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# Clinical Protocol

## 207451

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## SUMMARY INFORMATION

<b>Title:</b>	A Proof of Concept (POC) Clinical Study to Investigate the Effects of a Developmental Cosmetic Moisturising Cream on the Barrier Function of Human Skin on the Face and Forearm
<b>Protocol Number:</b>	207451
<b>Sponsor:</b>	GlaxoSmithKline Consumer Healthcare (GSKCH) St. George's Avenue, Weybridge, Surrey, KT13 0DE, UK Tel: PPD
<b>Product Name:</b>	Moisturiser cream
<b>Development Phase:</b>	N/A

<b>Expert Advice Outside of Normal Working Hours:</b>	Tel: PPD
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	Germany
<b>Study Site Telephone Number:</b>	Tel: PPD
<b>Study Examiner(s):</b>	To be assigned per site staff designation log at study start.

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## PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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


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

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

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


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




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## PROCESS FOR AMENDING THE PROTOCOL

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

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

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

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

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## PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.

To highlight the change, the following features will be used:

To add text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**


To delete text: Use of Strikethrough e.g. ~~striketthrough~~


Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1	Non-Substantial/Minor <input checked="" type="checkbox"/>	Typo correction to details of the areas on the face and forearms at Day 30	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Synopsis – Study Design (Day 30) 3.1 Study Design (Day 30)	Signature: PPD
Protocol Version No.: 2.0	Substantial/ Major <input type="checkbox"/>				
Amendment No.: 2	Non-Substantial/Minor <input checked="" type="checkbox"/>	Typo correction to details of the areas on the face and forearms.  Correction to symbol error due to rendition pdf function error < replaced throughout	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Study design 3 Study Plan 6.4.1 D-Square Challenge  Study Design Diagnosis and Main Criteria for Inclusion	Signature: PPD
Protocol Version No.: 3.0	Substantial/ Major <input type="checkbox"/>				PPD



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	with <b><u>less than</u></b>		3. Study Plan (Visit 1 3.3 Type and Planned Number of Subjects 3.4 Study Design and Amount Justification 4.1 Inclusion Criteria 6.1.5 Assessment of Overall Dryness 6.2 Visit 2 – Baseline Visit 12.2 Appendix 2
	General corrections and clarifications throughout as indicated by <b><u>CAPITAL LETTERS, BOLD AND UNDERLINE</u></b> text		Study Design 3. Study Plan 3.2 Subject Restrictions 3.4 Study Design and Amount Justification 6.4.1.1 Measurement of Protein from D-Squame Discs

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Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 3	Non-Substantial/Minor <input checked="" type="checkbox"/>	Correction to the details of the Corneometry data storage.	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	6.2.2 Corneometry	Signature:  PPD
Protocol Version No.: 4.0	Substantial/ Major <input type="checkbox"/>				
Amendment No.:	Non-Substantial/Minor <input type="checkbox"/>		Informed Consent <input type="checkbox"/> Yes <input type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input type="checkbox"/> No CRF <input type="checkbox"/> Yes <input type="checkbox"/> No		Signature:
Protocol Version No.:	Substantial/ Major <input type="checkbox"/>				Date:





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Procedure	Visit 1 (Screening)	Regression Period (no product use)																
	D-7 to D-5	Visit 2 Day 1 Baseline Visit	Visit 3 Day 2 (24±1hr <sup>6</sup> )	Visit 4 Day 15 (± 24 hrs)	Visit 5 Day 29 (± 48 hrs) D-Squame Challenge		Visit 6 Day 30	Visit 7 Day 31	Visit 8 Day 32	Visit 9 Day 33	Visit 10 Day 34							
TEWL - Area 5 & 7 (Face) and Area 2 & 4 (Forearm) <b>BEFORE</b> D-Squame challenge					Pre X	Post												
D-Squame Challenge – Area 5 & 7 (Face) and Area 2 & 4 (Forearm)					X <sup>6</sup>													
TEWL Area 5 & 7 (Face) and Area 2 & 4 (Forearm) <b>AFTER</b> D-Squame challenge <sup>6</sup> (TEWL assessed after each set of 4 discs removed (total of 12) from the forearms and each set of 3 discs removed (total of 9) from the each side of the face)					X													
Measure protein content from all discs from each forearm and side of the face.					X													
Return Standard Soap												X						
Return Study Product (s) & Diary Cards					X													
Adverse event assessment <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X						
Study Conclusion/Subject Exit												X						

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**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 24 hours (hrs)  $\pm$  1hr after supervised application at Visit 2

- 1) Inclusion criteria 6 - Trained examiner assessments and subject response for measures of dryness on each side of the face and each forearm at Screening and Baseline visits (Appendix 2).
- 2) Including subject self-reported dry, sensitive skin on the face and body at Screening.
- 3) Visit 2 consists of Baseline Transepidermal water loss (TEWL) assessments at Face Area 6 (RIGHT) and Area 8 (LEFT) and Forearm Area 1 (RIGHT) and Area 3 (LEFT), prior to supervised product application.
- 4) Visit 2 consists of Baseline pre-application corneometry assessments at Face Area 6 (RIGHT) and Area 8 (LEFT) and Forearm Area 1 (RIGHT) and Area 3 (LEFT) prior to supervised product (s) application, as well as 30 minutes and 6 hours post supervised product application.
- 5) Supervised product (s) application following completion of all visit assessments and measurements.
- 6) D-Squame challenge on Face Area 5 (RIGHT) and Area 7 (LEFT) and Forearm Area 2 (RIGHT) and Area 4 (LEFT).

*Note:* 4, 8, 12 discs removed from the right and left forearms and 3, 6, 9 discs removed from the right and left side of the face.

- 7) Adverse events will be reported following first use of the standard soap. The use of any concomitant medication will be reported following subject provision of informed consent until completion of the study.

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## PROTOCOL SYNOPSIS FOR STUDY 207451

### Brief Summary


This is a randomised, evaluator-blind, single-centre, 3-arm, positive- and untreated-controlled, split body proof-of-concept clinical study designed to evaluate the impact on skin barrier function and moisturisation (on the forearm and face) of 4 weeks of twice daily topical application of a developmental cosmetic moisturising cream in subjects with dry, sensitive skin.

The chosen application sites for the treatment period are the volar forearms and the face. The forearms will be designated right and left, and the face will be split to right or left side. There are three treatment groups included in this study; Test Product/ No Treatment, Test Product/Positive Control and Positive Control/No Treatment. Treatments will be further randomised to which side of the face or volar forearm product will be applied.


Instrumental assessments of skin barrier function measured by Transepidermal Water Loss (TEWL) (using a Tewameter) and skin moisturisation (using a Corneometer) will be performed at various time points. Evaluation of the impact of a physical challenge to the skin barrier of both forearms and both sides of the face will be performed, by D-Squame tape stripping. A regression period of 5 days of no product use following the 4 week treatment phase will also evaluate skin barrier function by TEWL and moisturisation by corneometry on a daily basis.

### Objectives and Endpoints

Objectives	Endpoints
<b>Primary</b>	
To assess skin barrier function on the forearm after 4 weeks of using the test product compared to no treatment.	Change from baseline in TEWL measurements on Day 29 of test product treated site vs untreated site on the forearm (Area 1 and 3).
<b>Secondary</b>	
To assess skin barrier function on the face after 4 weeks of using the test product compared to no treatment.	Change from baseline in TEWL measurements on Day 29 of test product treated site vs untreated site on the face (Area 6 and 8).
To assess changes in skin moisturisation and barrier function of the forearm and	Change from baseline in corneometry and TEWL measurements at Area 1 and 3 of test

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face during 4 weeks of using the test product compared to no treatment.	product treated site vs untreated site on the forearm and Area 6 and 8 of the face at Day 1 (30 minutes after application and 6 hours after application - corneometry only), Day 2, 15, and 29. As well as Standardised Area Under Curves (AUCs) calculated using change from baseline in TEWL and corneometry over treatment period (Days 1, 2, 15, and 29)
To assess the impact on skin barrier function after physical challenge following 4 weeks of using the test product on the forearm.	Change from pre-challenge TEWL measurements of D-Squame discs following 4, 8 and 12 adhesive discs removal from skin of both test product treated and untreated sites on the forearm on Day 29 at Area 2 and 4
To assess the impact on skin barrier function after physical challenge following 4 weeks of using the test product on the face.	Change from pre-challenge TEWL measurements of D-Squame discs following 3, 6 and 9 adhesive discs removal from skin of both test product treated and untreated sites on the face on Day 29 at Area 5 and 7.
To assess the levels of protein present on D-Squame discs following 4 weeks of using the test product from sites on the forearm.	Protein analysis (SquameScan) of D-Squame discs following removal of 4, 8 and 12 adhesive discs from skin of both test product treated and untreated sites on the forearm on Day 29.
To assess the levels of protein present on D-Squame discs following 4 weeks of using the test product from sites on the face.	Protein analysis of D-Squame discs following removal of 3, 6 and 9 adhesive discs from skin of both test product treated and untreated sites on the face on Day 29.
To assess skin barrier function on the forearm and face through a Regression Period following 4 weeks of test product use.	Change from baseline and from Day 29 in TEWL measurements on Days 30, 31, 32, 33 and 34 in test product treated site vs untreated sites on the forearm and face. As well as standardised AUCs calculated using change from baseline and from Day 29 in TEWL over regression period (Days 30, 31, 32, 33 and 34) at Area 1 and 3 (Forearm) and Area 6 and 8 (Face).
To assess moisturisation levels on the forearm and face through a Regression Period following 4 weeks of test product use.	Change from baseline and from Day 29 in Corneometry measurements on Days 30, 31, 32, 33 and 34 in test product treated site vs untreated site on the forearm and face. As well as Standardised AUCs calculated using change from baseline and from Day 29 in

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	corneometry over regression period (Days 30, 31, 32, 33 and 34) at Area 1 and 3 (Forearm) and Area 6 and 8 (Face).
Validation of trial with respect to skin barrier function on the forearm after 4 weeks via comparison of the positive control to no treatment.	Change from baseline in TEWL measurements on Day 29 of test product treated site vs untreated site on the forearm (Area 1 and 3).
To evaluate the local tolerance.	Frequency and severity of Adverse Events.

## Study Design


### Overall Design

This is a randomised, evaluator-blind, single-centre, 3-arm, positive- and untreated-controlled, split body clinical study designed to evaluate the impact on skin barrier function and moisturisation benefits provided by 4 weeks of twice daily topical application of a developmental cosmetic moisturising cream in subjects with dry, sensitive skin.

Subjects will give their written consent prior to any study procedures taking place. At the Screening visit (Visit 1) only subjects with a trained evaluator (including subject assessment of tightness) visual grading score of overall dryness  $\geq 3$  (with a score of at least 1 in the roughness parameter) on each side of the face and each forearm (Appendix 2) will be enrolled. In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face. Any individual parameter score of 4 on either the face or the forearms will exclude the subject from the trial.

Eligible subjects will undergo a 5 to 7 day washout period, during which only the provided standard soap (Simple Soap<sup>®</sup>) will be used. This standard soap will also be used throughout the study to cleanse the arms (below the elbow) and face. At Visit 2 (Baseline) only subjects with a trained evaluator (including subject assessment of tightness) visual grading score of overall dryness  $\geq 3$  (with a score of at least 1 in the roughness parameter) on each side of the face and each forearm (Appendix 2) will be enrolled. In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face. Any individual parameter score of 4 on either the face or the forearms will exclude the subject from the trial.

<sup>®</sup> Simple Soap is a registered trademark of Unilever.

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Eligible subjects will be randomised to one of three treatment groups: test product/no treatment, test product/positive control, or positive control/no treatment, at the baseline visit.

Product application within each treatment group will be further randomised to either the right or left forearm and either right or left side of the face. Subjects will be dispensed study product(s) to use twice daily on the assigned side of the face and volar forearm. First application will be performed at the site under supervision.

Instrumental assessments of skin barrier function (measured by TEWL) and skin moisturisation (measured by corneometry) will be performed at various time points. Evaluation of the impact of a physical challenge to the skin barrier will be performed, by D-Squame tape stripping after 4 weeks of product use. A regression period of 5 days of no study product use following the 4 week treatment phase is also included to evaluate skin barrier function and moisturisation.


Two areas on the volar surface of each forearm, assigned below each elbow and above each wrist; Forearm RIGHT (Area 1 assigned closer to the wrist and Area 2 closer to the elbow) and LEFT (Area 3 assigned closer to the wrist and Area 4 closer to the elbow) will be selected as close together as possible, without overlap, for all measurements of TEWL and corneometry to be conducted throughout the study.

Two areas on each side of the face, along the cheek bone; Face RIGHT (Area 6 assigned closer to the ear and Area 5 assigned closer to the nose) and LEFT (Area 7 assigned closer to the nose and Area 8 assigned closer to the ear) will also be selected as close together as possible, without overlap, for all measurements of TEWL and corneometry to be conducted throughout the study.

#### **Visit 1 - Screening Visit (Day -7 to Day -5)**

The following assessments will be conducted:

1. Subject Informed Consent taken
2. Subject demographics collected
3. Medical history details
4. Details of current and concomitant medication collected
5. Fitzpatrick Skin Type grading (I-IV) (Appendix 3).
6. Trained examiner assessments (including subject self-assessment of tightness) of overall dryness  $\geq 3$  with a score of at least 1 in the roughness parameter and **< LESS THAN 4** (for any individual parameter) on the forearms and face

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(Appendix 2).

Note: There will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face.

Note: Subjects do not need to be acclimatised for these assessments.

7. Inclusion and Exclusion criteria, including subject self-reported dry, sensitive skin on the face and body.
8. Determination for eligibility to participate in the study
9. Dispense Washout Soap and instructions for use/**DIARY CARD**
10. Adverse events will be collected from after the point of Washout soap dispensed.

#### **Visit 2 - Baseline Visit (Day 1)**

The following assessments will be conducted:


1. Current/Concomitant Medications review
2. Review of Inclusion and Exclusion criteria trained examiner assessments (including subject self-assessment of tightness) of overall dryness  $\geq 3$  with a score of at least 1 in the roughness parameter and  $< \text{LESS THAN } 4$  (for any individual parameter) on the forearms and face (Appendix 2).  
Note: There will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face.  
Note: Subjects do not need to be acclimatised for these assessments.
3. Continued eligibility check
4. Randomisation
5. Subject acclimatised in standard room conditions for at least 30 minutes.
6. Baseline TEWL and corneometry assessments on Area 1 (RIGHT) and Area 3 (LEFT) locations on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) each side of the face (pre-product application).
7. Dispense study products and diary cards
8. Supervised product application.
9. Corneometry assessments on the forearm Area 1 (RIGHT) and Area 3 (LEFT) and side of face Area 6 (RIGHT) and Area 8 (LEFT) at 30 minutes and 6 hours post supervised product application (with at least 30 minutes of acclimatisation prior to each time point.)
10. Adverse Event check.

#### **Visit 3 – Day 2**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check



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3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and 8 (LEFT) on each side of the face locations.\*
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations. \*
6. Supervised product application (after all assessments have been completed)
7. Adverse Event check.

**\* Assessments to be performed 24±1 hr after supervised test product application at Visit 2**

#### **Visit 4 – Day 15 (± 24 hours)**

The following assessments will be conducted:


1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Supervised product application (after all assessments have been completed)
7. Adverse Event check.

#### **Visit 5 – Day 29 (± 48 hours) D-Squame Challenge *no study product use***

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations (*PRE D-Squame challenge*)
5. Corneometry assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations (*PRE D-Squame challenge*)
6. TEWL assessments on Area 2 (RIGHT) and Area 4 (LEFT) on the forearms and side of the face Area 5 (RIGHT) and Area 7 (LEFT) locations – *PRE D-Squame challenge*
7. D-Squame challenge

Forearm; Area 2 (RIGHT) and Area 4 (LEFT) of the forearms will be stripped with D-Squame discs through the sequential application and

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removal of 12 adhesive discs in groups of 4 discs.

Face; Area 5 (RIGHT) and Area 7 (LEFT) of each side of the face will be stripped with D-Squame discs through the sequential application and removal of 9 adhesive discs in groups of 3 discs.

8. TEWL will be measured on Area 2 (RIGHT) and Area 4 (LEFT) after each stripping of 4, 8 and 12 discs from the each forearm.
9. TEWL will be measured on Area 5 (RIGHT) and Area 7 (LEFT) after each stripping of 3, 6 and 9 adhesive discs from each side of the face.
10. The D-Squame discs will be collected and the amount of protein recovered will be measured (by SquameScan).
11. Return study product(s).
12. Adverse Event check.

#### **Visit 6 – Day 30 – Regression Period (*no study product use*)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 1 6 (RIGHT) and Area 4 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 1 6 (RIGHT) and Area 4 8 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 7 – Day 31 – Regression Period (*no study product use*)**


The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 8 – Day 32 – Regression Period (*no study product use*)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check

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3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 9 – Day 33 – Regression Period (*no study product use*)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.


#### **Visit 10 – Day 34 – Regression Period (*no study product use*)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.
7. Return standard soap
8. Study Conclusion/Subject Exit from study.

### **Type and Planned Number of Subjects**

Healthy female subjects aged 18 to 65 with self-reported dry, sensitive skin on their face and body will be included.

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The sample size is based on clinical considerations. Approximately 90 subjects will be screened to randomise approximately 66 subjects and ensure at least 40 subjects per treatment arm (test product, positive control, no treatment) or 20 subjects per treatment group (test product/no treatment, test product/positive control, positive control/no treatment) complete the entire study.

### Diagnosis and Main Criteria for Inclusion

Healthy female volunteers aged 18 to 65 with self-reported dry, sensitive skin on their face and body, with a trained examiner visual grading assessment score (including subject self-assessment of tightness) of overall dryness  $\geq 3$  and **< LESS THAN 4** (for any individual parameter) including a score of at least 1 in the roughness parameter on each of the forearms and each side of the face (Appendix 2) at the Screening visit (Visit 1) and Baseline visit (Visit 2). In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face at the Screening and Baseline visits. Any individual parameter score of 4 on either the face or the forearms will be excluded.

There should be minimal hair on the volar forearms of subjects included in the study.

### Product Information


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

	Test Product	Reference Product (Positive Control)
Product Name	Moisturising Cream	Olay® ProX Wrinkle Smoothing Cream
Product Formulation Code (MFC)	CCI [REDACTED]	N/A Market place cosmetic product
Application Amount	2 milligrams (mg) per square centimetre (cm <sup>2</sup> )	2 mg/cm <sup>2</sup>

### Statistical Methods

The primary evaluation will be the change from baseline in TEWL measurements on Day 29 of test product versus no treatment on the forearm. The only previous data

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available in a 29-day model is a study (GSKCH Clinical Study: CCI [REDACTED]), which assessed TEWL on the leg. In that study, the change from baseline in TEWL following 4 weeks of treatment with a similar product on the leg was not normally distributed. Using the data from that study and applying a Wilcoxon sample size adjustment to the paired t-test, 40 subjects treated with test product would be required to detect a difference of 1.5 points in change from baseline in TEWL at  $\alpha=0.05$  with at least 90% power assuming a standard deviation of 2.7 points.

With this study design, 66 subjects would need to be randomised to ensure at least 40 subjects are treated with each of the 3 treatments (test product, positive control, no treatment).

Change from baseline in TEWL and Corneometry for each subject at Days 1 (30 minutes and 6 hours post first application – corneometry only), 2, 15, 29, 30, 31, 32, 33, and 34 will be compared for test product versus no treatment and positive control versus no treatment, separately for the forearms and the face, using analysis of covariance (ANCOVA) with subject as a random effect, treatment (test treatment, positive control, no treatment) and side of arm or face treatment applied (right, left) as main effects and baseline value as covariate. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and for the difference between treatments arms together with p-values and 95% confidence intervals.

If the data are sufficiently non-normal in distribution, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In this case, median differences will be presented, together with 95% confidence intervals based on the Hodges-Lehmann method.

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

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## 1. INTRODUCTION

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 characterised by a rough, flaky profile which has lost a portion of its otherwise flexible and elastic properties. The stratum corneum (SC) is a highly organised, structural layer of dead skin cells that is essential for the maintenance of the water gradient between the uppermost layers of the skin.


A number of factors can render the skins moisture barrier prone to perturbation and potentially induce dryness, irritation or itch, having an overall impact on the quality of the skin (Harding, 2004). Dry skin conditions are prevalent in many people, moisturisers or hydrating agents are commonly used by sufferers of dry skin conditions and by those with healthy skin for better protection and to help restore, or recover the skins moisture barrier.

There are numerous methods to evaluate the potential of topically applied cosmetic products to help repair and prevent skin barrier disruption, enhance moisturisation and/or reduce the severity of existing skin conditions. Barrier damage and rate of repair can be measured by the physical change in the skin moisturisation levels and in the rate of transepidermal water loss (TEWL). TEWL is the rate at which water permeates the stratum corneum and evaporates from the skin surface and quantifying TEWL can provide the most direct measure of the barrier function and can be used to assess the efficacy of a product at preventing excessive water loss.

The objective of this proof of concept clinical study is to investigate the impact of the test product on skin barrier function and skin moisturisation on the forearm and face after 4 weeks of twice daily application compared to no treatment.

A physical challenge to the skin barrier after 4 weeks of twice daily test product application is included to give a secondary indication of the strength of the skin barrier at test product treated and untreated sites.

The physical challenge is a minimally invasive and commonly used technique known as Squamometry (Charbonnier, 1998) 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, 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.

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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 through assessment of TEWL and corneometry when application has stopped. Zhai and Maibach reported that a single application of a moisturiser does not cause long-lasting effects, but that repeated applications of a moisturiser (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, 1998).

The relatively high amount of body hair on the forearms of male subjects makes visual scoring of dryness difficult, in addition the removal of facial hair by male subjects will have a detrimental effect on the skin barrier and moisturisation of the face therefore only female subjects will be recruited.


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. The forearm has been selected as the test site location in addition to the face in this study due to the homogenous nature of the skin. The volar forearm has a minimal amount of hair and sebaceous glands that could affect instrumental assessments compared to the variations in facial skin which may have been exposed to varying amounts of UV radiation (sun exposure) in addition to a higher sebum production. By including both volar forearm and the face in this study the cosmetic benefit provided by 4 weeks of twice daily application can be assessed at both locations.

Bazin and Fanchon, reported that the volar forearm is a good representation of the face for studying moisturisation and biomechanical properties, and that results derived from tests on the volar forearm are relevant for the assessment of the efficacy of a product destined for facial use. (Bazin, 2006).

A commercially available cosmetic moisturiser (Olay<sup>®</sup> ProX Wrinkle Smoothing Cream) which is claimed to deliver clinically proven barrier repair benefits with regular use, has been included in the study as a positive control to support validation of the clinical model.

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## 2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
To assess skin barrier function on the forearm after 4 weeks of using the test product compared to no treatment.	Change from baseline in TEWL measurements on Day 29 of test product treated site vs untreated site on the forearm (Area 1 and 3).
<b>Secondary</b>	
To assess skin barrier function on the face after 4 weeks of using the test product compared to no treatment.	Change from baseline in TEWL measurements on Day 29 of test product treated site vs untreated site on the face (Area 6 and 8).
To assess changes in skin moisturisation and barrier function of the forearm and face during 4 weeks of using the test product compared to no treatment.	Change from baseline in corneometry and TEWL measurements at Area 1 and 3 of test product treated site vs untreated site on the forearm and Area 6 and 8 of the face at Day 1 (30 minutes after application and 6 hours after application - corneometry only), Day 2, 15, and 29. As well as Standardised Area Under Curves (AUCs) calculated using change from baseline in TEWL and corneometry over treatment period (Days 1, 2, 15, and 29)
To assess the impact on skin barrier function after physical challenge following 4 weeks of using the test product on the forearm.	Change from pre-challenge TEWL measurements of D-Squame discs following 4, 8 and 12 adhesive discs removal from skin of both test product treated and untreated sites on the forearm on Day 29 at Area 2 and 4
To assess the impact on skin barrier function after physical challenge following 4 weeks of using the test product on the face.	Change from pre-challenge TEWL measurements of D-Squame discs following 3, 6 and 9 adhesive discs removal from skin of both test product treated and untreated sites on the face on Day 29 at Area 5 and 7.
To assess the levels of protein present on D-Squame discs following 4 weeks of using the test product from sites on the forearm.	Protein analysis (SquameScan) of D-Squame discs following removal of 4, 8 and 12 adhesive discs from skin of both test product treated and untreated sites on the forearm on Day 29.
To assess the levels of protein present on D-Squame discs following 4 weeks of using the test product from sites on the	Protein analysis of D-Squame discs following removal of 3, 6 and 9 adhesive discs from skin of both test product treated and untreated




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face.	sites on the face on Day 29.
To assess skin barrier function on the forearm and face through a Regression Period following 4 weeks of test product use.	Change from baseline and from Day 29 in TEWL measurements on Days 30, 31, 32, 33 and 34 in test product treated site vs untreated sites on the forearm and face. As well as standardised AUCs calculated using change from baseline and from Day 29 in TEWL over regression period (Days 30, 31, 32, 33 and 34) at Area 1 and 3 (Forearm) and Area 6 and 8 (Face).
To assess moisturisation levels on the forearm and face through a Regression Period following 4 weeks of test product use.	Change from baseline and from Day 29 in Corneometry measurements on Days 30, 31, 32, 33 and 34 in test product treated site vs untreated site on the forearm and face. As well as Standardised AUCs calculated using change from baseline and from Day 29 in corneometry over regression period (Days 30, 31, 32, 33 and 34) at Area 1 and 3 (Forearm) and Area 6 and 8 (Face).
Validation of trial with respect to skin barrier function on the forearm after 4 weeks via comparison of the positive control to no treatment.	Change from baseline in TEWL measurements on Day 29 of test product treated site vs untreated site on the forearm (Area 1 and 3).
To evaluate the local tolerance.	Frequency and severity of Adverse Events.

### 3. STUDY PLAN

#### 3.1. Study Design

Overall Design
<p>This is a randomised, evaluator-blind, single-centre, 3-arm, positive- and untreated-controlled, split body clinical study designed to evaluate the impact on skin barrier function and moisturisation benefits provided by 4 weeks of twice daily topical application of a developmental cosmetic moisturising cream in subjects with dry, sensitive skin.</p> <p>Subjects will give their written consent prior to any study procedures taking place. At the Screening visit (Visit 1) only subjects with a trained evaluator (including subject assessment of tightness) visual grading score of overall dryness <math>\geq 3</math> (with a score of at least 1 in the roughness parameter) on each side of the face and each forearm</p>

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(Appendix 2) will be enrolled. In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face. Any individual parameter score of 4 on either the face or the forearms will exclude the subject from the trial.

Eligible subjects will undergo a 5 to 7 day washout period, during which only the provided standard soap (Simple Soap<sup>®</sup>) will be used. This standard soap will also be used throughout the study to cleanse the arms (below the elbow) and face. At Visit 2 (Baseline) only subjects with a trained evaluator (including subject assessment of tightness) visual grading score of overall dryness  $\geq 3$  (with a score of at least 1 in the roughness parameter) on each side of the face and each forearm (Appendix 2) will be enrolled. In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face. Any individual parameter score of 4 on either the face or the forearms will exclude the subject from the trial.


Eligible subjects will be randomised to one of three treatment groups: test product/no treatment, test product/positive control, or positive control/no treatment, at the baseline visit.

Product application within each treatment group will be further randomised to either the right or left forearm and either right or left side of the face. Subjects will be dispensed study product(s) to use twice daily on the assigned side of the face and volar forearm. First application will be performed at the site under supervision.

Instrumental assessments of skin barrier function (measured by TEWL) and skin moisturisation (measured by corneometry) will be performed at various time points. Evaluation of the impact of a physical challenge to the skin barrier will be performed, by D-Squame tape stripping after 4 weeks of product use. A regression period of 5 days of no study product use following the 4 week treatment phase is also included to evaluate skin barrier function and moisturisation.

Two areas on the volar surface of each forearm, assigned below each elbow and above each wrist; Forearm RIGHT (Area 1 assigned closer to the wrist and Area 2 closer to the elbow) and LEFT (Area 3 assigned closer to the wrist and Area 4 closer to the elbow) will be selected as close together as possible, without overlap, for all measurements of TEWL and corneometry to be

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conducted throughout the study.

Two areas on each side of the face, along the cheek bone; Face RIGHT (Area 6 assigned closer to the ear and Area 5 assigned closer to the nose) and LEFT (Area 7 assigned closer to the nose and Area 8 assigned closer to the ear) will also be selected as close together as possible, without overlap, for all measurements of TEWL and corneometry to be conducted throughout the study.

#### Visit 1 - Screening Visit (Day -7 to Day -5)

The following assessments will be conducted:

1. Subject Informed Consent taken
2. Subject demographics collected
3. Medical history details
4. Details of current and concomitant medication collected
5. Fitzpatrick Skin Type grading (I-IV) (Appendix 3).
6. Trained examiner assessments (including subject self-assessment of tightness) of overall dryness  $\geq 3$  with a score of at least 1 in the roughness parameter and  $\leq$  **LESS THAN** 4 (for any individual parameter) on the forearms and face (Appendix 2).

Note: There will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face.

Note: Subjects do not need to be acclimatised for these assessments.


7. Inclusion and Exclusion criteria, including subject self-reported dry, sensitive skin on the face and body.
8. Determination for eligibility to participate in the study
9. Dispense Washout Soap and instructions for use/ **DIARY CARD**
10. Adverse events will be collected from after the point of Washout soap dispensed.

#### Visit 2 - Baseline Visit (Day 1)

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Review of Inclusion and Exclusion criteria trained examiner assessments (including subject self-assessment of tightness) of overall dryness  $\geq 3$  with a score of at least 1 in the roughness parameter and  $\leq$  **LESS THAN** 4 (for any individual parameter) on the forearms and face (Appendix 2).

Note: There will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each

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side of the face.

Note: Subjects do not need to be acclimatised for these assessments.

3. Continued eligibility check
4. Randomisation
5. Subject acclimatised in standard room conditions for at least 30 minutes.
6. Baseline TEWL and corneometry assessments on Area 1 (RIGHT) and Area 3 (LEFT) locations on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) each side of the face (pre-product application).
7. Dispense study products and diary cards
8. Supervised product application.
9. Corneometry assessments on the forearm Area 1 (RIGHT) and Area 3 (LEFT) and side of face Area 6 (RIGHT) and Area 8 (LEFT) at 30 minutes and 6 hours post supervised product application (with at least 30 minutes of acclimatisation prior to each time point.)
10. Adverse Event check.

#### Visit 3 – Day 2

The following assessments will be conducted:


1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and 8 (LEFT) on each side of the face locations.\*
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations. \*
6. Supervised product application (after all assessments have been completed)
7. Adverse Event check.

*\* Assessments to be performed 24±1 hr after supervised test product application at Visit 2*

#### Visit 4 – Day 15 (± 24 hours)

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.

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6. Supervised product application (after all assessments have been completed)
7. Adverse Event check.

#### **Visit 5 – Day 29 (± 48 hours) D-Squame Challenge *no study product use***

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations (*PRE D-Squame challenge*)
5. Corneometry assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations (*PRE D-Squame challenge*)
6. TEWL assessments on Area 2 (RIGHT) and Area 4 (LEFT) on the forearms and side of the face Area 5 (RIGHT) and Area 7 (LEFT) locations – *PRE D-Squame challenge*
7. D-Squame challenge
 


Forearm; Area 2 (RIGHT) and Area 4 (LEFT) of the forearms will be stripped with D-Squame discs through the sequential application and removal of 12 adhesive discs in groups of 4 discs.

Face; Area 5 (RIGHT) and Area 7 (LEFT) of each side of the face will be stripped with D-Squame discs through the sequential application and removal of 9 adhesive discs in groups of 3 discs.
8. TEWL will be measured on Area 2 (RIGHT) and Area 4 (LEFT) after each stripping of 4, 8 and 12 discs from the each forearm.
9. TEWL will be measured on Area 5 (RIGHT) and Area 7 (LEFT) after each stripping of 3, 6 and 9 adhesive discs from each side of the face.
10. The D-Squame discs will be collected and the amount of protein recovered will be measured (by SquameScan).
11. Return study product(s).
12. Adverse Event check.

#### **Visit 6 – Day 30 – Regression Period (*no study product use*)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 1 6 (RIGHT) and Area 4 8 (LEFT) on each side of the face locations

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5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 4 (RIGHT) and Area 6 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 7 – Day 31 – Regression Period (no study product use)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 8 – Day 32 – Regression Period (no study product use)**

The following assessments will be conducted:


1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 9 – Day 33 – Regression Period (no study product use)**

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.

#### **Visit 10 – Day 34 – Regression Period (no study product use)**

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The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Subject acclimatised in standard room conditions for at least 30 minutes.
4. TEWL assessments on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations
5. Corneometry assessment on Area 1 (RIGHT) and Area 3 (LEFT) on the forearms and Area 6 (RIGHT) and Area 8 (LEFT) on each side of the face locations.
6. Adverse Event check.
7. Return standard soap
8. Study Conclusion/Subject Exit from study.

### 3.2. Subject Restrictions

#### Lifestyle/ Dietary

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

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


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

No use of any product on the volar forearms or face, including the standard soap and test product, within 10-16 hours of all instrumental measurements on visit days (no showering/bathing permitted with soaps/shampoo within this period).

Subjects who are assigned to use the test and positive control products should wash their hands between the two product applications.

No application of water on the volar forearms or face, within 2 hours of all instrumental measurements on visit days.

On study visit days for Visits 2, 3 and 4 the morning product application will be performed at the site after all assessments have been completed.

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Subjects who smoke will be excluded (including use of e-cigarettes).

Subjects must not consume coffee or any product containing caffeine or alcohol on the day of the study visit days and until after the instrumental measurements are completed.

Hard physical exercises (with heavy sweating), sauna or swimming, are prohibited within 24 hrs of the site visit **(VISIT 2)**.

Exposure to artificial ultraviolet (UV) light or cosmetic procedures (includes tanning beds, Intense Pulsed Light (IPL), etc.) are prohibited on the test areas for the duration of the study.

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

Avoid wearing tight or restrictive clothing on the arms or around the face.

Chemical or physical hair removal methods or bleaching or dying of the hair on the arms and face is not permitted during the course of the study.

#### **Medications and Treatments**

During the entire study (Screening – Visit 10) the following medications and treatments should be avoided:

Any medications prohibited in the exclusion criteria

Oral and Topical steroids

Regular use of inhaled steroids (occasional use is permitted)

Regular use of topical anti-itch medications (occasional use permitted; the product should be applied with an applicator but not to the treated area)


Immunosuppressive drugs

Topical drugs or medication in test areas

### **3.3. Type and Planned Number of Subjects**

Healthy female volunteers aged 18 to 65 with self-reported dry, sensitive skin on their face and body, with a trained examiner visual grading assessment score (including



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subject self-assessment of tightness) of overall dryness  $\geq 3$  and  $< \text{LESS THAN } 4$  (for any individual parameter) including a score of at least 1 in the roughness parameter on each of the forearms and each side of the face (Appendix 2) at the Screening visit (Visit 1) and Baseline visit (Visit 2). In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face at the Screening and Baseline visits. Any individual parameter score of 4 on either the face or the forearms will **EXCLUDE THE SUBJECT FROM THE STUDY** be excluded.

There should be minimal hair on the volar forearms of subjects included in the study.

Approximately 90 subjects will be screened to randomise approximately 66 and ensure at least 40 subjects per treatment arm (test product, positive control, no treatment) or 20 subjects per treatment group (test product/no treatment, test product/positive control, positive control/no treatment) complete the entire study.

### 3.4. Study Design and Amount Justification


#### Study Design:

This is a randomised, evaluator-blind, single-centre, 3-arm, positive- and untreated-controlled, split body clinical study designed to evaluate the impact on skin barrier function and moisturisation benefits provided by 4 weeks of twice daily topical application of a developmental cosmetic moisturising cream in subjects with moderately dry to very dry sensitive skin.

The chosen application sites for the treatment period are the volar forearms and the face. The forearms will be designated right and left, and the face will be split to right or left side. There are three treatment groups included in this study; Test Product/ No Treatment, Test Product/Positive Control and Positive Control/No Treatment. Treatment groups will be further randomised to which side of the face or volar forearm product will be applied.

The relatively high amount of body hair on the arms and face of male subjects makes visual scoring of dryness and measurements difficult. In addition the removal of facial hair impacts the skin dryness and barrier function. Therefore, only female subjects will minimal volar forearm hair will be recruited.

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


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Eligible subjects will undergo a 5 to 7 day washout period, during which only the washout soap (Simple Soap), will be used twice daily. This same soap will also be used throughout the study to cleanse the face and forearms.

Two areas on the volar surface of each forearm, assigned below each elbow and above each wrist (RIGHT Arm Area 1 and Arm Area 2 and LEFT Arm Area 3 and Arm Area 4) and two areas on each side of the face, below the cheek bone (RIGHT Face Area 6 and Face Area 5 and LEFT Face Area 7 and Face Area 8) will be selected as close together as possible, without overlap, for all measurements of TEWL and corneometry to be conducted throughout the study.

Area 2 and 4 on the RIGHT and LEFT forearm will be where the D-Squame challenge is carried out.

Area 5 and 7 on the RIGHT and LEFT side of the face will be where the D-Squame challenge is carried out.

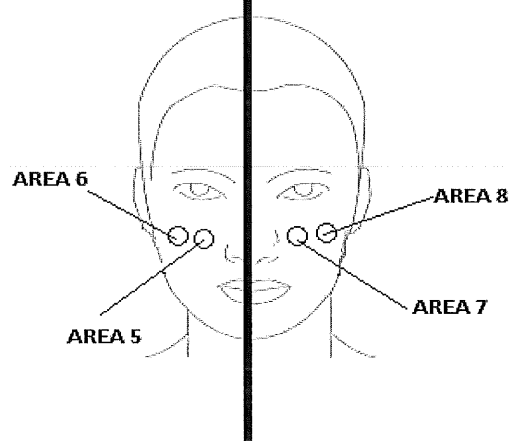
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### Layout of Test Areas:

**AREA 6 and 8 Face**  
TEWL/Corneometry assessments throughout

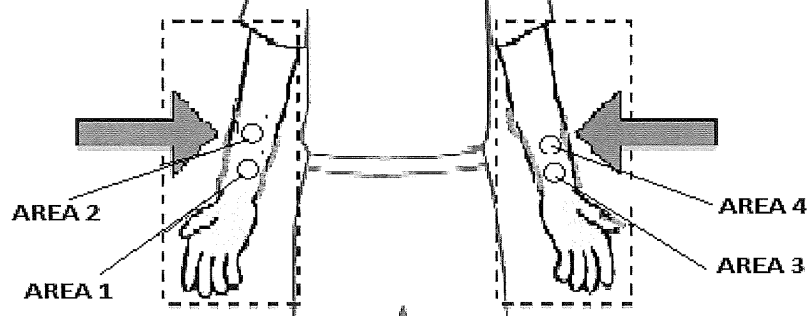
**AREA 5 and 7 Face**  
D-Squame Challenge location

RIGHT SIDE OF FACE      LEFT SIDE OF FACE




RIGHT VOLAR FOREARM

LEFT VOLAR FOREARM



**AREA 1 and 3 Forearm**  
TEWL/Corneometry assessments throughout

**AREA 2 and 4 Forearm**  
D-Squame Challenge location

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Only subjects with a trained examiner visual grading assessment score (including subject self-assessment of tightness) of overall dryness  $\geq 3$  with a score of at least 1 in the roughness parameter and  $\leq$  **LESS THAN 4** (for any individual parameter) on both volar arms and both sides of the face at the Screening (Visit 1) to be eligible for the study and again at the Baseline visit (Visit 2) to continue in the study (Appendix 2). In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face at the Screening and Baseline visits. Any individual parameter score of 4 on either the face or the forearms will **EXCLUDE THE SUBJECT FROM THE STUDY**. ~~be excluded.~~

At the Baseline visit following visual grading assessment and randomisation, study staff will dispense product(s) and diary cards to subjects. Subjects will be instructed to apply their product(s) to the randomly designated side of face and forearm, as applicable, (approximately 2 mg/cm<sup>2</sup>) twice daily (in the morning and evening, approximately 8-12 hours apart), for 4 weeks (28 days  $\pm$  2 days) ensuring that the randomly designated volar forearm and side of the face is covered (including forehead, chin and nose) with the product. First on-site application of product(s) will be supervised by the study site staff.


Subjects will return to the site on Day 2 (Visit 3), 24 hours ( $\pm$ 1hr) after first site application, without applying product at home that morning.

Every effort will be made to ensure subject site visits are scheduled for similar times of day for all subjects throughout the study.

There will be no cleansing or product application prior to the morning visits (Visits 3, 4 and 5). Product application will be performed under site supervision following TEWL and corneometry assessments at Visits 3 and 4. There will be no product application at Visit 5. Last application will be by the subjects on the evening of Day 28  $\pm$  2 days).

Subjects will be acclimatised in a controlled environment (temperature 20-22°C, relative humidity 40-60%) for a period of at least 30 minutes before all TEWL and corneometry measurements throughout the study (EEMCO, 1997).

Area 1 and 3 on the forearms and Area 6 and 8 on the face will have TEWL measured at Baseline (pre product application) on Day 1, and on Days 2, 15, 29, 30, 31, 32, 33 and 34.

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Area 1 and 3 on the forearms and Area 6 and 8 on the face will also have corneometry measured at Baseline (pre product application) and at 30 minutes and 6 hours post first supervised application on Day 1, and on Days 2, 15, 29, 30, 31, 32, 33 and 34.

Area 2 and 4 on the forearm and Area 5 and 7 on the face will be where the D-Squame challenge will be conducted. At Day 29 (Visit 5), following 4 weeks of twice daily application, subjects will return to the site. TEWL will be measured on Area 5 and 7 of the face and Area 2 and 4 on the forearms prior to the D-Squame challenge.

The areas will be challenged through the sequential application and removal of D-Squame adhesive discs. TEWL will be measured after each stripping of groups of discs (dependant on location). The amount of protein recovered by each D-Squame disc will be measured (by SquameScan) (Lu *et al*). Subjects will return study product(s) at Visit 5 (Day 29) and the subject diary cards will be reviewed. Missed or additional applications will be recorded in the CRF.

A Regression Period of 5 days during which subjects will not use the study product (s) will start on Day 30 (Visit 6). Subjects will continue to use the standard soap provided. TEWL and Corneometry will be measured on Area 1 and 3 on the forearms and Area 6 and 8 of the face at Days 30, 31, 32, 33 and 34.


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

#### Assessments:

Corneometry is a standard measurement of skin moisturisation which uses an electrical capacitance method to model the water content of the skin (Eisner, *et al*, 1994). This assessment has been included to give objective measurements of skin moisturisation throughout the product use and regression periods of this study.

TEWL assessments are included in this study to provide an objective measure of skin barrier function.

D-Squame discs will be analysed for levels of protein, this has been shown to be an indicator of skin barrier strength (Voegeli, 2007).

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*Application Quantity Justification:*

Based on the premise of home use testing, this study will evaluate parameters of skin barrier function, skin moisturisation and duration of lasting effect, following 28 days of twice daily product application and a 5 day regression period of no product use on both the face and forearms. Barrier strength will also be assessed after the skin is subjected to a physical challenge by tape stripping with D-Squame discs.

The application quantity of the study products has been selected to reflect typical consumer usage of these types of products; approximately 2 mg/cm<sup>2</sup>. (Simion, 2006). The first administration is to be supervised by a trained technician when the subjects are at the site. An 8 hour minimum period between product applications is required (except for Day 1).


Subjects will be instructed to apply two pumps of test product (equating to approximately 0.6 ml) and/or a pea-sized amount (equating to approximately 0.5 g) of the positive control product to their selected volar forearm, from the wrist to the elbow (approximately 2 mg/cm<sup>2</sup>), as per the randomisation schedule, twice daily (in the morning and evening).

In addition subjects will be instructed to apply two pumps of test product (equating to approximately 0.6 ml) and/or a pea-sized amount (equating to approximately 0.5 g) of the positive control product to their selected side of the face, including forehead and chin (approximately 2 mg/cm<sup>2</sup>), as per the randomisation schedule twice daily (in the morning and evening).

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.

A 5-7 day washout period using a standard soap is included in order to standardise product use across the study population and normalise the skin condition of all subjects prior to randomisation.

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

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## 4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA


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

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

### 4.1. Inclusion Criteria

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

<b>1. CONSENT</b>
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form.
<b>2. AGE</b>
Aged between 18 and 65 years inclusive.
<b>3. GENERAL HEALTH</b>
a) Good general and mental health with, in the opinion of the investigator or medically qualified designee no clinically significant and relevant abnormalities in medical history or upon physical examination.
b) Self-reported dry, sensitive skin on the face and body.
<b>4. GENDER</b>
Subject is female
<b>5. COMPLIANCE</b>
Agreement to comply with the procedures and requirements of the study and to attend the scheduled assessment visits.
<b>6. SKIN TYPE – DRYNESS</b>
Trained examiner visual grading assessment score (including subject self-assessment)

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of tightness) of overall dryness  $\geq 3$  with a score of at least 1 in the roughness parameter and  $< \text{LESS THAN } 4$  (for any individual parameter) on each of the forearms and each side of the face at the Screening visit (Visit 1) and Baseline visit (Visit 2).

In addition, there will be no greater than 0.5 point difference between trained examiner visual grading scores of each volar forearm and each side of the face at the Screening and Baseline visits. (Appendix 2).

#### 7. FITZPATRICK SKIN TYPE

Fitzpatrick skin type I-IV (Appendix 3)

## 4.2. Exclusion Criteria

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

#### 1. PREGNANCY

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


#### 2. BREAST-FEEDING

Women who are breast-feeding

#### 3. CONCURRENT MEDICATION/ MEDICAL HISTORY

- a) Any history of significant dermatological diseases or conditions or medical conditions known to alter skin appearance or physiologic response (e.g. diabetes,) which could, in the opinion of the Investigator, preclude topical application of the investigational products and/or interfere with the evaluations.
- b) Presence of open sores, pimples, or cysts at the application site.
- c) Active dermatosis (local or disseminated) that might interfere with the results of the study.
- d) Considered immune compromised.
- e) Currently using any medication which in the opinion of the investigator, may affect the evaluation of the study product, or place the subject at undue risk.
- f) Use of the following topical or systemic medications: immunosuppressants,



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antihistamines, non-hormonal anti-inflammatory drugs, and corticosteroids up to 2 weeks before screening visit.

- g) Intention of using any oral or topical steroids
- h) Regular use of inhaled steroids (occasional use is permitted)
- i) Regular use of topical anti-itch medications (occasional use permitted; the product should be applied with an applicator but not to the proposed application areas.
- j) Use of any topical drug or medication in the proposed application areas.
- k) Intention of being vaccinated during the study period or has been vaccinated within 3 weeks of the screening visit.
- l) Currently receiving allergy injections, or received an allergy injection within 7 days prior to Visit 1, or expects to begin injections during study participation

#### 4. ALLERGY/ INTOLERANCE

- a) Previous history of atopy, allergic reactions, irritation or intense discomfort feelings to topical-use products, cosmetics or medication.
- b) Known or suspected intolerance or hypersensitivity to any of the study materials (or closely related compounds) or any of their stated ingredients

#### 5. CLINICAL STUDY/ EXPERIMENTAL PRODUCT

- a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 14 days of the screening visit.
- b) Previous participation in this study.

#### 6. SUBSTANCE ABUSE


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

#### 7. SMOKING STATUS

Smoker (including e-cigarettes)

#### 8. DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

- a) Moles, tattoos, scars, hairs, etc. at the test areas if it is likely that they could

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affect the assessments.

- b) Subject has visible sunburn on the test sites.
- c) Use of self-tanning products on the test areas (face and arms) within 2 weeks prior to the screening visit.
- d) Any individual parameter score 4 on any test areas of the face or either of the forearms as assessed by a trained examiner (Appendix 2).
- e) Any Subject who, in the judgment of the Investigator, should not participate in the study.

## 9. PERSONNEL

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

### 4.3. Screening/ Baseline Failures


Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events (SAEs).

Re-screening of subjects will not be allowed in this study.

### 4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws or is withdrawn from the study, all human biological samples collected before they left will be analysed and reported unless the subject requests otherwise. A subject may request for their human biological samples to be destroyed. In these cases, the investigator must document this in the site study records and the samples should not be used for any further research.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the

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outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilises, is otherwise explained, or the subject is lost to follow-up.

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

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

#### 4.5. Subject Replacement

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

#### 4.6. Subject and Study Completion

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


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

### 5. PRODUCT INFORMATION

#### 5.1. Study Product

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

	<b>Test Product</b>	<b>Positive Control</b>
<b>Product Name</b>	Moisturising Cream	Olay ProX Wrinkle Smoothing Cream
<b>Product Formulation Code (MFC)</b>	CCI [REDACTED]	N/A Commercial market place cosmetic product
<b>Application</b>	2 mg/cm <sup>2</sup>	2 mg/cm <sup>2</sup>

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Quantity		
<b>Dosing Instructions</b>	<p><b>Face</b> - Subjects will be instructed to apply two pumps of test product (approximately 0.3 ml x 2 = 0.6 ml) to the randomly assigned side of the face, including forehead and chin (equating to approximately 2 mg/cm<sup>2</sup>), twice daily (in the morning and evening).</p> <p><b>Forearm</b> - Subjects will be instructed to apply two pumps of test product (approximately 0.3 ml x 2 = 0.6 ml) to the randomly assigned forearm ensuring that the volar forearm below the elbow and above the wrist is covered with the product (equating to approximately 2 mg/cm<sup>2</sup>) twice daily (in the morning and evening).</p>	<p><b>Face</b> - Subjects will be instructed to apply a pea-sized amount of the positive control product (equating to approximately 0.5 g) to the randomly assigned side of the face, including forehead and chin (approximately 2 mg/cm<sup>2</sup>), twice daily (in the morning and evening).</p> <p><b>Forearm</b> - Subjects will be instructed apply a pea-sized amount of the positive control product (equating to approximately 0.5 g) to the randomly assigned forearm ensuring that the volar forearm below the elbow and above the wrist is covered with the product (approximately 2 mg/cm<sup>2</sup>) twice daily (in the morning and evening).</p>


Other items to be supplied by the Clinical Supplies Department, GSKCH:

Name of Item	Purpose
Simple Soap	Standard soap for use as a washout soap and for standard use during the study period.
Soap holder	To contain the soap between use

## 5.2. Application Schedule

The application quantity of each product(s) has been selected to reflect typical consumer usage of these types of product; approximately 2 mg/cm<sup>2</sup>. (Simion, 2006)

The first application of the study product(s) will be under supervision at the study site at Baseline (Day 1), following all Baseline assessments. Subsequent use of the study product(s) will be applied by the subjects at home, twice daily (morning and evening) as instructed by site staff, or if at site by a trained technician after TEWL and corneometry measurements at Visits 3 and 4 (Days 2 and 15). There will be no

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product application on Day 29 (Visit 5). Product(s) will be returned at Day 29 (Visit 5). The standard soap will be returned at Day 34 (Visit 10).

A 5 day Regression Period where subjects will not use any product(s) will begin on Day 30. Subjects will continue to use the standard soap as before.

Subjects will be reminded to bring all of their study products (test and/or positive control products and standard soap) 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 forearms with anything other than water on the day of site visit, until the evening after all site assessments have been performed.

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.

### 5.3. Application Modification

Subjects will be instructed to apply the test products as per the usage instructions provided. Additional and/or missed applications will be logged in the CRF.

### 5.4. Product Compliance


Subjects will be supervised when using the study product at the Baseline (Day 1) visit for the first time and on study days at the site to ensure compliance. A record of the dispensing and administration of the study products will be kept using the dispensing and administration log and the CRF.

Diary Cards will be used to promote compliance and familiarisation during the study days.

Subjects will not be excluded due to missed applications but will be reminded to use the product as per the instructions provided and to complete the diary card on a daily basis to encourage compliance. Number of missed or additional applications will be noted in the CRF.

### 5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol.

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## 5.6. Overdose

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

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

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

## 5.7. Rescue Therapy

No rescue therapy is required in this study.

## 5.8. Product Assignment

Subjects will be randomised to one of 3 treatment groups in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software:

Test product/no treatment

Test product/positive control


Positive control /no treatment

Randomisation will further include specification of which forearm and side of the face to which each of the treatments is to be applied. This will ensure that each treatment will be applied to each forearm and side of the face across all subjects.

### 5.8.1. Randomisation

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria at Visit 2 will be randomised according to the randomisation schedule.

Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

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The randomisation number will be associated with the treatment group and which forearm and side of face (either right and/or left) to which study product is to be applied.

### 5.8.2. Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the randomly designated treatment group assignments. Investigators dispensing the product will be aware of the randomly designated treatment group including side of face and forearm but must not divulge information to the other study staff or assessors. The assessor performing the measurements (including the D-Squame challenge) will also be blinded to the randomly designated treatment group.

### 5.8.3. Code Breaks

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


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

## 5.9. Packaging and Labelling

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

The test product (CCI [REDACTED]) will be supplied in pump tubes with a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number, treatment group code, application side (Right or Left) and directions for storage.

The positive control product (Olay ProX Wrinkle Smoothing Cream) will be supplied in commercial packs that will be over-wrapped with opaque vinyl to obscure any commercial branding as much as possible. The jars will be supplied with a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol

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number, treatment group code, application side (Right or Left) and directions for storage.

The standard soap (Simple) will be supplied in a labelled soap holder. Each study label will contain, but not be limited to, protocol number and directions for storage.

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

#### **5.9.1. Accountability of Product**

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

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

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

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies should not be destroyed without prior written authorization by the Sponsor. When destruction of the study products takes place a dated certificate of, or receipt for destruction, will be provided to the Sponsor.


#### **5.9.2. Storage of Product**

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

## **6. STUDY ASSESSMENTS AND PROCEDURES**

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



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

## 6.1. Visit 1 - Screening Visit

### 6.1.1. Telephone Screening

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

Prior to the screening visit potential subjects may be provided with the Subject Information Sheet and given the opportunity to ask any questions with the dermatologist prior to signing the informed consent form at the screening visit.


### 6.1.2. Informed Consent

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

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

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

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

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### 6.1.3. Demographics

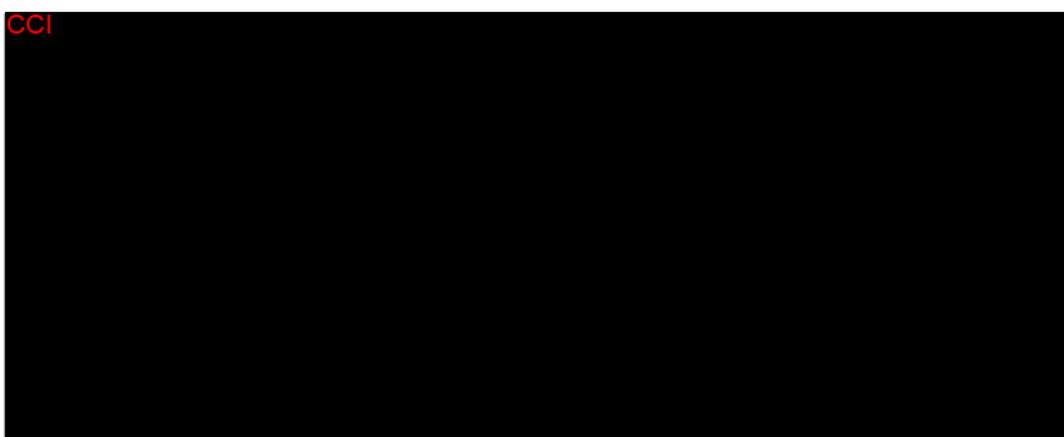
The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, race and Fitzpatrick skin type.

### 6.1.4. Medical History and Concomitant Medication

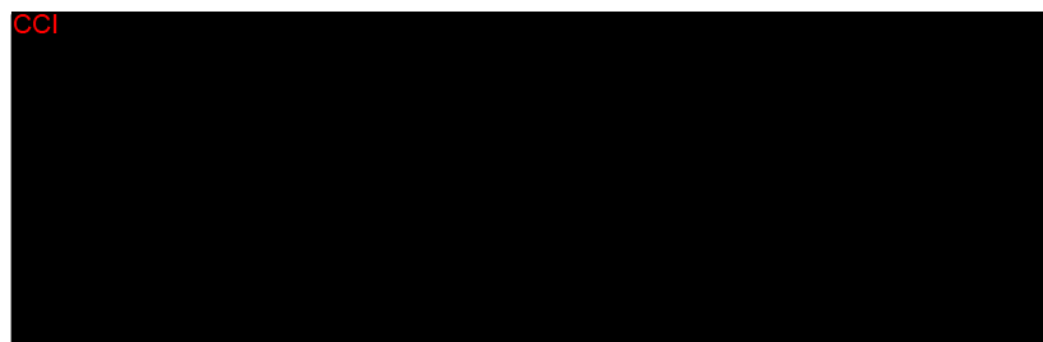
Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy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


Only subjects with self-reported dry, sensitive skin will be included.

### 6.1.5. Assessment of Overall Dryness



### 6.2. Visit 2 - Baseline Visit (Day 1)



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Eligible subjects will be randomised to a treatment group and forearm and side of face (Left or Right) to which each product(s) should be applied. First use of the study product(s) will be supervised by site staff as per directions provided.

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

Instrumental measurements of TEWL and skin moisturisation (corneometry) will be conducted by the Investigator or designee and recorded.


### 6.2.1. Transepidermal Water Loss (TEWL)

TEWL will be initially measured at the Baseline visit (Visit 2) prior to any study product application on both forearm and sides of the face sites. Then measured throughout the study period per the study schedule.

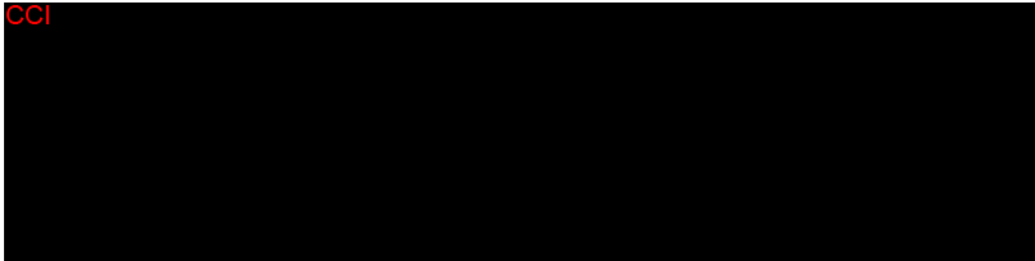
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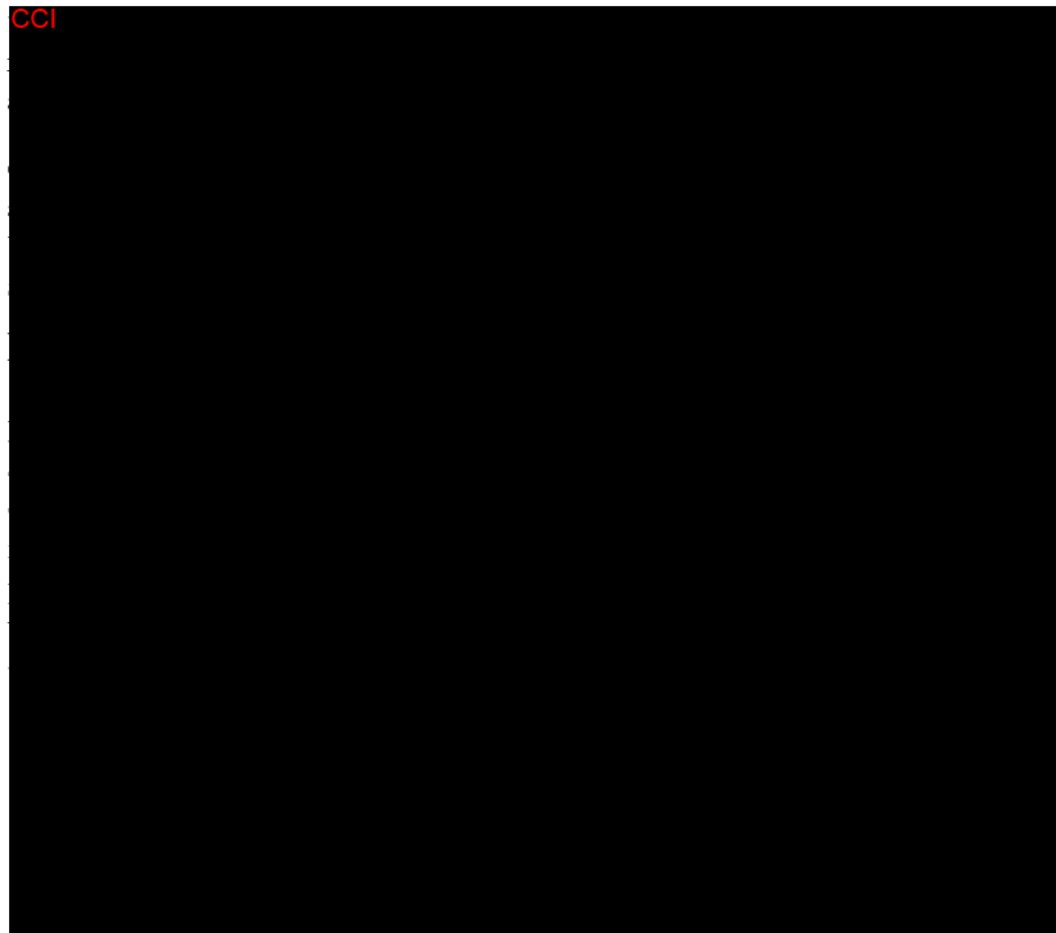
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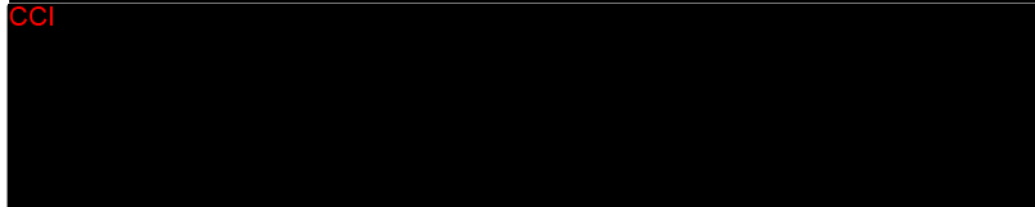



### 6.2.2. Corneometry

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Corneometer data will be stored in a proDERM data base (4D) and will be provided to GSK. **CORNEOMETRY DATA WILL BE STORED IN THE CORNEOMETER SOFTWARE, EXPORTED INTO AN EXCEL FILE AND WILL BE PROVIDED TO GSK THROUGH A SECURE PORTAL.**

### 6.3. Visits 3 and 4 (Day 2 and 15)

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

Measures of TEWL and corneometry per section 6.2.1 and 6.2.2 will be taken on Area 1 (RIGHT) and Area 3 (LEFT) of the forearms and Area 6 (RIGHT) and Area 8 (LEFT) of the face. Following the assessments subjects will apply the study product(s) under site supervision.

### 6.4. Visit 5 (Day 29) – D-Squame Challenge

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


Measures of TEWL and corneometry per section 6.2.1 and 6.2.2 will be taken on Area 1 (RIGHT) and Area 3 (LEFT) of the forearms and Area 6 (RIGHT) and Area 8 (LEFT) of the face. Additionally TEWL will be measured prior to the D-Squame challenge at Area 2 (RIGHT) and Area 4 (LEFT) on the forearms and Area 5 (RIGHT) and Area 7 (LEFT) on the face.

The four designated D-Squame sites (Area 2 and 4 of the forearms and Area 5 and 7 of the face) will then be stripped with repeated application and removal of D-Squame discs.

Subjects will return all study product(s), and continue to use the standard soap only.

#### 6.4.1 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 12 D-Squame discs (in groups of 4) removed from each forearm (Area 2 and 4) repeatedly. TEWL will be measured (per section 6.2.1) pre challenge and after 4, 8 and 12 discs have been removed from Area 2 and 4 on the forearms. There will be a maximum of 9 D-Squame discs (in groups of 3) removed from Area 5 and 7 on the face repeatedly. TEWL will be measured

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(per section 6.2.1) pre challenge and after 3, 6 and 9 discs have been removed from Area ~~2~~ 5 and ~~3~~ 7 on the face.

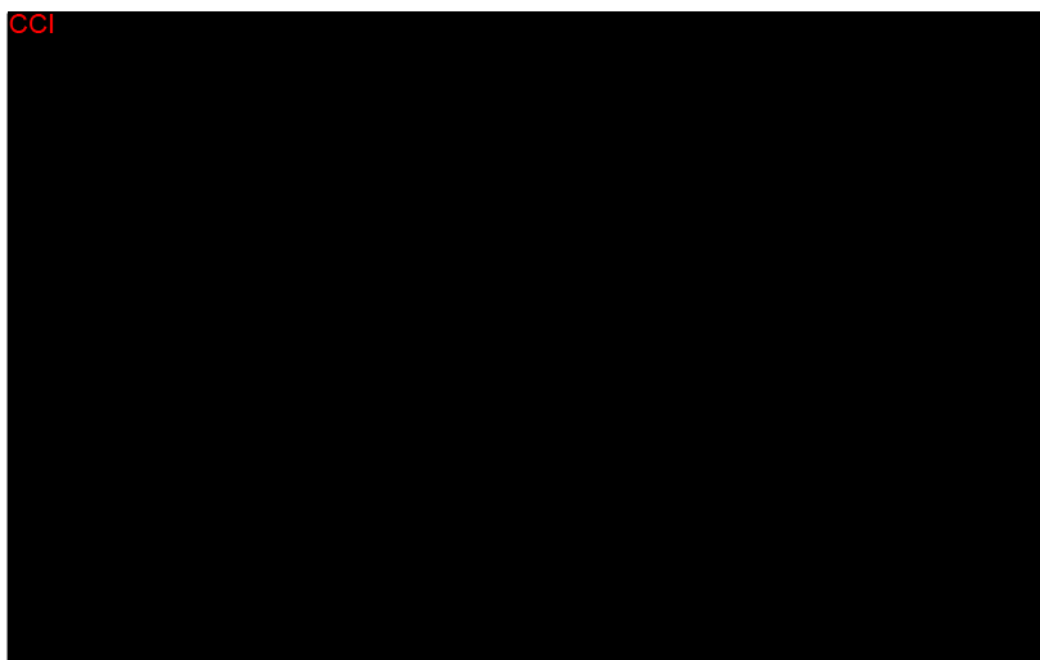
A total of 42 D-Squame discs will be taken from each subject (two sets of 12 discs from the two separate sites of each volar forearm, and two sets of 9 discs from each side of the face). The D-Squame discs will be collected and analysed for protein content. Staff will continuously assess the subject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


The D-Squame discs will be stored and analysed at the study site the same day. Further analyses of the discs may be performed at a later date and subjects will be asked to consent for this at screening. Discs will be stored at -80°C until further analysis or destructions.

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-Squames. 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.

#### 6.4.1.1 Measurement of Protein from D-Squame Discs

CCI



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## 6.5. Visit 6, Visit 7, Visit 8, and Visit 9 (Days 30, 31, 32, and 33) - Regression Period

Subjects will continue to apply the standard cleanser (Simple Soap) in the evening and will return to the study site each day, having cleansed their skin with water (only) 2 hours prior to assessments.

Measures of TEWL and corneometry per Sections 6.2.1 and 6.2.2 will be taken on Area 1 and Area 3 of the forearms and Area 6 and 8 of the face each day following acclimatisation.

## 6.6. Visit 10 (Day 34) and Study Conclusion

Subjects will return to the study site on the final day; Visit 10 (Day 34) having cleansed their skin with water (only). Subjects will return the standard soap at this visit.

Final review of any concomitant therapy taken and continued eligibility before final measures of TEWL and Corneometry per Sections 6.2.1 and 6.2.2 will be taken on Area 1 and Area 3 for the forearms and Area 6 and Area 8 of the face.

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


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

## 7. SAFETY ASSESSMENTS

### 7.1. Definitions of an Adverse Event and Serious Adverse Event

#### 7.1.1. Adverse Events

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

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#### **Adverse Event Definition:**

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout product.

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

#### **Events meeting AE definition include:**

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

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

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

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

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

#### **Events NOT meeting definition of an AE include:**


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

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

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

Any localised response to the D-Squame disc application and removal on the face and



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forearms, unless more severe than expected in which case will be captured as an AE.

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

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

### 7.1.2. Serious Adverse Events

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

#### A. Results in death

#### B. Is life-threatening

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


#### C. Requires hospitalisation or prolongation of existing hospitalisation

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

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

#### D. Results in disability/incapacity

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

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

#### **E. Is a congenital anomaly/birth defect**

#### **F. Other Situations**

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

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

## **7.2. Recording Adverse Events and Serious Adverse Events**


### **Recording of adverse events and serious adverse events:**

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

The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.

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

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory

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tract infection, seasonal allergy, etc. instead of runny nose).

AEs will be collected from the start of the use of the washout soap product and until 5 days following last administration of the study product.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

### 7.3. Evaluating Adverse Events and Serious Adverse Events

#### Assessment of Intensity:

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

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

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


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

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

#### Assessment of Causality:

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

A "reasonable possibility" is meant to convey that there are facts/evidence or

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arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

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

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

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

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

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

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

#### 7.4. Reporting Adverse Events and Serious Adverse Events


##### AE Reporting to GSKCH:

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

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

AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee must ask the subject the following question during each visit including any follow-up visits:

***"Have you felt unwell, experienced any symptoms or taken any medication (since***

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*your last visit) (today) (since your last application) (since the last session)?”*

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

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

#### **SAE Reporting to GSKCH:**

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see section 7.3)
- Criterion for seriousness.


The following are desirable and are of particular relevance for investigator and GSKCH 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 on study product
- Outcome if known

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

**Fax Serious Adverse Events to:**  
**UK: PPD**  
**(email: PPD )**

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

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appropriate via email.

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

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

### Follow-up of AEs and SAEs:

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

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

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

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


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

### Regulatory and ethics reporting requirements for SAEs:

The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.

Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for

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a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IEC, if appropriate according to local requirements.

## 7.6. Collection of Pregnancy Information

### 7.6.1. Time Period for Collecting of Pregnancy Information

#### Collection of Pregnancy Information:

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


### 7.6.2. Action to be Taken if Pregnancy Occurs

#### Action to be Taken:

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product (or washout product). The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSKCH. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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

A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as

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possibly related to the investigational product, must be promptly forwarded to GSK.

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

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

## 8. DATA MANAGEMENT

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

### 8.1. Source Documents/ Data

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


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

### 8.2. Electronic Case Report Form

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

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



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

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

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

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

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


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

### 8.3. Data Handling

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

#### 8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary

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Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) are reported appropriately.

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

#### 8.4. 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 GSKCH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is 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 GSKCH via secured web portal or CD/DVD via mail carrier with tracking capabilities.


Proper 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.

### 9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

#### 9.1. Sample Size Determination

The primary evaluation will be the change from baseline in TEWL measurements on Day 29 of test product versus no treatment on the forearm (Area 1 and 3). The sample size is based on clinical considerations. Approximately 90 subjects will be screened to randomise approximately 66 to ensure at least 40 subjects per treatment arm (test product, positive control, no treatment) or 20 subjects per treatment group (test product/no treatment, test product/positive control, positive control/no treatment) complete the entire study

The only previous data available in a 29-day model is a study (GSKCH Clinical Study; CCI [REDACTED]), which assessed TEWL on the leg. In that study, the change from baseline in TEWL following 4 weeks of treatment with a similar product on the leg

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was not normally distributed. Using the data from that study and applying a Wilcoxon sample size adjustment to the paired t-test, 40 subjects treated with test product and no treatment would be required to detect a difference of 1.5 points in change from baseline in TEWL at  $\alpha=0.05$  with at least 90% power assuming a (within-subject) standard deviation of 2.7 points.

## 9.2. General Considerations

### 9.2.1. Definition of Analysis Populations

The ‘Intent to treat’ (ITT) population includes all subjects who are randomised into the study and have at least one post-baseline measurement available. All efficacy analyses will be based on the ITT population.

The Per Protocol (PP) population will consist of the subset of ITT subjects which excludes those subjects with significant protocol deviations. Protocol deviations will be identified prior to database unblinding and will include, but not be limited to, non-compliance with the protocol or product application and use of prohibited concomitant medications. Confirmatory analyses of at least the primary efficacy endpoint will be performed on the PP population.

The Safety population will include all subjects who applied any of the study products. All safety analyses will be performed using the Safety population.

### 9.2.2. Exclusion of Data from Analysis


No data will be excluded from any analysis.

### 9.2.3. Criteria for Evaluation

The primary objective will be to assess the skin barrier function of the test product formulation based on change from baseline in TEWL after 4 weeks of twice daily product application on the forearm (Area 1 and 3). Given this proof of concept study, the study will be considered a success if at least a trend in favor of the test product in change from baseline at Day 29 in TEWL (Area 1 and 3) is found compared to the untreated forearm. There will be no adjustment to the critical alpha level of 0.05 to account for inflation due to multiplicity. P-values resulting from inferential testing will be considered primarily as summary statistics.

### 9.2.4. Handling of Dropouts and Missing Data

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

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### 9.3. Statistical Methods and Analytical Plan

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

#### 9.3.1. Demographic and Baseline Characteristics


Age and baseline forearm and face dryness and roughness (face only) scores will be summarised descriptively by treatment arm (test product, positive control, no treatment) using means, medians and standard deviations. Race and Fitzpatrick Skin Type will be summarised using frequency counts and percentages.

#### 9.3.2. Primary Analysis(es)

Change from baseline in TEWL for each subject at Day 29 (Area 1 and 3 on the forearms and Area 6 and 8 on the face) will be summarised for each of the three treatment arms (test product, positive control and no treatment) of both the forearm and face using descriptive statistics (means, medians, standard deviations, 95% confidence intervals).

Test product versus no treatment and positive control versus no treatment will be compared for the change from baseline at Day 29 of both the forearms (Area 1 and 3) and face (Area 6 and 8) using analysis of covariance (ANCOVA) with subject as a random effect, treatment arm (test product, positive control and no treatment) and side of body (right, left) as main effects and baseline value as covariate. This approach allows for the inclusion of data from all subjects treated with a given treatment arm (test product, positive control or no treatment) regardless of the treatment group (test product/no treatment, test product/positive control, positive control/no treatment) to which they were randomized to derive estimates of treatment effect. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and for the difference between each pair of treatment arms together with p-values and 95% confidence intervals.

If the assumption of normality is rejected, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In the case of a non-parametric analysis, median differences will be presented, together with 95% confidence intervals based on the Hodges-Lehmann method.

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### 9.3.3. Secondary Analysis(es)

Change from baseline in TEWL and Corneometry for each subject at Days 1 (30 minutes and 6 hours post first application – corneometry only), 2, 15, 30, 31, 32, 33, and 34 (Area 1 and 3 on the forearms and Area 6 and 8 on the face) will be summarised for all 3 treatment arms of both the forearm and face using descriptive statistics (means, medians, standard deviations, 95% confidence intervals).

Test product versus no treatment and positive control versus no treatment will be compared for the change from baseline at each time point of both the forearms (Area 1 and 3) and face (Area 6 and 8) using analysis of covariance (ANCOVA) with subject as a random effect, treatment arm (test product, positive control and no treatment) and side of body treatment applied (right, left) as main effects and baseline value as covariate. This approach allows for the inclusion of data from all subjects treated with a given treatment arm (test product, positive control or no treatment) regardless of the treatment group (test product/no treatment, test product/positive control, positive control/no treatment) to which they were randomized to derive estimates of treatment effect. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and for the difference between each pair of treatment arms together with p-values and 95% confidence intervals.

If the assumption of normality is rejected, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In the case of a non-parametric analysis, median differences will be presented, together with 95% confidence intervals based on the Hodges-Lehmann method.

Standardised AUCs will be calculated for each subject for change from baseline in TEWL and corneometry (Area 1 and 3 on the forearms and Area 6 and 8 on the face) over the treatment period; i.e. through Day 29 (Days 1, 2, 15, and 29) and separately over the Regression period; i.e. through Day 34 (Days 30, 31, 32, 33 and 34). Each AUC will be similarly summarized and compared for both the forearm and face using analysis of covariance (ANCOVA) with subject as a random effect, treatment arm (test product, positive control and no treatment) and side of body treatment applied (right, left) as main effects and baseline value as covariate. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and for the difference between each pair of treatment arms together with p-values and 95% confidence intervals.

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If the assumption of normality is rejected, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In the case of a non-parametric analysis, median differences will be presented, together with 95% confidence intervals based on the Hodges-Lehmann method.

Day 29 change from pre-challenge in TEWL (Area 2 and 4 of the forearms and Area 5 and 7 of the face) will be summarised for all 3 treatment arms of both the forearm and face after each set of discs (4, 8 and 12 discs for the forearm and 3, 6 and 9 discs for the face) using descriptive statistics (means, medians, standard deviations, 95% confidence intervals). Comparisons of the changes from pre-challenge after each set of discs between the test product and no treatment for both the forearm and face will be performed using analysis of covariance (ANCOVA) with subject as a random effect, treatment arm (test product, positive control and no treatment) and side of body treatment applied (right, left) as main effects and baseline value as covariate. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and for the difference between each pair of treatment arms together with p-values and 95% confidence intervals.

If the assumption of normality is rejected, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In the case of a non-parametric analysis, median differences will be presented, together with 95% confidence intervals based on the Hodges-Lehmann method

ANCOVA as described above or analysis based on transformed data or an appropriate non-parametric analysis will also be used to compare the protein present on D-Squame discs at Day 29 separately for forearms and face. P-values resulting from these analyses as well as 95% confidence intervals for the differences in the protein levels between each pair of treatment arms will also be provided.

Change from Day 29 to Days 30, 31, 32, 33 and 34 in TEWL and corneometry (Area 1 and 3 on the forearms and Area 6 and 8 on the face) and the standardised AUC calculated over the Regression period will be summarised and compared between each pair of treatment arms, separately for forearm and face, as described above for the changes from baseline.

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#### 9.3.4. Safety Analysis(es)

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

### 10. STUDY GOVERNANCE CONSIDERATIONS

#### 10.1. Posting of Information on Publicly Available Clinical Trials Registers


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

#### 10.2. Regulatory and Ethical Considerations, Including the Informed Consent

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

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

1. Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IEC for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
2. Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
3. Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)

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4. GSK will provide full details of the above procedures, either verbally, in writing, or both.

### 10.3. Quality Control (Study Monitoring)

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

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

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

- 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 GSKCH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.


### 10.4. Quality Assurance

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

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

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



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## 10.5. Conditions for Terminating the Study

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

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

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


In addition:

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

## 10.6. Records Retention

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

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

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

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


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

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

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

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

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

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


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

## 11. REFERENCES

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## 12. APPENDICES

### 12.1. Appendix 1 - Abbreviations and Trademarks

#### Abbreviations

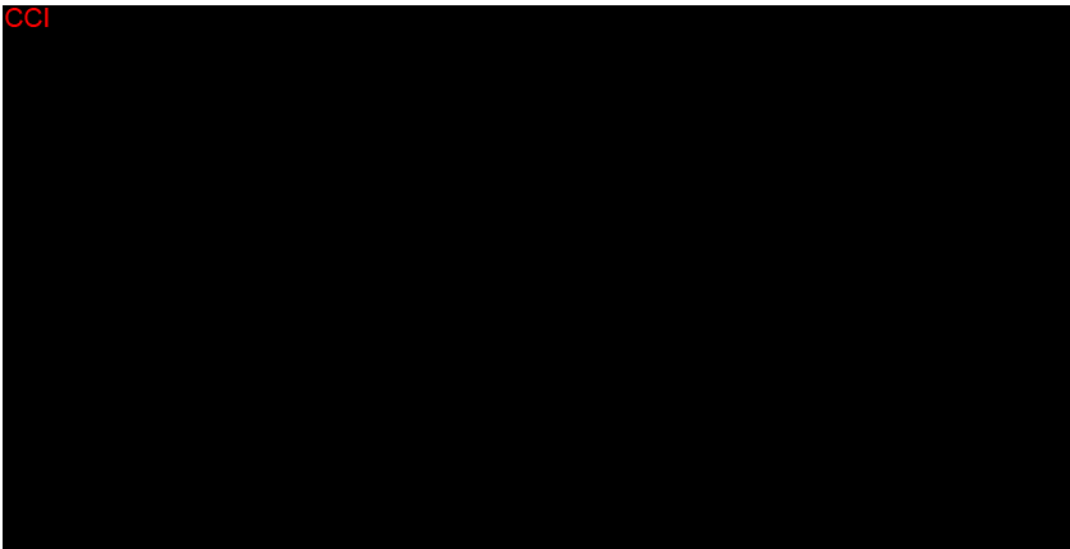
µl	Microliters
AE	Adverse Event
ANCOVA	Analysis of Covariance
aq	Aqueous
AUC	Area under Curve
CD	Compact Disc
cm <sup>2</sup>	Centimetre squared
CRF	Case Report Form
DVD	Digital Versatile Disc
EDC	Electronic Data Capture
EEMCO	European Group for Efficacy Measurements on Cosmetics and Other Topical Products
FSFV	First Subject First Visit
g	Gram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
hr	Hour(s)
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
LSLV	Last Subject Last Visit
m <sup>2</sup>	Square metre
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
min	Minute
ml	Milliliters
nm	Nanometers
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Stratum Corneum
SLS	Sodium Lauryl Sulphate


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TEWL	Transepidermal Water Loss
w/w	Weight by Weight

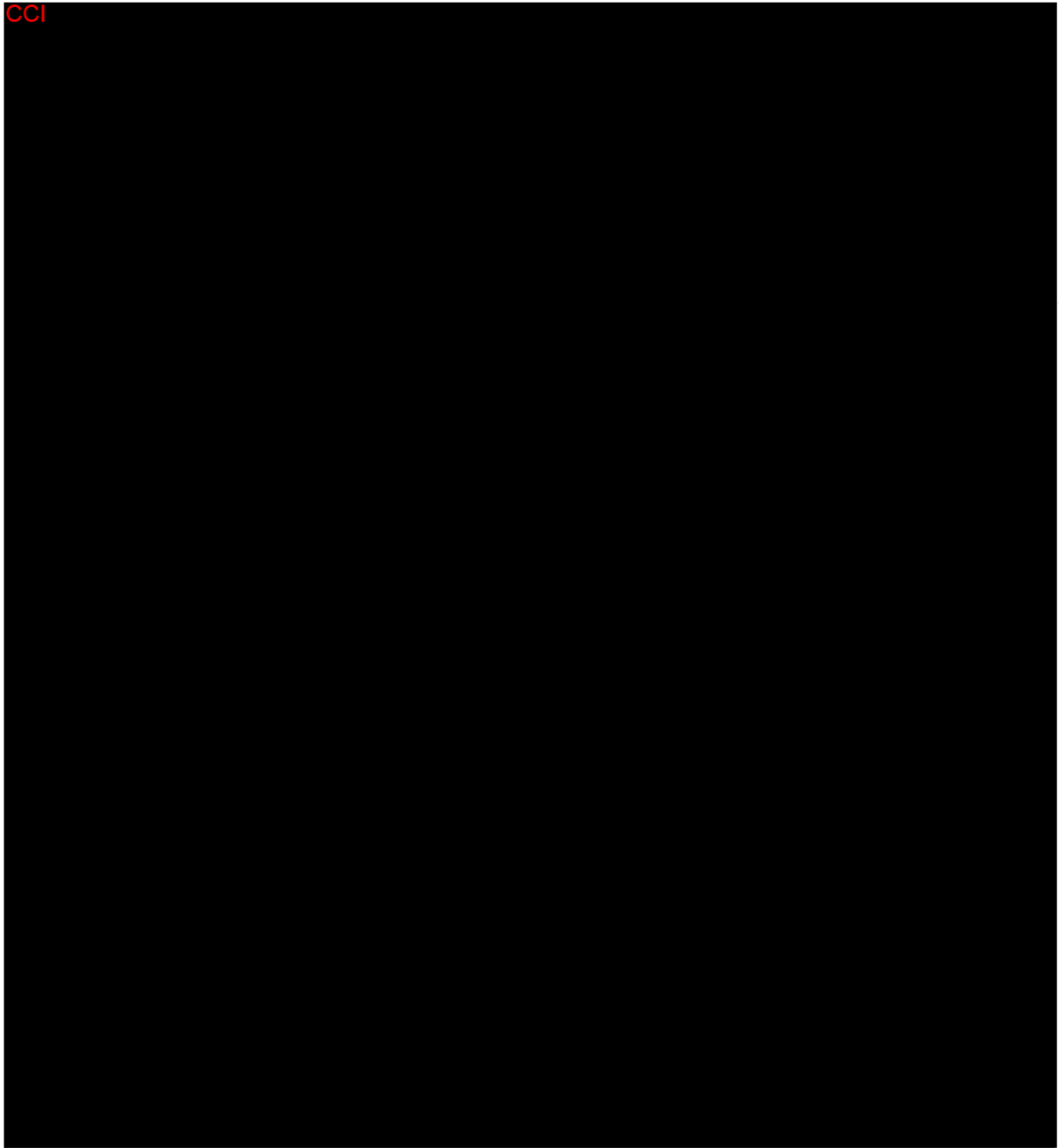
## 12.2. Appendix 2 – Screening and Baseline Assessments


### Assessment of Overall Dryness - Face and Forearm



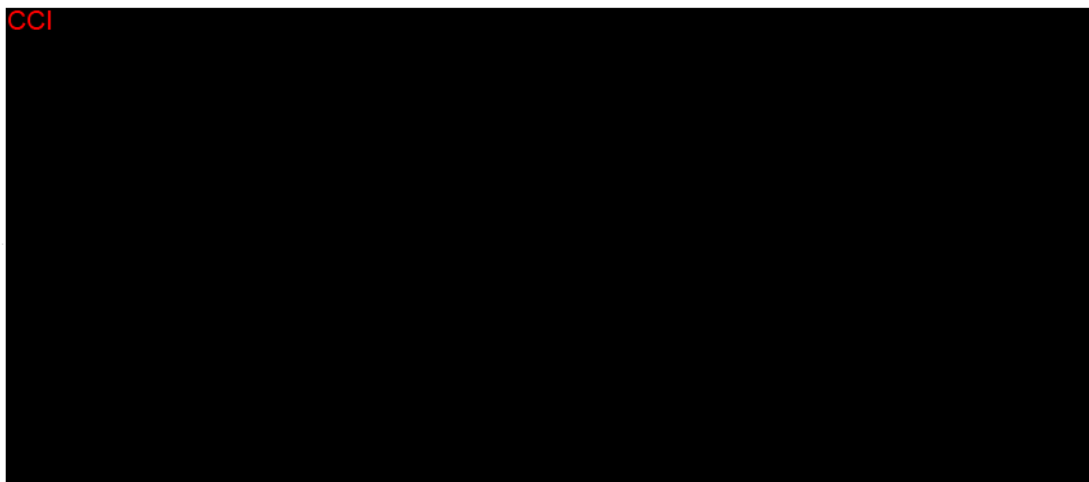
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### 12.3. Appendix 3 - Fitzpatrick Skin Type Grading





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