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CLINICAL PROTOCOL

A Clinical Study to Investigate the Effects of Two Developmental Cosmetic Moisturizing Cream Formulations on the Barrier Function of Human Skin on the Face and Legs.

Protocol Number:	209638
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Sponsor Name & Legal Registered Address	**GlaxoSmithKline (GSK) Research & Development Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSK CH)** St Georges Avenue, Weybridge, Surrey, KT13 0DE, UK

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Amendment 2		

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

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

Background and Rationale

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed two cosmetic moisturizer formulations intended to be suitable for use by consumers with dry, sensitive skin.

The skin is a vital organ which primarily separates and defends the body from the external environment. Dry skin is common in the general population, and is characterized by a rough, flaky profile which has lost a portion of its otherwise flexible and elastic properties. The stratum corneum (SC) is the outermost layer of the skin which is a highly organized, structural layer of dead skin cells that is essential for the maintenance of the water gradient between the uppermost layers of the skin.

Several factors can render the skin's moisture barrier prone to disturbance and potentially induce dryness, irritation or itch, having an overall impact on the quality of the skin (Harding, 2004). Dry skin conditions are common and topical moisturizing creams are regularly used by those who suffer from dry skin to help restore and protect the skin's disturbed moisture barrier.

There are numerous methods to evaluate the potential of topical cosmetic products to moisturize the skin, reduce the severity of existing skin conditions caused by dryness, repair the skin barrier function and protect against further damage. Barrier function damage and rate of repair can be measured by physiological changes in the level of moisturization in the stratum corneum and in the rate of trans-epidermal water loss (TEWL). Objective measurements of the moisturization of the stratum corneum are usually taken with a Corneometer, a non-invasive instrumental probe. TEWL is the rate at which water permeates the stratum corneum and evaporates from the skin surface and objective measurements of TEWL are usually taken with non-invasive instrumental probes such as the Tewameter and Aqua-flux.

The objective of this clinical study is to evaluate the impact of 4-weeks of twice-daily topical application of two developmental moisturizing cream formulations on skin barrier function in healthy subjects with dry, sensitive skin on the face and lower legs.

Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the impact of 4 weeks of twice-daily facial application of the investigational products and standard soap on skin barrier function compared to the use of standard soap only.	Change from baseline in TEWL at Day 29 (Area 1 compared to area 2)
Secondary	
Efficacy	
To evaluate the impact of 4 weeks of twice-daily leg application of the investigational products and standard soap on skin barrier function compared to the use of standard soap only.	Change from baseline in TEWL at Day 29 (Area 5 compared to area 6)
To evaluate the impact of 2 weeks of twice-daily face and leg application of the investigational products and standard soap on skin barrier function compared to the use of standard soap only.	Change from baseline in TEWL at the following time-points: • Day 15. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)

To evaluate the impact of single face and leg application of the investigational products on skin moisturization.	Change from baseline in Corneometer values at the following time-points: • Day 1: 30 minutes after first supervised application; • Day 1: 6 hours after first supervised application; • Day 2: 24 hours after first supervised application. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of 2 and 4 weeks of twice-daily face and leg application of the investigational products and standard soap on skin moisturization compared to the use of standard soap only.	Change from baseline in Corneometer values at the following time-points: • Day 15; • Day 29. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of a post-treatment regression period of 6-days of no investigational product application on skin barrier function.	Change from baseline in TEWL at the following time-points: • Day 30; • Day 31; • Day 32; • Day 33; • Day 34. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of a post-treatment regression period of 6-days of no investigational product application on skin moisturization.	Change from baseline in Corneometer values at the following time-points: • Day 30; • Day 31; • Day 32; • Day 33; • Day 34. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of a repeated tape-strip challenge on skin barrier function following 4 weeks of twice-daily face and leg application of the investigational products and standard soap compared to the use of standard soap only.	Change from pre-challenge TEWL at Day 29 to the following time points: • Removal of 3 tape strips (face) and 4 tape strips (legs); • Removal of 6 tape strips (face) and 8 tape strips (legs); • Removal of 9 tape strips (face) and 12 tape strips (legs). (Face: area 3 compared to area 4; leg: area 7 compared to area 8)
To evaluate the impact of a repeated tape-strip challenge on skin barrier integrity following 4 weeks of twice-daily face and leg application of the investigational products and standard soap compared to the use of standard soap only.	Total protein content extracted from all tape-strips: (Face: area 3 compared to area 4; leg: area 7 compared to area 8)
Safety	
To evaluate local tolerance.	Frequency and severity of adverse events.

Study Design

This is a randomized, evaluator-blind, single-centre, two treatment regimen (test product 1 and test product 2), controlled (standard cleanser soap use only), split-body (left and right; side of the face and lower legs), parallel group clinical study designed to evaluate the impact of 4-weeks of twice-daily topical application of two developmental moisturizing cream formulations on skin barrier function in healthy subjects with dry, sensitive skin on the face and lower legs.

The chosen application sites are the face and the lower legs. The legs will be designated right and left, and the face will be split to right or left side.

There will be two treatment regimens included in this study;

- Treatment Regimen 1 = Test Product 1 + Standard Soap
- Treatment Regimen 2 = Test Product 2 + Standard Soap

Instrumental measurements of skin barrier function (TEWL; using a Tewameter) and skin moisturization (using a Corneometer) will be performed at specified time points. These measurements have been included to objectively model skin barrier function and moisturization throughout the product use and regression periods of this study.

Evaluation of the impact of a physical challenge to the skin barrier after 4-weeks of product use, on both legs and both sides of the face, will be performed using a repeat tape-stripping method. This physical challenge is a minimally-invasive and commonly-used technique which consists of the consecutive removal of corneocytes from the stratum corneum with adhesive discs. Quantification of the amount of protein material removed from the stratum corneum with the adhesive discs will provide a measure of the degree of adhesion of the corneocytes, and therefore an indicator of the strength of the skin barrier.

TEWL measurements will also be taken at the tape-stripped sites to provide a direct measure of the ability of the skin to resist damage caused by physical insult and to monitor the recovery of skin barrier function post-challenge.

A 6-day regression period which will commence after the 4-week treatment period will enable an assessment of the lasting effects of the study products on skin moisturization and barrier function through TEWL and Corneometer measurements.

Study Products

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed two cosmetic moisturizer formulations intended to be suitable for use by consumers with dry skin, sensitive skin.

Subjects will be assigned to 1 of 2 treatment regimens in accordance with the randomization schedule.

- Test Product 1 + Standard Soap vs. Standard Soap, and
- Test Product 2 + Standard Soap vs. Standard Soap.

The application quantity of the study products has been selected to reflect typical consumer usage of these types of products. The first application will be supervised by a trained technician when the subjects are at the study site. Subjects will be instructed to self-apply the study products at home, twice-daily (morning and evening) for 4 weeks.

Type and Planned Number of Subjects

The sample size is determined with the success criteria of the study in mind, that each of the developmental moisturizer products will be significantly beneficial based on TEWL measurements on the face, at Day 29 (Visit 5), following 4 weeks of twice-daily use.

Approximately 220 subjects will be screened to randomize up to 150 to ensure 60 evaluable subjects per treatment regimen complete the entire study.

Healthy female volunteers aged 18 to 65 with self-reported dry, sensitive skin on their face and legs, with a trained examiner visual grading assessment score and a subject self-assessment score will be enrolled into this study.

1.1 Schedule of Activities

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

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

Table 1-1 Schedule of Activities

Procedure	Visit 1 (Screening)		Visit 2 Day 1 Baseline	Visit 3 Day 2	Visit 4 Day 15 (± 1 day)	Visit 5 Day 29 (± 2 days) D-Squame Challenge		Visit 6 Day 30	Visit 7 Day 31	Visit 8 Day 32	Visit 9 Day 33	Visit 10 Day 34
	Days -7 to -5					Pre Challenge	Post Challenge	Regression Period (no product use/soap use only)				
Informed Consent (Date and Time Captured)	X	WASHOUT PERIOD (5-7 Days)										
Demographics	X											
Medical History	X											
Current/Concomitant Medication Review	X		X	X	X	X		X	X	X	X	X
Clinical and Subject Assessment of Dryness [1]	X		X									
Fitzpatrick Skin Type Assessment	X											
Inclusion and Exclusion criteria	X		X									
Subject Eligibility for Enrollment	X											
Dispense Standard Soap, Razor and Standard Soap Diary Card	X											
Subject Eligibility to Continue in the Study (including diary card review)			X	X	X	X		X	X	X	X	X
Baseline TEWL Measurements – Area 1 & 2 (Face) and Area 5 & 6 (Leg)			X									

Procedure	Visit 1 (Screening)		Visit 2 Day 1 Baseline	Visit 3 Day 2	Visit 4 Day 15 (± 1 day)	Visit 5 Day 29 (± 2 days) D-Squame Challenge		Visit 6 Day 30	Visit 7 Day 31	Visit 8 Day 32	Visit 9 Day 33	Visit 10 Day 34
	Days -7 to -5					Pre Challenge	Post Challenge	Regression Period (no product use/soap use only)				
Baseline Corneometer Measurements – Area 1 & 2 (Face) and Area 5 & 6 (Leg)			X									
Randomization			X									
Dispense Randomized Product and Product Diary Card			X									
Randomized Product Application (Site Supervision) [2]			X	X	X							
TEWL Measurements – Area 1 & 2 (Face) and Area 5 & 6 (Leg)					X	X		X	X	X	X	X
Corneometer Measurements – Area 1 & 2 (Face) and Area 5 & 6 (Leg)				X	X	X		X	X	X	X	X
Post First Application; 30 minute and 6-hour Corneometer Measurements – Area 1 & 2 (Face) and Area 5 & 6 (Leg)			X									
TEWL and Corneometer Measurements **BEFORE** D-Squame Challenge Area 3 & 4 (Face) and Area 7 and 8 (Leg)						X						
D-Squame Challenge Area 3 & 4 (Face) and Area 7 and 8 (Leg)						X						
TEWL and Corneometer Measurements **AFTER** D-Squame Challenge[3] Area 3 & 4 (Face) and Area 7 and 8 (Leg)							X					
D-Squame Discs Protein Content Measurements							X					
Return Study Products and Product Diary Card (Subjects do not Return Standard Soap)						X						

Procedure	Visit 1 (Screening)		Visit 2 Day 1 Baseline	Visit 3 Day 2	Visit 4 Day 15 (± 1 day)	Visit 5 Day 29 (± 2 days) D-Squame Challenge		Visit 6 Day 30	Visit 7 Day 31	Visit 8 Day 32	Visit 9 Day 33	Visit 10 Day 34
	Days -7 to -5					Pre Challenge	Post Challenge	Regression Period (no product use/soap use only)				
Return Soap Dish and Standard Soap Diary Cards												X
Adverse Event Assessment [4]	X		X	X	X	X	X	X	X	X	X	X
Study Conclusion/Subject Exit												X

Abbreviations:

TEWL = Trans-epidermal water loss

Footnotes:

All Subjects will have their visits scheduled at approximately the same time of day for each visit for the duration of the study (Except Day 29). Assessments will be conducted 24hrs ± 1hr after supervised application at Visit 2

The diary (for both soap and product use) will be used to maintain and record compliance and to capture subject comments, recording of medications taken or adverse events experienced.

The diary (for both soap and product use) will be reviewed by the Investigator or their designee at each visit.

First product application will be conducted at the site under the supervision of the investigator or their designee.

1. Trained examiner assessments and subject self-assessments of face and leg dryness will be conducted at screening and baseline visits to confirm compliance with inclusion criterion 6 (face) and 7 (legs). As per Appendix 2.
2. Supervised product application will occur following completion of all visit assessments and measurements, except at Visit 2, where additional post-baseline corneometer measurements will be conducted 30 minutes and 6-hours after first supervised product.
3. During the D-Squame challenge, TEWL will be assessed after each set of 3 discs have been applied and removed (total of 9) from each side of the face and each set of 4 discs have been applied and removed (total of 12) from each leg.
4. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by completing the Informed Consent Form (ICF).

2 INTRODUCTION

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

The skin is a vital organ which primarily separates and defends the body from the external environment. Dry skin is common in the general population, and is characterized by a rough, flaky profile which has lost a portion of its otherwise flexible and elastic properties. The stratum corneum (SC) is a highly organized, structural layer of dead skin cells that is essential for the maintenance of the water gradient between the uppermost layers of the skin.

Several factors can render the skin's moisture barrier prone to disturbance and potentially induce dryness, irritation or itch, having an overall impact on the quality of the skin (Harding, 2004). Dry skin conditions are common and topical moisturizing creams are regularly used by those who suffer from dry skin to help restore and protect the skin's disturbed moisture barrier.

There are numerous methods to evaluate the potential of topical cosmetic products to moisturize the skin, reduce the severity of existing skin conditions caused by dryness, repair the skin barrier function and protect against further damage. Barrier function damage and rate of repair can be measured by physiological changes in the level of moisturization in the stratum corneum and in the rate of trans-epidermal water loss (TEWL). Objective measurements of the moisturization of the stratum corneum are usually taken with a Corneometer, a non-invasive instrumental probe. TEWL is the rate at which water permeates the stratum corneum and evaporates from the skin surface and objective measurements of TEWL are usually taken with non-invasive instrumental probes such as the Tewameter and Aqua-flux.

The objective of this clinical study is to evaluate the impact of 4-weeks of twice-daily topical application of two developmental moisturizing cream formulations on skin barrier function in healthy subjects with dry, sensitive skin on the face and lower legs.

This study will be considered successful if twice-daily application of both investigational products with the standard soap results in a statistically significant ($p \leq 0.05$) decrease in change from baseline in facial TEWL at Day 29, compared to the use of standard soap only.

2.1 Study Rationale

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed two cosmetic moisturizer formulations intended to be suitable for use by consumers with dry, sensitive skin.

Clinical data are required to demonstrate the efficacy of the developmental formulations in the target population.

Instrumental measurements of skin barrier function (TEWL; using a Tewameter) and skin moisturization (using a Corneometer) will be performed at specified time points. These measurements have been included to objectively model skin moisturization and barrier function throughout the product use and regression periods of this study.

Measuring TEWL with a Tewameter is a standard, non-invasive method to characterize the integrity of the skin's barrier function by determining the water vapour gradient between two pairs of vertically-aligned sensors (Rogiers, 2001)

Measuring skin moisturization with a Corneometer is also a standard, non-invasive method and uses electrical capacitance to model the water content of the skin (Heinrich *et al*, 2003).

Evaluation of the impact of a physical challenge to the skin barrier after 4-weeks of product use, at both legs and both sides of the face, will be performed using a repeat tape-stripping method. This physical challenge is a minimally-invasive and commonly-used technique known as Squamometry (Charbonnier *et al*, 1998) and consists of the consecutive removal of corneocytes from the stratum corneum with adhesive discs. Quantification of the amount of protein material removed from the stratum corneum with the adhesive discs will provide a measure of the degree of adhesion of the corneocytes, and therefore an indicator of the strength of the skin barrier.

TEWL measurements will also be taken at the tape-stripped sites to provide a direct measure of the ability of the skin to resist damage caused by physical insult and to monitor the recovery of skin barrier function post-challenge.

A 6-day regression period, which will commence after the 4-week treatment period, will enable an assessment of the lasting effects of the study products on skin moisturization and barrier function through TEWL and Corneometer measurements. It has been reported that a single application of a topical moisturising cream does not cause long-lasting effects, but that repeated applications (i.e. twice-daily for at least seven days) can result in a significant increase in moisturization for at least one week after application has ceased (Zhai and Maibach, 1998)

Complete information for the developmental moisturizer formulations may be found in the single reference safety document (SRSD), which for this study is the Safety Statement.

2.2 Background

Water constantly evaporates from the deeper layers of the skin, an effect known as transepidermal water loss (TEWL). Dry skin is brittle and rigid and any increase in the water content of dry skin contributes to an improvement in skin quality. The ability of skin to retain moisture depends on the lipid bilayer between the corneocytes. Healthy skin on the cheeks of the face has a reported TEWL of 12.9-16.1g/m²/hr and the healthy skin of the calf area of the legs has a reported TEWL of 6.9-12.2g/m²/hr (Kottner *et al*, 2013)

Topical moisturizers prevent evaporation of water from the skin by forming an occlusive coating on the surface of the stratum corneum. A layer of petrolatum, for example, applied to normal skin can reduce the TEWL by 50–75% for several hours. The higher the lipid content of a formulation, the greater the emollient effect.

The investigational products are developmental formulations intended to be used as cosmetic moisturizers by healthy consumers with dry, sensitive skin and have been formulated to include lipids that are similar to those present in the stratum corneum which form a lamellar structure to promote skin barrier function restoration. The formulations have also been designed to provide topical moisturization while minimizing the quantity of known irritants and allergens.

2.3 Mechanism of Action/Indication

The European Union Cosmetics Directive defines a cosmetic as any substance or preparation intended to be placed in contact with the external parts of the human body with a view

exclusively or mainly to cleaning, perfuming, changing appearance and/or correcting body odours and/or protecting or keeping in good condition (European Commission (EC), 2009).

The investigational products are cosmetic moisturizing creams intended to be applied topically by consumers with dry, sensitive skin on the face and lower legs. They contain humectants to increase the water content of the stratum corneum and lipids to form an occlusive layer on the skin surface to prevent the water evaporating.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the impact of 4 weeks of twice-daily facial application of the investigational products and standard soap on skin barrier function compared to the use of standard soap only.	Change from baseline in TEWL at Day 29 (Area 1 compared to area 2)
Secondary	
Efficacy	
To evaluate the impact of 4 weeks of twice-daily leg application of the investigational products and standard soap on skin barrier function compared to the use of standard soap only.	Change from baseline in TEWL at Day 29 (Area 5 compared to area 6)
To evaluate the impact of 2 weeks of twice-daily face and leg application of the investigational products and standard soap on skin barrier function compared to the use of standard soap only.	Change from baseline in TEWL at the following time-points: • Day 15. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of single face and leg application of the investigational products on skin moisturization.	Change from baseline in Corneometer values at the following time-points: • Day 1: 30 minutes after first supervised application; • Day 1: 6 hours after first supervised application; • Day 2: 24 hours after first supervised application. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of 2 and 4 weeks of twice-daily face and leg application of the investigational products and standard soap on skin moisturization compared to the use of standard soap only.	Change from baseline in Corneometer values at the following time-points: • Day 15; • Day 29. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of a post-treatment regression period of 6-days of no investigational product application on skin barrier function.	Change from baseline in TEWL at the following time-points: • Day 30; • Day 31; • Day 32; • Day 33;

	• Day 34. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of a post-treatment regression period of 6-days of no investigational product application on skin moisturization.	Change from baseline in Corneometer values at the following time-points: • Day 30; • Day 31; • Day 32; • Day 33; • Day 34. (Face: area 1 compared to area 2; leg: area 5 compared to area 6)
To evaluate the impact of a repeated tape-strip challenge on skin barrier function following 4 weeks of twice-daily face and leg application of the investigational products and standard soap compared to the use of standard soap only.	Change from pre-challenge TEWL at Day 29 to the following time points: • Removal of 3 tape strips (face) and 4 tape strips (legs); • Removal of 6 tape strips (face) and 8 tape strips (legs); • Removal of 9 tape strips (face) and 12 tape strips (legs). (Face: area 3 compared to area 4; leg: area 7 compared to area 8)
To evaluate the impact of a repeated tape-strip challenge on skin barrier integrity following 4 weeks of twice-daily face and leg application of the investigational products and standard soap compared to the use of standard soap only.	Total protein content extracted from all tape-strips: (Face: area 3 compared to area 4; leg: area 7 compared to area 8)
Safety	
To evaluate local tolerance.	Frequency and severity of adverse events.

This study will be considered successful if twice-daily application of both investigational products with the standard soap results in a statistically significant ($p \leq 0.05$) decrease in change from baseline in facial TEWL at Day 29, compared to the use of standard soap only.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, evaluator-blind, single-centre, two treatment regimen (test product 1 and test product 2), controlled (standard cleanser soap use only), split-body (left and right; side of the face and lower legs), parallel group clinical study designed to evaluate the impact of 4-weeks of twice-daily topical application of two developmental moisturizing cream formulations on skin barrier function in healthy subjects with dry, sensitive skin on the face and lower legs.

The chosen application sites are the face and the lower legs. The legs will be designated right and left, and the face will be split to right or left side.

There will be two treatment regimens included in this study;

- Treatment Regimen 1 = Test Product 1 + Standard Soap
- Treatment Regimen 2 = Test Product 2 + Standard Soap

Subjects will be randomized to one of these two treatment regimens. Subjects will be further randomized to have their treatments within regimen randomized to Left and Right side. Subjects will apply their allocated moisturizer to the designated side, per the randomization, the same side of the face and the same leg (left or right) will be used throughout.

Subjects will give their written informed consent prior to any study procedures taking place.

Healthy female volunteers aged 18 to 65 with self-reported dry and sensitive skin on their face and very dry skin on their legs will be recruited for this study.

To confirm whether subjects have sensitive skin they will be required to answer "yes" to the following inclusion criteria question: "Do you consider yourself to have dry, sensitive skin on your face and very dry skin on your legs?".

To confirm (per Appendix 1) whether subjects have dry skin on **both sides of their face** at the screening visit (Visit 1) and baseline visit (Visit 2) they will:

- Self-assess the feeling of tightness they are currently experiencing on each side of the face (scale range 0-4);
- Undergo dermatologist assessment of dullness, scaling and roughness on each side of the face (scale range 0-4 for each parameter).

The sum of the subject self-assessment and dermatologist assessment scores for each side of the face will be calculated. The total possible score for each side of the face is 16.

To be eligible to participate in this study, a subject must:

- Have a total score of ≥3 for each side of the face;
- Have no more than a 0.5-unit difference in total score between each side of the face;
- Have a dermatologist score of ≥1 (slight) for roughness for each side of the face;
- Have no scores of 4 (very severe) for tightness, dullness, scaling or roughness.

To confirm (per Appendix 1) whether subjects have very dry skin on **both their legs** at the screening visit (Visit 1) and Baseline visit (Visit 2) they will:

- Undergo dermatologist assessment of dullness, scaling and roughness on both legs (scale range 0-4 for each parameter).

The sum of the dermatologist assessment scores for each leg will be calculated. The total possible score for each leg is 12.

To be eligible to participate in this study, a subject must:

- Have a total score of ≥6 for each leg;
- Have no more than a 1-unit difference in total score between each leg;
- Have no scores of 4 (very severe) for dullness, scaling or roughness.

Subjects considered eligible to participate in the study will undergo a 5 to 7-day washout period, during which only the standard soap will be used on the face and legs as a standard cleanser. Subjects will be instructed to use the standard soap to cleanse the face and lower legs, as needed. Subjects will be provided a paper diary to complete during the washout period to record compliance with the soap use. This standard soap will also be used throughout the study.

At the baseline visit (Day1/Visit 2), after completion of the washout period, subjects who are deemed eligible to continue in the study will be randomized to one of the two treatment regimens. Baseline instrumental assessments of TEWL and skin moisturization (using a Corneometer) will be taken before prior to any test product application (moisturizer). Study staff will dispense study products and product use diary cards to subjects. First application of

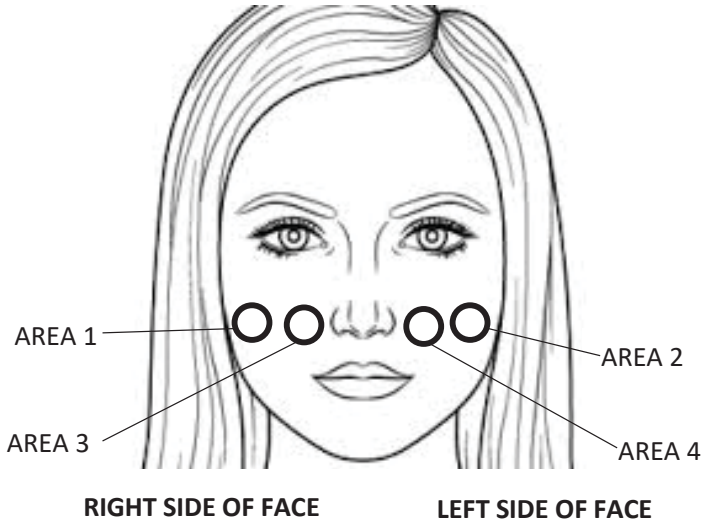
study product will be supervised by the study site staff. Subjects will be instructed to apply their assigned study product (moisturizer) to the designated side of the face and leg. Instrumental measurement of skin moisturization (using a Corneometer) will be performed at 30 minutes and 6 hours following the first single product application.

A total of 8 areas will be assigned to each subject:

Two areas on each side of the face, at the cheekbone between the nose and ear, will be assigned as close together as possible, without overlap, for all facial measurements of TEWL and moisturization as indicated in Figure 4-1:

- Area 1 (right face) and 2 (left face) will be the site used for face TEWL and Corneometer assessments throughout the treatment phase (Days 1 to 29) and the regression period (Days 29-34);
- Area 3 (right face) and 4 (left face) will be the site used for the face tape-strip challenge at Day 29.

Figure 4-1 Layout of Test Areas (Face):



Face:

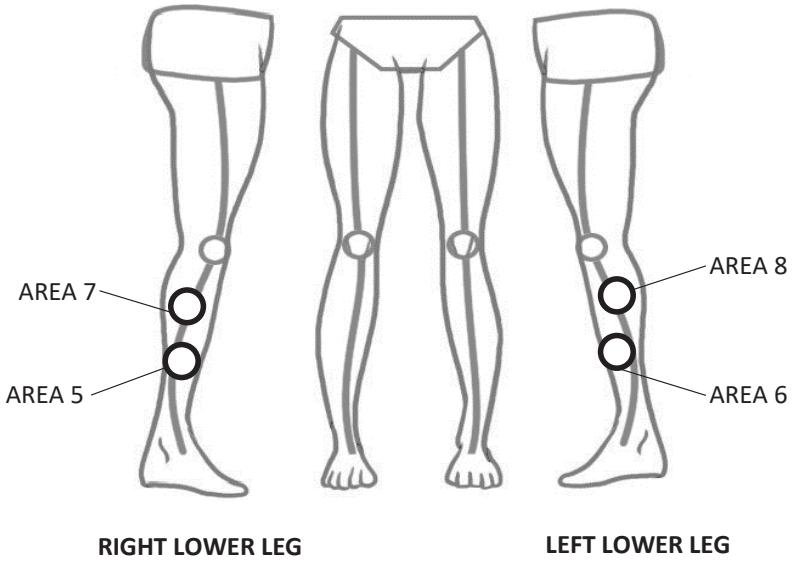
AREA 1 and 2 - TEWL and corneometry assessments throughout only

AREA 3 and 4 – D-Squame challenge location only

Two areas on the outside of each lower leg assigned below each knee and above each ankle will be assigned as close together as possible, without overlap, for all leg measurements of TEWL and moisturization as indicated in Figure 4-2:

- Area 5 (right leg) and 6 (left leg) will be the site used for leg TEWL and Corneometer assessments throughout the treatment phase (Days 1 to 29) and the regression period (Days 29-34);
- Area 7 (right leg) and 8 (left leg) will be the site used for the leg tape-strip challenge at Day 29.

Figure 4-2 Layout of Test Areas (Leg):



Lower Leg:

AREA 5 and 6 - TEWL and corneometry assessments throughout only

AREA 7 and 8 – D-Squame challenge location only

Subjects will return to the site on Day 2 (Visit 3), 24 hours (±1hr) after first single product application on Day 1, without applying any products (no cleansing/standard soap use or study product application) at home since the first supervised use. Subjects will be permitted to wash their face and legs with tap water only as needed, but not within 2 hours of the visit time. Instrumental measurement of skin moisturization (using a Corneometer) will be performed at 24 hours (±1hr) after first single product application on Day 1.

Second application of study moisturizer will be performed under site supervision following completion of the Corneometer measurements at Day 2 (Visit 3).

Subjects will be instructed to cleanse with the standard soap and continue to apply their study product (moisturizer) to the randomly designated side of the face and leg, twice-daily (in the morning and evening, approximately 8-12 hours apart), for 4 weeks (28±2 days).

There will be no cleansing/standard soap use or study product application in the morning of each of the assessment study site visits (i.e. visits 3, 4, and 5) of the treatment phase. Subjects will be permitted to wash their face and legs with tap water only as needed, but not within 2 hours of the visit time. Study product application (moisturizer only) will be performed under site supervision following Corneometer assessments at Day 2 (Visit 3), and TEWL and Corneometer assessments at Day 15 (Visit 4) There will be no product application at Day 29 (Visit 5). Last application will be by the subjects at home on the evening of Day 28±2 days.

During the treatment phase, TEWL will be measured at Areas 1 and 2 (face) and Areas 5 and 6 (legs) on Day 1 at baseline (pre-product application) and on Day 15 (Visit 4), and Day 29 (Visit 5). Moisturization will be measured at Areas 1 and 2 (face) and Areas 5 and 6 (legs) on Day 1 at baseline (pre-product application), 30 minutes and 6 hours post first supervised application, on Day 2 (Visit 3), Day 15 (Visit 4), and Day 29 (Visit 5).

These measurements have been included to objectively model skin moisturization and barrier function throughout the product use and regression periods of this study.

The D-Squame physical challenge will be conducted at Areas 3 and 4 (face) and Areas 7 and 8 (legs) at Day 29 (Visit 5). These areas will be subject to the sequential application and removal of D-Squame adhesive discs; 3, 6, and 9 discs will be removed from the right and left side of the face and 4, 8, 12 discs removed from the right and left leg. TEWL will be measured prior to tape-stripping and after each set of 3 (face) or 4 (leg) discs. The amount of protein recovered by each disc will also be measured with a SquameScan device (Lu *et al*, 2014).

A regression period of 6 days during which subjects will only use the standard soap twice-daily on their face and lower legs will also start on Day 29 (Visit 5). Subjects will return their assigned study product at Day 29 (Visit 5).

During the regression phase, TEWL and moisturization will be measured at Areas 1 and 2 (face) and Areas 5 and 6 (legs) on Days 30, 31, 32, 33 and 34 (Visits 6-10).

Day 34 (Visit 10) is the final assessment day and subjects will exit the study after all procedures and assessments have been completed. The soap dish and diary cards will be returned at this visit.

Subject diary cards will be reviewed at each visit and missed, or additional applications will be recorded in the CRF.

Throughout the study, every effort will be made to ensure subject study site visits are scheduled for similar times of day for all subjects throughout the study. Subjects will be acclimatized to the environment of a controlled temperature (20-22ºC) and relative humidity (40-60%) room for a period of at least 30 minutes before all TEWL and Corneometer measurements are conducted throughout the study (Berardesca *et al*, 1997)

4.2 Rationale for Study Design

A 5 to 7-day washout period is included to standardize product use across the study population prior to randomization. The standard soap will also be used throughout the study duration as a standard cleanser for all subjects to maintain a level of standard cleansing.

A 4-week study duration is selected to allow for at least one complete turnover of corneocytes in the stratum corneum. A 6-day regression period is included to evaluate any lasting effects on skin dryness and barrier function following 4 weeks twice daily usage.

TEWL assessments are included in this study to provide an objective measure of skin barrier function throughout the product use and regression periods of this study.

Corneometer assessments are included in this study to give objective measurements of skin moisturization throughout the product use and regression periods of this study.

The physical challenge is a minimally invasive and commonly used technique and consists of the consecutive removal of corneocytes, the cells which compose most of the SC and contribute to the barrier function of the skin, from the skin surface, using adhesive discs. The quantification of the amount of protein material removed from the SC using these adhesive discs provides a measure of the degree of adhesion of the corneocytes and therefore the strength of the skin barrier (Voegeli *et al*, 2007).

The inclusion of a regression period following the treatment period will be used to assess the lasting effects of the test product on the skin barrier function and moisturization, through TEWL and Corneometer assessment for up to 6 days after product application has stopped. Zhai and Maibach reported that a single application of a moisturizer does not cause long-lasting effects, but that repeated applications of a moisturizer (that is, two times a day for at least seven days)

can result in a significant conductance increase for at least one week after application has ceased, demonstrating both short term and long-term benefits. (Zhai and Maibach, 1998)

The typical amount of body hair of male subjects makes objective instrumental assessments of moisturization and TEWL challenging, therefore, only female subjects will be recruited. To avoid confounding effects, subjects will be instructed to shave their legs (no other hair removal methods are permitted) on the first day of the washout phase and will not be permitted to shave their legs (or use any other hair removal process) at any other point during the study period until they exit the study.

There is a degree of heterogeneity between different areas of the body with regards to hair follicles, number of sebaceous and sweat glands and varying levels of exposure to sunlight and the resultant effects of ultraviolet (UV) radiation. While the study products have been designed to repair barrier function at all areas of the body, the magnitudes and variability of TEWL and Corneometer benefits at the face and leg are expected to differ.

4.3 Justification for Dose

The application quantity of the study products has been selected to reflect typical consumer usage of these types of products at approximately 2 mg/cm^2 (Simion *et al*, 2006). The first administration will be supervised by a trained technician when the subjects are at the study site.

An 8-hour minimum period between study product applications is required, except for Day 1, where measurements of TEWL and moisturization will be further taken at 24-hours following the first supervised application. Study product will be applied following completion of all assessments and measurements.

For the home-use period, after cleansing with the supplied standard soap, subjects will be instructed to apply 2 pumps of their assigned moisturizing cream to the allocated side of their face, including forehead and chin, twice-daily (in the morning and evening). Two pumps of moisturizing cream over the surface area of a typical half-face equates to approximately 0.6 mL or 2 mg/cm^2. In addition, after cleansing with the standard soap, subjects will be instructed to apply a further 6 pumps of their assigned moisturizing cream to the outside of the allocated lower leg, from the bottom of the knee to above the ankle, twice-daily (in the morning and evening). 6 pumps of moisturizing cream over the surface area of the outer side of a typical lower leg equates to approximately 1.8 mL or 2 mg/cm^2. This will be the same application quantities for the side of the face and leg when performed at the study site, but subjects will not use the soap cleanser when at the study site.

Subjects will be reminded that, as with all skin care products when topically applied to the face, care should be taken to avoid getting the products into the eyes. If contact does occur, then subjects will be instructed to rinse the eyes thoroughly with water.

4.4 End of Study Definition

A subject is considered to have completed the study if she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Healthy female volunteers aged 18 to 65 with self-reported dry and sensitive skin on their face and very dry skin on their legs will be recruited for this study.

The typical amount of body hair of male subjects makes objective instrumental assessments of moisturization and TEWL dryness challenging, therefore, only female subjects will be recruited.

Approximately 220 subjects will be screened to randomize approximately 150 and ensure at least 60 subjects for each treatment regimen complete the entire study.

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

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

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is female who, at the time of screening, is between the ages of 18 and 65 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, the product application schedule, the Lifestyle Considerations, and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee (if the investigator is not suitably qualified), no clinically significant/relevant abnormalities in medical history or upon dermatologist examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements
5. A subject who responds "Yes" to the following question: Do you consider yourself to have dry, sensitive skin on your face and very dry skin on your legs?
6. A subject with an overall dryness assessment total score of ≥3 for each side of the face at screening visit (Visit 1) and baseline visit (Visit 2). With no more than 0.5-unit score difference between each side of the face. Including an examiner score of at ≥ 1 (slight) for the roughness parameter (Appendix 1)
7. A subject with an overall dryness assessment total score of ≥6 for each leg at screening visit (Visit 1) and baseline visit (Visit 2). With no more than 1-unit score difference between each leg. (Appendix 1)
8. A subject with a Fitzpatrick skin type I-IV (Appendix 2).

5.3 Exclusion Criteria

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

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product application or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A female subject who is pregnant (self-reported) or intending to become pregnant.
5. A female subject who is breastfeeding.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
8. A subject with current or recent (within 6 months before the start of the study) history of atopic lesions and/or eczema.
9. A subject with a history of allergic reactions to topical-use products, cosmetics or medications or their ingredients.
10. A subject with any history of significant diseases or medical conditions known to alter skin or eye appearance or physiologic response (e.g. Type 2 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.
11. A subject presenting open sores, pimples, or cysts at the application site (face or lower legs).
12. A subject with an active dermatosis (local or disseminated) that might interfere with the results of the study.
13. A subject currently using any medication which in the opinion of the investigator, may affect the evaluation of the investigational product, or place the subject at undue risk
14. A subject who has used any of the following topical or systemic medications up to 1 month before the screening visit or intends to use during the study period: immuno-suppressants, antihistamines, non-steroidal anti-inflammatory drugs (NSAIDS), and corticosteroids.
15. A subject who has used oral or topical treatment with vitamin A acid and/or its derivatives up to 1 month before the screening visit or intends to use during the study period.
16. A subject who intends to use any topical drug or medication on the proposed application areas.

17. A subject who has been vaccinated up to 1 month before the screening visit or is intending to receive a vaccination during their participation in the study.
18. A subject currently receiving allergy injections, or received an allergy injection within 7 days prior to Visit 1, or expects to begin injections during study participation
19. A subject with a recent history (within the last 5 years) of alcohol or other substance abuse.
20. A subject with any skin marks on the face or lower legs that might interfere with the evaluation of possible skin reactions (e.g. pigmentation disorders, vascular malformations, scars, tattoos, excessive hair, numerous freckles).
21. Subjects with corneal ulcers, keratoconus, blepharitis, meibomitis, pterygium, chemosis, moderately or severe hyperemia or other active ocular diseases.
22. A subject who has previously been enrolled in this study.
23. A subject who is unwilling to abstain from smoking tobacco or using any other nicotine-containing products.
24. A subject with visible sunburn on any of the test sites.
25. A subject with moles, tattoos, scars, hairs, etc. at the test areas if it is likely that they could affect the assessments.
26. A subject who has used self-tanning products on the test areas (face and arms) within 2 weeks prior to the screening visit.
27. A subject who intends to expose their skin to natural or artificial ultraviolet (UV) light (e.g. sunbathing or tanning beds).
28. A subject with any subject self-assessed or dermatologist dryness parameter score 4 (very severe) on the test areas of the lower legs or face (Appendix 1).
29. Any subject who, in the judgment of the Investigator, should not participate in the study.

5.4 Randomization Criteria

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

5.5 Lifestyle Considerations

During the entire study (screening – Visit 10) the following restrictions apply:

Subjects may be asked to remove their facial make-up at the screening visit to allow for the visual assessments to be made.

Subjects will not be permitted to use any other skin care products, including but not limited to: leave-on cosmetics, moisturizers, lotions, creams, sunscreens, soaps, cleansing, exfoliation products, etc. on their face or legs, other than the standard soap and study product(s) provided.

At all post baseline study visit days, subjects must cleanse their face and legs with the standard soap and then apply the test product (s) approximately 10-16 hrs before each study appointment (i.e. evening before).

No use of any product on the face or legs, including the standard soap and test product, within 10 hours of all instrumental measurements on visit days (no showering/bathing permitted with soaps/shampoo within this period) will be permitted.

Subjects will be permitted to wash their face and legs with water only on the day of site visit. However, on the day of site visit, subjects should not wash their face or legs less than 2 hours before the first instrumental measurement is taken.

On site visit days for visits 2 and 4, the morning product application will be performed at the site after all assessments have been completed. The second application on each of the days will be performed by the subjects at home approximately 8-12 hours following the on-site application.

There should be no introduction of new products during the study including but not limited to soap, laundry detergent, or fabric softener.

Subjects should avoid wearing tight or restrictive clothing on, or around the face or over the legs.

Chemical or physical hair removal methods or bleaching or dying of the hair on the face and legs is not permitted during the study. To avoid confounding effects, subjects will be instructed to shave their legs on the first day of the washout phase and will not be permitted to shave their legs (or use any other hair removal process) at any other point during the study period until they exit the study. Subjects may use the soap provided to create a lather to shave their legs on the first day of the washout period.

5.5.1 Alcohol and Caffeine

Subjects will abstain from alcohol on study visit days until all instrumental measurements have been taken.

Subjects will abstain from consuming caffeine-containing products on study visit days until all instrumental measurements have been taken.

5.5.2 Activity

Subjects will abstain from strenuous exercise, with heavy sweating (e.g. heavy lifting, weight training, calisthenics, aerobics) at least for 24 hours prior to study site visits.

5.6 Screen Failures

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

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

5.7 Sponsor’s Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems,

subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

All clinical assessments will be made by a single suitable trained examiner for all subjects throughout the study. The assessor will visually assess subjects for inclusion into the study at screening visit (Visit 1) and continued eligibility at the baseline visit (Visit 2).

Appendix 1 - Assessment of Overall Dryness will be used for examiner visual grading and subject self-assessment of the feeling of tightness for each side of the face and each of the legs, with half-point scores used as necessary to better describe the clinical condition. There should be no greater than 0.5-unit difference in scores between each side of the face and no greater than 1-unit different for each leg at the screening visit and at the baseline visit assessments to ensure a balance in the skin across the test sites at the visits. The examiner should be trained in the correct use of the assessment scale.

Any observed cutaneous response that can be described by the assessment of overall dryness scale will not typically be considered an adverse event. Only in the case of unusual reactions, in the opinion of the qualified dermatologist, will these reactions and the consequences observed upon evaluation be documented as AE's.

6 INVESTIGATIONAL/STUDY PRODUCTS

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Test Product 1	**Test Product 2**	**Standard Cleanser Soap**
Product Name	Developmental Moisturizing Cream 1	Developmental Moisturizing Cream 2	Simple Pure Soap
Pack Design	40ml Bottle with piston pump		125g bar soap
Dispensing Details	A kit will be dispensed to each subject containing 5 bottles		2 bars of soap with a soap holder

Product Master Formulation Code (MFC)	CCI [redacted]	CCI [redacted]	UK market place product
Usage Instructions	**FACE:** Apply 2 pumps of test product (approximately 0.3 ml × 2 = 0.6 ml) to the randomly assigned side of the face, including forehead and chin, twice-daily (in the morning and evening) after cleansing. **LEG:** Apply 6 pumps of test product (approximately 0.3 ml × 6 = 1.8 ml) to the randomly assigned lower leg (below the knee; above the ankle) twice-daily (in the morning and evening) after cleansing. Avoid contact with eyes. If contact occurs, rinse thoroughly with water. An 8-hour minimum period between daily study product applications is required, except for Day 1, where measurements of TEWL and moisturization will be further taken at 24-hours following the first supervised single application. On evening prior to study visit, apply the test product approximately 10-16 hrs before each study appointment. Study product will be applied following completion of all assessments and measurements under site supervision at the study site, and then 8 hours later by subject at home.		Wet soap with warm water and work into a lather. Cleanse the entire face and both lower legs (between the knees and the ankles). Avoid contact with eyes. If contact occurs, rinse thoroughly with water.
Route of Administration	Topical dermal application		
Return Requirements	All used/unused samples to be returned.		Used soap to be retained by the subjects.

Table 6-2 Sundry Items

Sundry Items to be supplied:

Item	**Supplied By**	**Pack Design**	**Dispensing Details**	**Return/Disposal Details**	
				Used Samples	**Unused Samples**
Soap dish	GSK CH	Commercial Pack	1 labelled soap dish will be dispensed to contain the soap during the study.	Destroy at site using site disposal procedures	Return
BiC® Twin Lady Sensitive Razors	GSK CH	Commercial Pack containing 5 razors	1 razor will be supplied per subject to shave their legs on the first day of the washout phase. Subjects will not be permitted to shave	Retained by the subjects	Return

			their legs or use any other hair removal process at any other point during the study period until they exit the study.		

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

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

6.1.1 Dosage Form and Packaging

Both the developmental test moisturizers will be supplied to the clinical site as packaged labelled bottles in kits for dispensing by site staff.

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

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

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

6.1.2 Preparation and Dispensing

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

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

6.2 Administration

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

The application quantity of each product has been selected to reflect typical consumer usage of these types of product; approximately 2 mg/cm^2 (Simion *et al*, 2006).

The first application of the assigned test moisturizer will be under supervision at the study site at baseline (Day 1/Visit 2), following all baseline assessments. This will be application of the test moisturizer product only; no cleansing (soap use) will be performed. Instrumental measurements of skin moisturization (using a Corneometer) will be performed at 30 minutes and 6 hours after first single product application.

Subjects will return to the site on Day 2 (Visit 3), 24 hours (±1hr) after first single product application, without applying any products (no cleansing/standard soap use or study product application) at home since the first supervised use. Subjects will be permitted to wash their face with tap water only, up to 2 hours prior to measurements. Instrumental measurements of skin moisturization (using a Corneometer) will be performed at 24 hours (±1hr) after first single product application.

Second application of study product (moisturizer only) will be performed under site supervision following completion of the Corneometer measurements at Day 2 (Visit 3).

The standard soap will be used to cleanse the entire face and both lower legs (between the knees and the ankles) as needed. Subjects will be instructed to continue to apply their study product (moisturizer) to the randomly designated side of the face and the lower leg, twice-daily (in the morning and evening, approximately 8-12 hours apart), for 4 weeks (28±2 days). An 8-hour minimum period between daily study product applications is required, except for Day 1,

There will be no standard soap use or study product application in the morning of each of the assessment study site visits (i.e. visits 3, 4, and 5) of the treatment phase. Study product application (moisturizer only) will be performed under site supervision following Corneometer assessments at Day 2 (Visit 3), and TEWL and Corneometer assessments at Day 15 (Visit 4).

There will be no product application at Day 29 (Visit 5). Last application will be by the subjects at home on the evening of Day 28±2 days. The assigned test moisturizer will be returned at Day 29 (Visit 5). Subjects do not return the standard soap. The soap dish with any unused (unopened) soap and the Diary Card are returned on Day 34 (Visit 10).

Subjects will be reminded to bring all their study products (test moisturizer) and their diary cards with them to each post-baseline visit, having applied study product (s) 10-16 hrs (evening) prior to their appointment time.

Subjects will not be permitted to cleanse face or legs with anything other than water (up to 2 hours prior to the visit time) on the day of each site visit, until after all site assessments have been performed

A 6-day Regression Period where subjects will not use any product, except the standard soap, will begin on Day 29. Subjects will continue to use the standard soap to cleanse their face and legs. There will be no other product application to these areas during the regression period.

Subjects will be reminded that as with all facial skin care products, care should be taken to avoid getting into the eyes. If contact does occur, then rinse thoroughly with water.

6.2.1 Dosing Errors

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

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

Such dosing errors occurring to a study subject are to be captured in the CRF. In the event of a dosing error, the sponsor should be notified immediately.

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

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

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

6.3 Investigational/Study Product Storage

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

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

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

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

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

6.4 Investigational/Study Product Accountability

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

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

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

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

Subjects should return their test moisturizer at Visit 5 (Day 29), and the labelled soap dish at Visit 10 (LSLV) or before if a subject withdraws or is withdrawn from the study. Any partially used soap and the supplied razor may be retained by subjects.

6.4.1 Destruction of Investigational/Study Product Supplies

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

6.5 Blinding and Allocation/Randomization

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

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

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

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

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

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

6.6 Breaking the Blind

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

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

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

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

6.7 Subject Compliance

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

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

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

6.8 Concomitant Medication/Treatment(s)

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

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

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

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

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

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion.

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

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

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

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening (Day -7 to -5)

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

The following procedures will be completed:

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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

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

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

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

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

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race. Fitzpatrick skin type (Appendix 2 - Fitzpatrick Skin Type Grading) will also be assessed by a trained evaluator and recorded on the CRF. The Fitzpatrick scale is a recognized tool for dermatological research into human skin pigmentation. This scale focuses on potentials for irritation, burns and hyperpigmentation, indicators for future product choices.

8.1.3 Medical History and Prior Medication/Treatment

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

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

Subjects will be reminded that during the study period they should inform the site if they experience any untoward medical occurrence or use any medications.

8.1.4 Clinical and Subject Assessment of Dryness

To confirm whether subjects have sensitive skin they will be required to answer "yes" to the following question at the screening Visit (Visit 1): "Do you consider yourself to have dry, sensitive skin on your face and very dry skin on your legs?". Inclusion criteria No.5 in the CRF.

To confirm whether subjects have dry skin (per Appendix 1) on **both sides of their face** at the screening visit (Visit 1) and baseline visit (Visit 2) they will:

- Self-assess the feeling of tightness they are currently experiencing on each side of the face (scale range 0-4);
- Undergo dermatologist assessment of dullness, scaling and roughness on each side of the face (scale range 0-4 for each parameter).

The sum of the subject self-assessment and dermatologist assessment scores for each side of the face will be calculated. The total possible score for each side of the face is 16.

To be eligible to participate in this study, a subject must:

- Have a total score of ≥3 for each side of the face;
- Have no more than a 0.5-unit difference in total score between each side of the face;
- Have a dermatologist score of ≥1 (slight) for roughness for each side of the face;
- Have no scores of 4 (very severe) for tightness, dullness, scaling or roughness.

To confirm whether subjects have very dry skin (per Appendix 1) on **both their legs** at the screening visit (Visit 1) and baseline visit (Visit 2) they will:

- Undergo dermatologist assessment of dullness, scaling and roughness on both legs (scale range 0-4 for each parameter).

The sum of the dermatologist assessment scores for each leg will be calculated. The total possible total score for each leg is 12.

To be eligible to participate in this study, a subject must:

- Have a total score of ≥6 for each leg;
- Have no more than a 1-unit difference in total score between each leg;
- Have no scores of 4 (very severe) for dullness, scaling or roughness.

Assessment results will be captured in the CRF.

8.1.5 Inclusion/Exclusion Criteria

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

8.1.6 Subject Eligibility

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

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

Eligible subjects will be dispensed the standard soap to use at home to cleanse their entire face and legs and a standard razor to shave their legs. A paper diary card will also be provided to complete at home.

8.1.7 Visit 2/Day 1 – Baseline Visit

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

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

8.1.8 Clinical and Subject Assessment of Dryness

Subjects will be re-assessed to confirm the overall dryness score. The same sites on the face and the legs will be visually assessed (touching of the skin is also acceptable) for parameters of dryness: dull appearance, roughness and scaling, by a trained examiner and the feeling of

tightness self-assessed by the subjects, under standard conditions of illumination. Per section Appendix 1 - Assessment of Overall Dryness and section 8.1.4.

Assessment results will be captured in the CRF.

8.1.9 Randomization

Each eligible subject may be randomized to one of the following four arms:

- Test Product 1 + Standard Soap (left); Standard Soap (right)
- Test Product 1 + Standard Soap (right); Standard Soap (left)
- Test Product 2 + Standard Soap (left); Standard Soap (right)
- Test Product 2 + Standard Soap (right); Standard Soap (left)

First use of the study product will be supervised by site staff as per directions provided.

8.1.10 Trans-Epidermal Water Loss

TEWL assessments for barrier function will be performed by a trained technician, using the Tewameter TM 300 (Courage & Khazaka (CK) electronic Cologne, Germany) device, following the European Expert Group on Efficacy Measurement of Cosmetics and Other Topical Products (EEMCO) Guidance for the Assessment of Transepidermal Water Loss in Cosmetic Sciences (Rogiers, 2001).

TEWL is a non-invasive method to measure the integrity of stratum corneum barrier function. The Tewameter probe measures the density gradient of the water evaporation from the skin indirectly by two pairs of sensors (temperature and relative humidity) inside a hollow cylinder. This is an open chamber measurement. A microprocessor analyses the values and expresses the evaporation rate in gram/square metre/hour ($g/m^2/hr$).

Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity 40-60%) for a period of at least 30 minutes before the instrumental assessments are performed (at each time point) (EEMCO, 1997).

TEWL will be measured at Area 1 and 2 on the face and Area 5 and 6 on the legs at baseline visit (Visit 2) prior to any study product application. Then measured throughout the study period per the study schedule.

The probe will be held in place on the skin for one measurement, for 40 seconds, to ensure that a stable value has been established. The probe should be placed keeping the same orientation of the probe on the subject's skin (relative to horizontal/vertical planes) for all measurements. The first part of the measurement belongs to the equilibration phase. The values of the last 10 seconds are averaged as the actual measurement values.

An increase in TEWL values shows damage to the skin barrier function.

Data are recorded by the device specific software CK Multi Probe and will be provided to GSK by direct entry of the values into the CRF.

8.1.11 Moisturization

Measurement of stratum corneum moisturisation will be performed by the electrical capacitance method with the Corneometer CM 825 (Courage & Khazaka, Cologne, Germany).

The measuring principle is based on changes in the capacitance of the measuring head, functioning as a condenser. Between the gold conductors of the probe an electrical field is built

which allows the dielectricity of the stratum corneum to be measured. Because the dielectricity of the skin varies as a function of its water content, the stratum corneum moisturisation can be measured.

Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity 40-60%) for a period of at least 30 minutes before the instrumental Corneometer assessments are performed (at each time point). (EEMCO, 1997).

Moisturization will be measured at Area 1 and 2 on the face and Area 5 and 6 on the legs at baseline visit (Visit 2) prior to any study product application. It will then be measured at 30 minutes post study product application and again 6 hours post study product application on Area 1 and 2 on the face and Area 5 and 6 on the legs. Then measured throughout the study period per the study schedule.

Corneometer values lower than 30 instrumental units (i.u.) usually represent very dry skin, while values between 30 und 50 i.u. are typical for dry skin on the forearm (Heinrich *et al*, 2003). These values should only be regarded as a rough estimation for the skin conditions mentioned, from which deviations are possible.

An increase in Corneometer values, therefore, corresponds to a skin-moisturising effect.

Corneometer data will be stored in a proDERM data base (4D) and will be provided to GSK by direct entry of the values into the CRF.

8.1.12 Supervised Product Application

Sufficient product will be provided to last the complete study period. Subjects will use the product at home, twice a day, during the study period.

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

Subjects will be asked to bring their assigned test product and the paper diary with them to each site visit; they will apply test product (moisturizer only) after completion of all study assessments at Visits 2, 3, 4 and 5, and the diary will be checked at each visit for completion.

8.1.13 Visit 3/Day 2 and Visit 4/Day 15

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

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

Subjects will return to the study site without having applied study products that morning.

Measures moisturization per sections 8.1.11 and 9.2.2 will be taken on Area 1 and Area 2 of the face and Area 5 and Area 6 of the legs at Visit 3 (Day 2).

Measures of TEWL per sections 8.1.10 and 9.2.1 and moisturization per sections 8.1.11 and 9.2.2 will be taken on Area 1 and Area 2 of the face and Area 5 and Area 6 of the legs at Visit 4 (Day 15. Following completion of all instrumental measurements, subjects will apply their assigned study product under site supervision.

8.1.14 Visit 5/Day 29 – D-Squame Challenge

Subjects will return to the study site without having applied study products that morning.

Measures of TEWL per sections 8.1.10 and 9.2.1 and moisturization per sections 8.1.11 and 9.2.2 will be taken on Area 1 and Area 2 of the face and Area 5 and Area 6 of the legs.

Additionally, TEWL will be measured prior to the D-Squame challenge at Area 3 and Area 4 on the face and Area 7 and Area 8 on the legs. TEWL will additionally be assessed after each set of 3 discs have been applied and removed (total of 9) from each side of the face and each set of 4 discs have been applied and removed (total of 12) from each leg.

The 4 designated D-Squame sites will be stripped with repeated application and removal of D-Squame discs.

Subjects will return all study test product, except the standard soap, which they will continue to use during the regression period only.

8.1.15 Visit 6/Day 30, Visit 7/Day 31, Visit 8/Day 32, Visit 9/Day 33 and Visit 10/Day 34 – Regression Period

Subjects will continue to apply the standard cleanser (Simple Soap) only in the morning and evening each day during the regression period, and will return to the study site each day, having cleansed their skin with water (only) no later than 2 hours prior to the first instrumental measurement.

Measures of TEWL per sections 8.1.10 and 9.2.1 and moisturization per sections 8.1.11 and 9.2.2 will be taken on Area 1 and Area 2 of the face and Area 5 and 6 of the legs each day of the Regression Period.

8.2 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

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

8.3 Study Conclusion

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

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

8.4 Follow-up Visit

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

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

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

9.2 Efficacy Assessments

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

9.2.1 Trans-Epidermal Water Loss

Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity 40-60%) for a period of at least 30 minutes before the instrumental assessments are performed (at each time point) (EEMCO, 1997).

TEWL measurements will be taken on different parts of each designated area on each location (face and legs) so the measured parts do not overlap. Measurements will be taken in triplicate for Area 1 and 2 of the face and Area 5 and 6 on the legs and in duplicate on the D-Squame Challenge area; Area 3 and 4 of the face and Area 7 and 8 of the legs. The average (mean) reading will be taken for each area and each time point. TEWL will be measured throughout the study period per the study schedule.

Additionally, TEWL will be measured prior to the D-Squame challenge at Area 3 and Area 4 on the face and Area 7 and Area 8 on the legs. The four designated D-Squame sites will then be stripped with repeated application and removal of D-Squame discs. TEWL will be measured after the removal of 3, 6 and 9 discs from the face and 4, 8 and 12 discs for the legs.

The same operator should be used throughout the study for any given measurement, in order to reduce the variability.

9.2.2 Moisturization

Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity 40-60%) for a period of at least 30 minutes before the instrumental Corneometer assessments are performed (at each time point) (EEMCO, 1997).

Moisturization will be initially measured at Area 1 and 2 of the face and Area 5 and 6 on the legs at baseline visit (Visit 2) prior to any study product application. It will then be measured at 30 minutes and 6 hours post first single study product application on Area 1 and 2 on the face and Area 5 and 6 on the legs. Then measured throughout the study period per the study schedule.

The Corneometer probe will be placed in contact with the skin of the subject's test site for 1-2 seconds per measurement. The Corneometer measurements will be taken 5 times in total and then an average (mean) reading will be calculated for each site and time point, following the EEMCO Guidance for the Assessment of Stratum Corneum Moisturisation (Berardesca *et al*, 1997).

The same operator should be used throughout the study for any given measurement, in order to reduce the variability.

9.2.3 D-Squame Challenge – Tape Stripping

A series of D-Squame discs will be gently smoothed over the designated D-Squame areas by applying a uniform pressure for 5 seconds with a stamp to ensure consistent adhesion to the skin. Each disc will be pulled off the skin with one fluent and decisive movement.

There will be a maximum of 9 D-Squame discs (in groups of 3) removed from Area 3 and 4 on the face repeatedly. TEWL will be measured (per section 9.2.1) pre-challenge and after 3, 6 and 9 discs have been removed.

There will be a maximum of 12 D-Squame discs (in groups of 4) removed from each leg (Area 7 and 8) repeatedly. TEWL will be measured (per section 9.2.2) pre-challenge and after 4, 8 and 12 discs have been removed.

A total of 42 D-Squame discs will be taken from each subject (two sets of 9 discs from each side of the face and two sets of 12 discs from the two separate sites of each lower leg). The D-Squame discs will be collected and analysed for protein content. Staff will continuously assess the subject for discomfort and visually assess the skin condition after removal of each disc.

The D-Squame discs will be analysed at the study site the same day and destroyed immediately afterwards.

The method of D-Squame stripping can provoke redness in the test areas. This is usually limited to areas of direct contact with the D-Squame. Since this reaction is anticipated and considered a normal reaction after D-Squame challenge, stripping reactions will not be documented as adverse events (AE). Only in case of unusual reactions, these reactions and the consequences upon the evaluation of the respective test areas will be documented as an AE.

9.2.4 Measurement of Protein from D-Squame Discs

The protein content of each D-Squame disc will be analysed at the study site on the same day as the stripping samples are taken, using a SquameScan 850 (Heiland electronic GmbH). Following the protein analysis, the D-Squame discs will be destroyed.

SquameScan 850 is the instrument used to indirectly measure the protein content extracted from the skin by D-Squame tape strips. Determination is performed by measuring the optical absorption of the strip at about 850 nanometres (nm; infrared light). The value displayed in % is proportionally related to the protein content.

The protein content will be analysed for each of the discs obtained from the D-Squame stripping on Area 3 and Area 4 of the face and Area 7 and Area 8 of the legs. The total amount for each challenge area will be captured in the CRF and reported to 2 decimal places.

The D-Squame discs will be classified by GSKCH as human biological samples. Disc destruction will occur the same day as the samples are taken and documented in the appropriate logs. A certificate of destruction will be provided to GSK.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

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

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

Events Meeting the AE Definition:

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

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Any observed cutaneous response that can be described by the assessment of overall dryness scale will not typically be considered an adverse event. Only in the case of unusual reactions, in the opinion of the qualified dermatologist, will these reactions and the consequences observed upon evaluation be documented as AE's
- Any localised response to the D-Squame disc application and removal on the face and legs, unless more severe than expected in which case will be captured as an AE.

10.2 Definition of a Serious Adverse Event (SAE)

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

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

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

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

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

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

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

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

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

10.4 Reporting Procedures

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

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

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

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

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

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

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

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

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form

(subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

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

It is essential to enter the following information:

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

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

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

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

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

10.5.2 Assessment of Causality

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

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

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

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

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

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

transmission of the SAE data to GSK CH. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of Adverse Events

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

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

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

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

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

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

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

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

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

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

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

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

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

10.8.2 Action to be Taken if Pregnancy Occurs

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

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

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

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

11 DATA MANAGEMENT

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

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

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

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, 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 Section 8 and 9. The CRF can be used as a source document at the discretion of data management.

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

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

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

11.2.1 Data Queries

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

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

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

11.3 Processing Patient Reported Outcomes

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

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

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

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

In this study subjects will be provided with a paper diary card to complete during the washout and home use period. Subject self-assessment responses will be collected directly in the CRF.

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

The sample size is determined with the success criteria of the study in mind, that each developmental product will be significantly beneficial (superior) on change from baseline in TEWL measurements following 28 days twice daily use on the face.

The distributional assumptions underlying the calculations are taken from the pilot study CCI (GSK data on file) for which change from baseline (BL) in TEWL for the face is used. The leg responses for this study are secondary and not considered in the sample size estimation. From the pilot study it is expected that leg treatment effects will be larger and also variability reduced compared to face values.

In the pilot study the mean change from baseline between active (test moisturizers) and control (soap only) groups in terms of face TEWL at Day 29 was -1.24. Each subject will receive a pair of products to be applied randomly to Left/Right or Right/Left sides consistently throughout the trial. The primary response will therefore be a pair of changes from BL in face TEWL for each test product vs. a control (soap only). The square root of the Mean Square Error (MSE) from the analysis of the pilot study (CCI is estimated as 2.199, with 60 subjects directly comparing test product with control with a mean difference in change from BL face TEWL of -1.24 the power to detect such a difference at the two-sided 5% significance level is approximately 86%. Via a simulation study (50,000 simulated studies) we can allow each group of 60 subjects receiving a test product to be compared to 120 subjects who receive control (soap only), 60 who received the test product, and 60 who got the other test product, so some contributions are within subject and some between. This results in an estimated power for any single test product versus control (soap only) of approximately 89.2% and for both test products to achieve significance of 80.0%.

The study is therefore powered (89%) to ensure individual treatments result in significant improvement in TEWL at Day 29 on the face compared to soap alone. For both test treatments to reach success it is estimated that there is 80% power.

12.2 Statistical Methods and Analytical Plan

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

12.2.1 Definition of Analysis Populations

- The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject actually received.
- The (Modified) Intent-To-Treat (MITT) population will comprise all randomized subjects who receive at least one dose of study product and have at least one post randomized assessment of efficacy. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.
- The PP population includes all MITT subjects who fully comply with all study procedures and restrictions. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters.

12.2.2 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.2.3 Demographic and Baseline Characteristics

Age and other continuous demographic and clinical (e.g. Clinical and Subject assessment of skin dryness) baseline variables will be summarized using descriptive statistics such as means, medians and standard deviation. Gender, race and other categorical demographic and clinical (e.g. Fitzpatrick Skin Type) baseline variables will be summarized using frequency counts and percentages for the safety and ITT populations.

12.2.4 Study Product Compliance

Compliance with the planned study product use will be tabulated and summarized for the safety and ITT populations.

12.2.5 Prior and Concomitant Medications

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

12.2.6 Primary Analysis(es)

The primary means of assessing the outcome of the study is the analysis of the change from BL in TEWL (face) of each of the two developmental products, compared to standard soap use only, at Day 29.

Secondary analysis will be considered exploratory if the primary criteria for success is not met.

The primary analysis will be via a mixed model analysis of covariance with change from baseline to day 29 in TEWL (face) as the response variable. The model will include treatment and side of face as factors and baseline TEWL (for that side of the face) as covariate. Subject will be included as a random effect.

Within treatment means and 95% CI's will be quoted as will differences between treatments and 95% CI's, p-values for each treatment product versus control (soap only) comparison will be provided. The percentage effect of each test product versus control (soap only) will also be quoted. In the case of the assumptions underlying the model not being supported, a suitable transformation or non-parametric procedure will be used.

No imputation for missing values (due to drop out) will be used, however the likely impact will be discussed.

The MITT population will be considered primary for this analysis. Analysis of the PP population will be secondary.

There are two primary comparisons, 1 for each treatment product versus control, for success, both have to achieve statistical significance, hence no correction to the testing level is required for multiple comparisons.

12.2.7 Secondary Analysis(es)

Secondary variables include change from baseline in face and leg TEWL at Days 15 and 29 and Corneometer values at 30 minutes and 6 hours (Day 1) and 24 hours (Day 2) following first

single supervised test product use and Days 15 and 29. These will be analysed in an identical fashion to that detailed in the primary analysis.

Other variables include change from baseline in TEWL and corneometer values during the regression phase to Days 30-34. These will be analysed in an identical fashion to that detailed in the primary analysis, with baseline value as the Day 1 value.

The change in TEWL values from pre- to post D-Squame challenge on Day 29 will be analysed in an identical fashion to that detailed in the primary analysis, with baseline value as the pre-D-Squame value. Analyses will be for values after 3, 6 and 9 discs from the face have been removed and 4, 8 and 12 discs from the legs have been removed.

The D-Squame total face disc protein values and the total leg disc protein values will be analysed between treatments, with subject as random effect, using similar methods to those for the primary endpoint.

All secondary analyses will only be conducted for the MITT population alone.

12.2.8 Safety Analysis(es)

Adverse events will be tabulated according to the current version of the MedDRA.

Frequencies and percentages will be presented overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related AEs, AEs leading to discontinuation, and serious AEs will be presented for each of the test products.

12.2.9 Other Analysis(es)

No other analyses will be performed for this study.

12.2.10 Handling of Dropouts and Missing Data

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

12.2.11 Handling of Dropouts and Missing Data

No imputations will be made for dropouts or missing data.

12.2.12 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

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

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

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for

International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

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

13.3.3 Subject Information and Consent

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

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

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

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

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, pre-screening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

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

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

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

13.7 Conditions for Terminating the Study

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

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

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

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

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15 APPENDICIES

15.1 Appendix 1 - Assessment of Overall Dryness

Table 15-1 will be used for examiner visual grading and subject self-assessment of the feeling of tightness of dryness of each area, with half-point scores used as necessary to better describe the clinical condition.

There should be no greater than 0.5-unit difference in scores between each side of the face and no greater than 1-unit different for each leg at the screening visit and at the baseline visit assessments to ensure a balance in the skin across the test sites at each of these visits.

Table 15-1 Grading Scale for Overall Dryness

Dryness Parameter	Score	Description
Dull appearance (by trained examiner)	0	None
	0.5	
	1	Slight
	1.5	
	2	Moderate
	2.5	
	3	Severe
	3.5	
	4	Very severe
Roughness (by trained examiner)	0	None
	0.5	
	1	Slight
	1.5	
	2	Moderate
	2.5	
	3	Severe
	3.5	
	4	Very severe
Scaling (by trained examiner)	0	None
	0.5	
	1	Slight
	1.5	
	2	Moderate
	2.5	
	3	Severe
	3.5	
	4	Very severe
Feeling of tightness (by subject) *Face only*	0	None
	0.5	
	1	Slight
	1.5	
	2	Moderate
	2.5	
	3	Severe
	3.5	
	4	Very severe

Appendix 2 - Fitzpatrick Skin Type Grading

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

Table 15-2 Fitzpatrick Skin Type Grading

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

Appendix 3 - ABBREVIATIONS

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

Table 15-3 Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
CI	confidence interval
CRF	case report form
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EEMCO	European Group for Efficacy Measurements on Cosmetics and Other Topical Products
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSFV	First subject first visit
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	institutional review board
ITT	Intention to treat
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
NSAIDS	non-steroidal anti-inflammatory drugs
PI	principal investigator
QC	quality control
SAE	serious adverse event
SC	Stratum corneum
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
TEWL	Trans-epidermal Water Loss
UK	United Kingdom
US	United States