at each time-point and for the sum across time points following test product application (sum of Baseline (Visit 2) and Visit 3) will be determined and summarised using descriptive statistics.

Data will also be presented by sub-groups, contact lens wearer status (yes, no) and skin type (dry, normal/combined) assessed at screening/baseline.

9.3.3. Secondary Analysis(es)

The secondary endpoints will be each subject self-assessment response (redness, dryness, burning, itching and stinging), as per Appendix 5.

The secondary endpoints will be summarised as for the primary endpoints. Each subject assessment (redness, dryness, burning, itching and stinging, as per Appendix 5) and combined score (summed across these 5 assessments) will be presented at each time point and for the sum across time points following test product (sum of Baseline (Visit 2) and Visit 3) for each of the test products.

9.3.4. 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.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

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

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

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

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

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

2. Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
3. Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB)
4. GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

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

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

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

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

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

10.4. Quality Assurance

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

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

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

10.5. Conditions for Terminating the Study

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

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

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

In addition:

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

10.6. Records Retention

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

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

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

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

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

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 20 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

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

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

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

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

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

11. REFERENCES

ANVISA, Guideline for the Safety Evaluation of Cosmetics Products, 2012
ANVISA; Resolution 79/00, Annex XXI and its updates
Berardesca E, Farage M, Maibach H. Sensitive skin: an overview. Int J Cosmet Sci. 2013 Feb;35(1):2-8.
Birmingham, J. Clinical Aspects of Cutaneous Irritation and Sensitization, Toxicology and Applied Pharmacology 7:(54-59)
Christensen M, Klingman A M. An improved procedure for conducting lactic acid stinging tests on facial skin. J. Soc. Cosmetic. Chem. 1996; 47:1-11.
De Groot A C, White IR, Flyvholm L MA, Lensen G & Coenraads, PJ. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Contact dermatitis 2010; 62:2-17
Dooms-Goossens A. Cosmetics as causes of allergic contact dermatitis. Cutis 1993; 52: 316-320.
Edward, M. Jackson, and FMT Robillard Norman. "The controlled use test in a cosmetic product safety substantiation program." Journal of Toxicology: Cutaneous and Ocular Toxicology1.2(1982):117-132
Farage, M. A., Katsarou, A. & Maibach, H. I. Sensory, clinical and physiological factors in sensitive skin: a review. Contact dermatitis 2006; 55:1-14.
Fitzpatrick TB, Pathak M, Parrish JA. Protection of human skin against the effects of the sunburn ultraviolet (290-320 nm). In: Fitzpatrick TB et al. (eds). Sunlight and man, normal and abnormal photobiological responses. Tokyo, p. 751-755.
Food and Drug Administration. ICH Topic E6: Guideline for Good Clinical Practice. Fed Reg 1997; 62(90): 25691-709.
ICH Topic 6 Guideline for Good Clinical Practice CPMP/ICH/135/95 17th July 1996.
Loretz LJ, Exposure data for cosmetic products: Facial cleanser, hair conditioner, and eye shadow. Food and Chemical Toxicology, 2008, 0278-6915, 46(5):1516
Lukacovic, Michael F., et al. "cleansing products." J. Soc. Cosmet. Chem 39 (1988): 355-366.
Lumelsky V J, Shur M S & Wagner S. Sensitive skin. Sensors Journal, IEEE. 2001; 1:41-51.
Lundov, M. D., Johansen, J. D., Carlsen, B. C., Engkilde, K., Menne, T. & Thyssen, J. P. Formaldehyde exposure and patterns of concomitant contact allergy to formaldehyde and formaldehyde-releasers. Contact dermatitis 2010; 63:31-36
National Health Surveillance Agency Brazil (ANVISA). Guideline for the Safety Evaluation of Cosmetic Products. Brasília; 2012.
Primavera G, Berardesca E. Sensitive skin: mechanisms and diagnosis.Int J Cosmet Sci. 2005 Feb;27(1):1-10.
Riestschel RL, Fowler JF Jr. Fisher´s contact dermatitis, 4th ed. Williams & Wilkins, Maryland: USA 1995.
Wilhelm KP, Surfactant-induced stratum corneum hydration in vivo: prediction of the

irritation potential of anionic surfactants Journal of Investigative Dermatology, The 1993, 0022-202X, 101(3):310
Wilkinson, D. S., et al. "Terminology of contact dermatitis." Acta Derm Venereol 50.4 (1970): 287-292.
World Medical Association Declaration of Helsinki, 59th General Assembly, Seoul 2008.
Youn SW, Regional and seasonal variations in facial sebum secretions: a proposal for the definition of combination skin type. Skin Research and Technology, 2005, 0909-752X, 11(3):189

12. APPENDICES

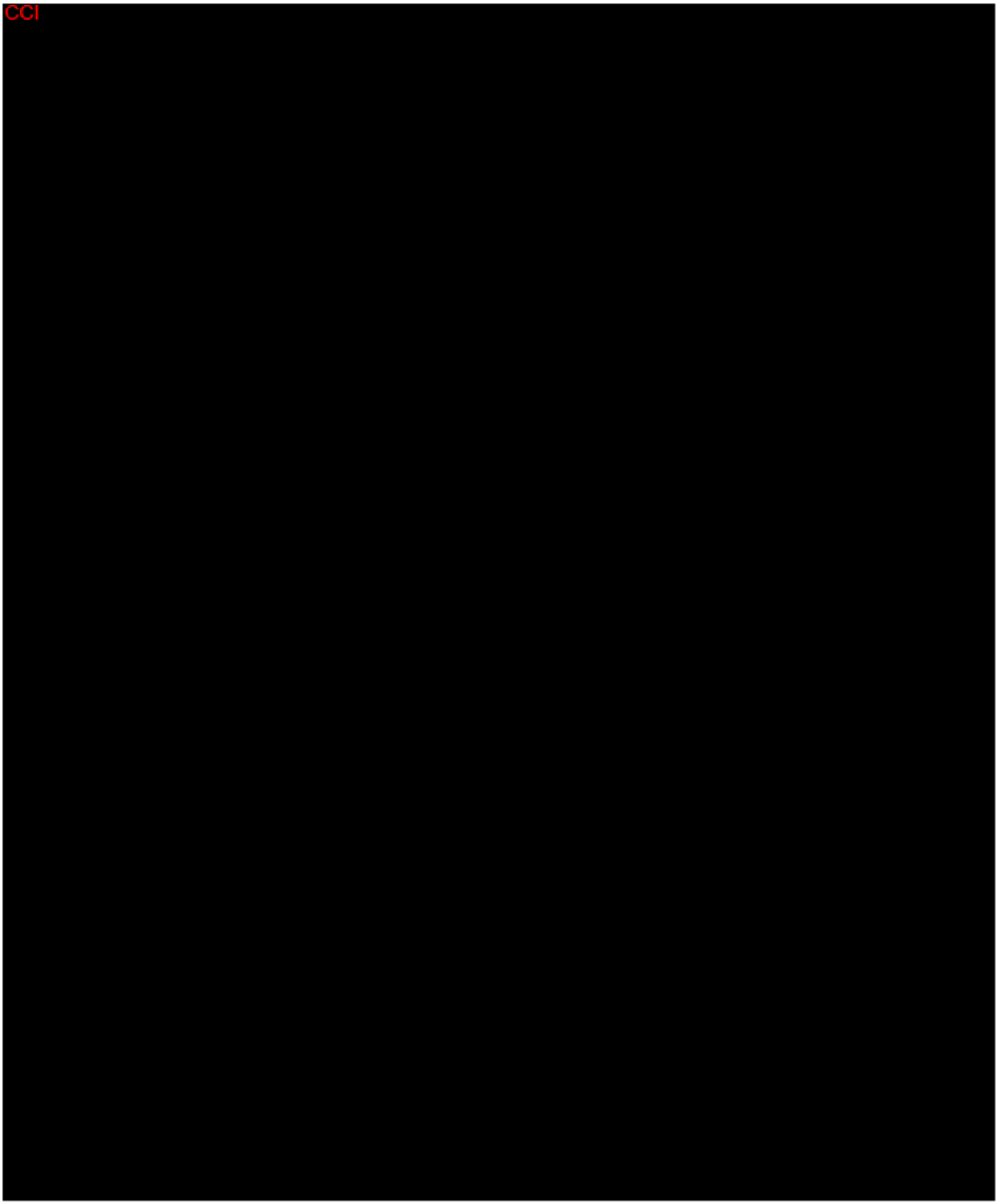
12.1. Appendix 1 - Abbreviations

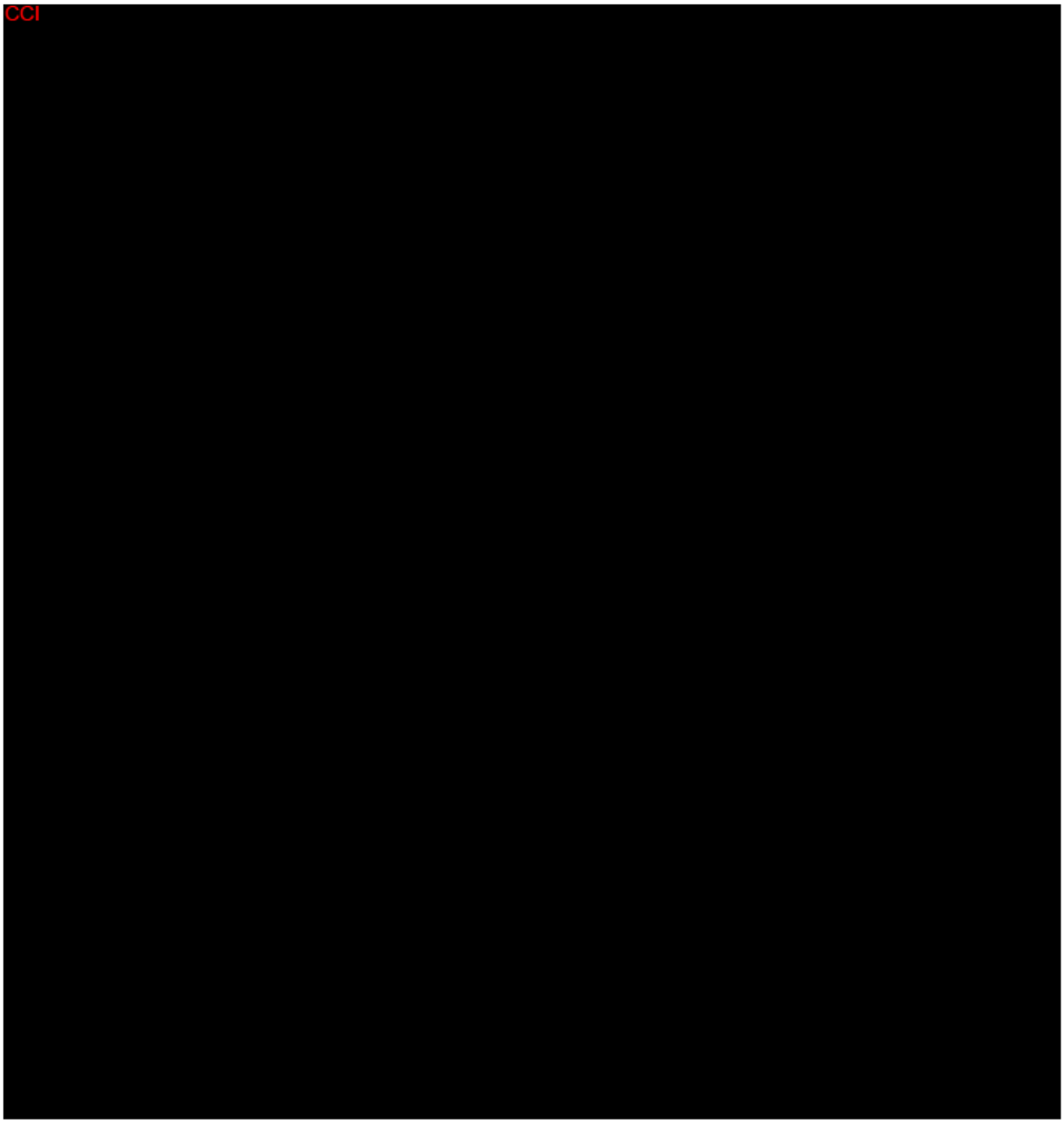
Abbreviations

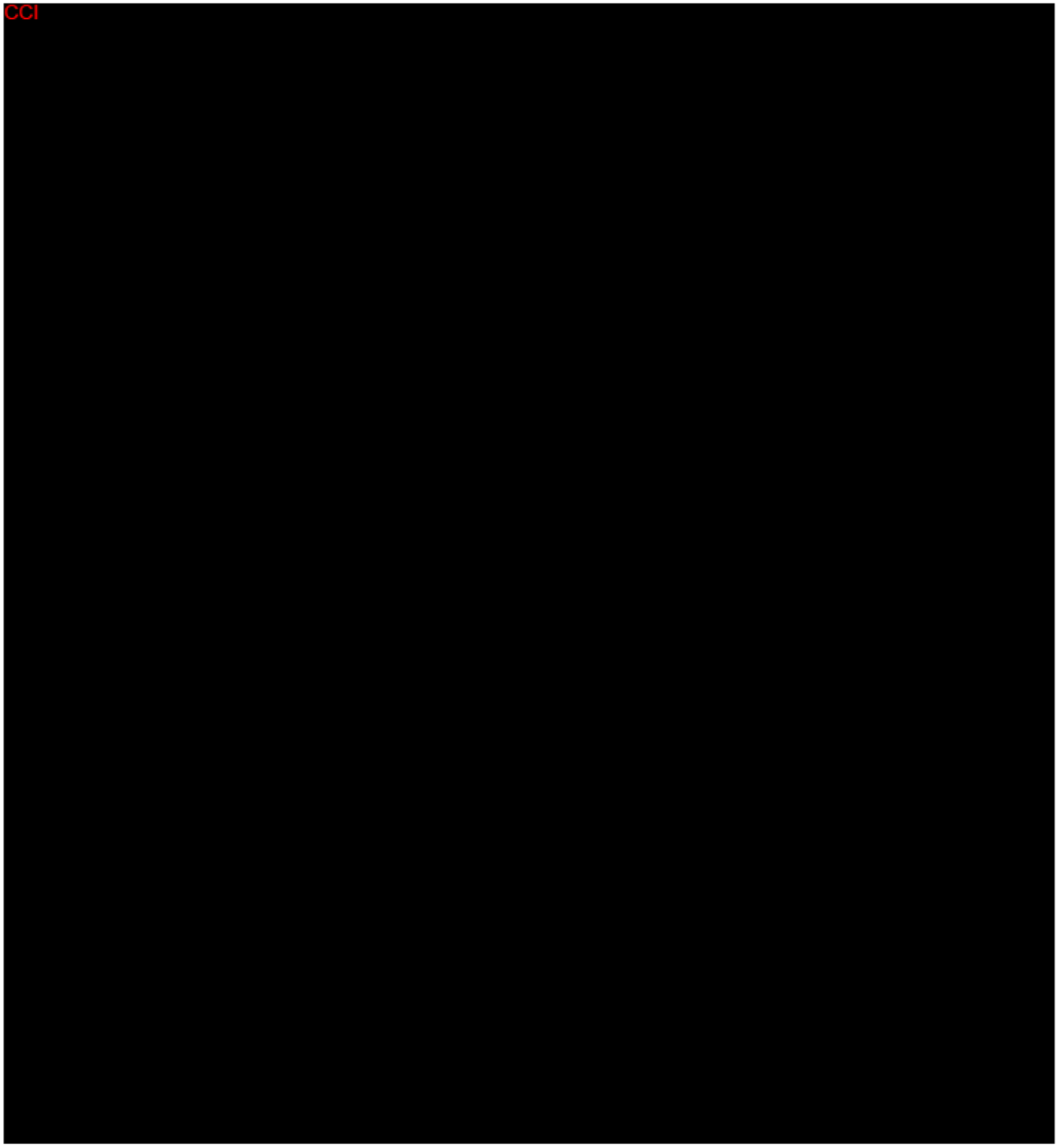
AE	Adverse Event
AUC	Area under Curve
CD	Compact Disc
cm^2	Square Centimeter
CRF	Case Report Form
DVD	Digital Versatile Disc
EDC	Electronic Data Capture
EEMCO	European Group for Efficacy Measurements on Cosmetics and Other Topical Products
FSFV	First Subject First Visit
g	Gram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
hr	Hour
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ITT	Intention to Treat
LSLV	Last Subject Last Visit
m^2	Square meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
ml	Milliliter
PII	Personally Identifiable Information

PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

CCI




CCI


CCI


CCI

SIGNATURE PAGE

Clinical Protocol 207782

Date	Signed By
25-May-2017 12:44:02	PPD
Justification	Approved

Date	Signed By
25-May-2017 17:46:01	PPD
Justification	Approved

Date	Signed By
25-May-2017 22:15:41	PPD
Justification	Clinical Operations Approval

Date	Signed By
26-May-2017 05:53:03	PPD
Justification	Biostatistics Approval

Date	Signed By
Justification	

Date	Signed By
Justification	