Clinical Protocol

207619

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Clinical Study to Assess the Mildness of a Cosmetic Cleanser in Healthy Subjects Using the Forearm-Controlled Application Technique (FCAT).
Protocol Number:	207619
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) Rua Hungria, 1240 4º andar, Jardim Europa São Paulo/SP – Brazil, CEP 01455-000 Tel: PPD
Product Name:	Facial micellar cleanser
Development Phase:	N/A

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

Key Protocol Authors:	
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Study Site Telephone Number:	PPD
Study Examiner(s):	Study examiner (s) will be assigned according to the site schedule (before First Subject First Visit) and documented in the site file.
Dermatologist:	Study Dermatologist will be assigned according to the site schedule (before First Subject First Visit) and documented in the site file.

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

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

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

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

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

Table of Content

PROCESS FOR AMENDING THE PROTOCOL

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

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

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

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

PROTOCOL AMENDMENT PAGE

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

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

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Protocol Version No.:	Substantial/ Major ☐				Date:

SCHEDULE OF EVENTS

	Screening		Treatment Period									
Study Day / Procedure/ Assessment	DAY -7 to DAY 0 VISIT 1		DAY 1 MON VISIT 2		DAY 2 TUE VISIT 3		DAY 3 WED VISIT 4		DAY 4 THU VISIT 5		DAY 5 FRI VISIT 6	
Time of Day	-		**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
Informed Consent	X	WASHOUT PERIOD (5-7 Days)										
Demographics	X											
Medical History	X											
Current/Concomitant medication review	X		X		X		X		X		X	
Fitzpatrick Skin Type Assessment	X											
Inclusion/Exclusion Criteria	X		X [a b]									
Subject Eligibility	X		X									
Examiner Visual Assessment of Dryness and Redness [b]	X [c]		X [d]	X [e]		X [e]		X [e]		X [e]		X
Dermatologist Assessment [a]	X		X									X
Continued Eligibility			X		X		X		X		X	
Dispense standard soap	X											
Compliance Check for soap use			X		X		X		X		X	
Acclimatisation *(for instrumental assessments)*			X									X
Corneometry Assessment			X									X
TEWL Assessment			X									X
Controlled Product Application/Wash procedure (at study site) [f]			X	X	X	X	X	X	X	X	X	
Return standard soap												X
Adverse Events [g]	X		X	X	X	X	X	X	X	X	X	X
Study Conclusion/Exit from Study												X

a. Inclusion criteria 3c Performed by a qualified dermatologist.

b. A trained (by a dermatologist) blinded examiner will perform visual assessments of dryness and redness of each volar forearm using the scoring system detailed in Appendix 2. (Inclusion Criteria 4b).

c. Screening assessment of dryness and redness of each volar forearm, will be performed using the scoring system detailed in Appendix 2. For inclusion in the study each volar forearm dryness score should be zero and each volar forearm redness score should be zero.

d. Baseline assessment of dryness and redness of each proposed test site on each volar forearm, will be performed prior to any wash application (Day 1 (AM) Visit 2) using the scoring system detailed in Appendix 2. For continuation in the study each site dryness score should be zero and each site redness score should be zero.

e. Examiner visual examination of dryness and redness using the scoring system detailed in Appendix 2 will be prior to the PM wash procedure, Except Day 5 (Visit 6) where the final examination will be 3 hours after the final AM wash procedure.

f. Subjects will report to the study site for 5 days for the FCAT wash procedure, 18 controlled wash applications of each product to each allocated test site in total (one site will remain unwashed), two in the morning (AM) and two in the afternoon (PM) (except Day 5 where only the AM wash procedure will take place). The first application will follow all Baseline assessments at Day 1 AM (Visit 2), the final application will be Day 5 AM (Visit 6). Each wash application (AM and PM) will be separated by at least 3 hours.

g. Subjects are asked to report any adverse events from use of the Standard soap and the use of any concomitant medications throughout the study.

PROTOCOL SYNOPSIS FOR STUDY 207619

Brief Summary

A cosmetic product that is freely available to the consumer must be free from adverse reactions when applied under normal or reasonably foreseeable conditions of use. As a general requirement, the safety and compatibility of a new formulation should be confirmed before it is commercialised (Guideline for the Safety Evaluation of Cosmetic Products; Agência Nacional de Vigilância Sanitária, ANVISA, 2012).

Mildness is a factor that contributes to consumer acceptance of a cleansing product, especially in those with dry or sensitive skin. The relative mildness (or irritation potential) of personal cleansing products is ideally judged under conditions of actual consumer use. However, these may not present the best conditions for discriminating product mildness differences, since normal use conditions typically do not induce differentiable product skin effects (Ertel, 1995).

The Forearm Controlled Application Technique (FCAT) is a method that offers an efficient means to estimate the relative mildness of personal cleansers. It provides greater precision and sensitivity and also minimises confounding effects due to biological diversity (Ertel, 1995).

Visual assessment of dryness and redness will be conducted by a trained blinded examiner at Baseline and on a daily basis throughout the 5-day FCAT wash procedure.

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 Baseline and after completion of the 5 day FCAT wash procedure.

The objective of this clinical study is to assess the relative mildness of a cosmetic facial cleanser in comparison to water through repeated application to the volar forearm using the FCAT wash procedure.

Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
To compare change from Baseline in examiner rating of dryness to 3 hours following last wash procedure on Day 5, for the test product versus water in the skin of healthy subjects.	Examiner assessment of dryness (Lukacovic, 1987) as per Appendix 2 at Day 5, 3 hours post last wash procedure.
Secondary	
To compare change from Baseline in the examiner rating of redness to 3 hours following last wash procedure on Day 5 for the test product versus water in the skin of healthy subjects.	Examiner assessment of redness (Lukacovic, 1987) as per Appendix 2 at Day 5, 3 hours post last wash procedure.
To compare change from Baseline in the examiner rating of dryness and redness each day for test product and the positive control versus water in the skin of healthy subjects.	Examiner assessment of redness and dryness (Lukacovic, 1987) as per Appendix 2 at Day 2, 3, 4 and 5, 3 hours post last wash procedure.
To assess change from Baseline in skin barrier function following the FCAT wash procedure for test product and positive control versus water.	TEWL measurements on Day 5, 3 hours post last wash procedure.
To assess change from Baseline skin moisturisation following the FCAT wash procedure for test product and positive control versus water.	Corneometer measurements on Day 5, 3 hours post last wash procedure.
To evaluate the general safety of the test product.	Assessment of frequency and severity of Adverse Events

Study Design

Overall Design
This is a test site randomised, examiner blinded, positive and negative-controlled, single-center; Forearm Controlled Application Technique clinical study in healthy subjects to assess the mildness potential of a cosmetic facial cleansing product.

Subjects will give their written consent prior to any study procedures taking place. Visual assessments of dryness and redness will be conducted (by a trained blinded examiner). Each subject should have a score of zero for dryness and zero for redness on each volar forearm to be eligible for inclusion in the study. Eligible subjects will undergo a 5 to 7-day washout period, during which only the provided standard soap (Simple Soap®) will be used. This standard soap will also be used throughout the study in place of current cleansing product(s), but subjects should avoid using anything other than water on the volar forearms throughout the study, including the washout period.

A qualified dermatologist will assess subjects at Screening (Visit 1) for eligibility and again at Visit 2 for continued eligibility, to ensure the subjects are free of any clinically-relevant dermatological conditions.

At the Baseline Visit (Visit 2, Day 1) examiner assessment of the dryness and redness of each proposed test site on each volar forearm will be performed prior to any wash application using the scoring system detailed in Appendix 2. Each subject should have a score of zero for dryness and zero for redness to be considered eligible to continue in the study.

Prior to any wash procedure, subjects will be acclimatized to the environment of controlled temperature and humidity room and instrumental measurements of skin barrier function (measured with a Tewameter) and skin moisturisation (measured with a Corneometer) will be performed at Baseline (Visit 2 (AM)) in addition to the Baseline examiner ratings of dryness and redness at each forearm test site.

This will be followed by 5 days of repeated FCAT wash procedure where subjects will be instructed to attend the site for two wash visits per day for the first 4 days (Visits 2-5, AM and PM) and one wash visit on Day 5 (Visit 6, AM only). The AM and PM wash procedures on any given day will be separated by a minimum of 3 hours.

Visual assessment of dryness and redness will be conducted (by a trained, blinded examiner) prior to each PM wash procedure for Days 1-4 (Visits 2-5). The final examiner assessment of dryness and redness will be conducted on Day 5 (Visit 6), a minimum of 3 hours following the final Day 5 AM wash procedure.

A trained technician will perform each wash procedure to ensure consistency and

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eliminate the risk of cross-contamination of the study test sites. The technician will wash each of the 4 designated sites with one of the randomly allocated products; test product, positive control (Imperial Leather bar soap), negative control (sterile water only) or unwashed. On Day 5, 3 hours after the last wash procedure, examiner ratings of dryness and redness and final instrumental measurements of skin barrier function and skin moisturisation will be performed. Additionally, a final clinical assessment by a qualified dermatologist will be performed to ensure that it is medically appropriate to discharge each subject from the study.
Visit 1 - Screening Visit (Day -7 to 0)
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 Assessment (Appendix 3) 6. Examiner assessment of dryness and redness (Inclusion criteria 4b) 7. Inclusion/Exclusion criteria 8. Dermatologist assessment for eligibility to participate in the study (including visual examination of the volar forearm region) 9. Subject Eligibility 10. Dispense standard soap and instructions for use 11. Adverse events will be reported following first use of the Standard soap.
Visit 2 - Baseline Visit - Day 1 AM & PM (FCAT Wash Period)
The following assessments will be conducted: 1. Current/Concomitant Medications review (AM only) 2. Compliance Check (for standard soap use – AM only) 3. Continued eligibility check (AM only) 4. Test Site allocation on each volar forearm (AM only) 5. Examiner assessment of dryness and redness AM (prior to AM wash procedure) and PM (3 hours post AM wash procedure and prior to Day 1 PM wash procedure). **NOTE:** To continue in the study subjects should have a dryness score of zero and a redness score of zero at each of the proposed test sites (Inclusion criteria 4b) at Baseline (AM only). 6. Inclusion criteria 3c and 4b review - AM only 7. Dermatologist determination for continued eligibility to participate in the study

(AM only)

8. Subject acclimatised to standard room conditions (AM only)
9. Baseline TEWL and Corneometer assessments (AM only)
10. Randomisation (AM only)
11. Controlled wash procedure by trained technician (AM and PM)
1. Adverse event assessment

Visit 3 to Visit 5 / Day 2 to Day 4 AM & PM (FCAT Wash period)

The following assessments will be conducted:

1. Current/Concomitant Medications review (AM only)
2. Continued eligibility check (AM only)
3. Compliance Check (for standard soap use – AM only)
4. Examiner assessment of dryness and redness (PM only prior to PM wash procedure)
5. Controlled wash procedure by a trained technician (AM and PM)
6. Adverse event assessment

Visit 6 - Day 5 AM (Final Test Product Application)

The following assessments will be conducted:

1. Current/Concomitant Medications review
2. Continued eligibility check
3. Compliance Check (for standard soap use)
4. Controlled wash procedure by a trained technician
5. Adverse event assessment

Visit 6 - Day 5 PM (Final Assessments) Exit from Study

The following assessments will be conducted:

1. Examiner assessment of dryness and redness
2. Subject acclimatised to standard room conditions
3. TEWL and corneometry assessments
4. Return Standard soap
5. Adverse event assessment
6. Dermatologist final assessment
7. Study discharge from the study site following completion of all study procedures.

Type and Planned Number of Subjects

A sufficient number of subjects will be screened in order to randomise approximately 45 subjects to ensure that at least 40 subjects complete the study.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects aged 18 to 65 with no dermatological disorders, a Fitzpatrick skin phototype I-IV and a blinded trained evaluator score for redness and dryness of zero (at Screening and Baseline visits) will be enrolled into this study.

Product Information

	Test Product	Positive Control	Reference Product
Product Name	Micellar Cleanser	Imperial Leather Original Bar Soap	Baxter Sterile Water
Product Formulation Code (MFC)	CCI [redacted]	N/A Market Place product	N/A Market Place product
Product Format	200ml Clear PET bottle	100g Bar	1000ml bottle
Application Quantity	0.09ml onto a Moistened Towel *(with sterile water)*	Moistened Towel *(with sterile water)* rubbed onto bar soap for 6 seconds to generate a lather	0.09ml onto a Moistened Towel *(with sterile water)*
Route of Administration	Topical dermal application		
Application Instructions	Applied on-site by technician		

Statistical Methods

The primary hypothesis is that the test product is not inferior to sterile water in the change from baseline in the examiner rating of dryness on Day 5. Assuming that the standard deviation of the within subject treatment difference in change from baseline in examiner rating of dryness is 0.25 (based on previous study; GSKCH Study: CCI [redacted] CCI [redacted].

The primary endpoint will be tested for non-inferiority of the test product to water in change from baseline to Day 5 in examiner rating of dryness using treatment estimates derived from an ANCOVA with subject (random effect), treatment and site

as factors with baseline value as a covariate. The treatment difference (test product – water) and upper one-sided 95% confidence limit will be presented. If this upper confidence limit is below 0.25, it will be concluded that the test product is not inferior to water in the examiner rating of dryness.

This will be corroborated by using a one-sided 0.05 level of significance Wilcoxon sign rank test performed on the adjusted difference (within subject change from baseline subtracted by 0.25) on Day 5 to test the hypothesis that the mean change from baseline for the test product is not greater than the change for water by 0.25 or more.

The same non-inferiority analyses will also be performed for the secondary endpoint based on examiner rating of redness.

For secondary endpoints based on examiner rating of dryness and redness to compare positive control versus water, the same ANCOVA model as above will be used and the treatment difference (positive control – water), p-value and 95% confidence interval will be presented.

For the other secondary endpoints of dryness and redness each day, TEWL and corneometer, the change from baseline will be analysed using ANCOVA with subject (random effect) treatment and site as factors with baseline value as a covariate. The treatment differences (test product – water and positive control - water), p-value and 95% confidence interval will be presented.

If data are sufficiently non-normal in distribution, the non-parametric Wilcoxon signed rank test will be used with median difference and 95% confidence intervals presented based on the Hodges-Lehmann method.

No interim or subgroup analyses are planned.

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

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

1. INTRODUCTION

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

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

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

Mildness is a factor that contributes to consumer acceptance of a personal cleansing product, especially in dry skin. The relative mildness (or irritation potential) of personal cleansing products is ideally judged under conditions of actual consumer use. However, these may not present the best conditions for discriminating product mildness differences, since normal use conditions typically do not induce differentiable product skin effects (Ertel, 1995).

The Forearm Controlled Application Technique (FCAT) is an exposure method that offers an efficient means to estimate the relative mildness (irritation) of personal cleansers through repeated overuse. It provides greater precision and sensitivity and minimises confounding effects due to biological diversity (Ertel, 1995). The FCAT is able to discriminate the relative mildness of personal cleansers in a wide variety of test conditions. Mildness can be defined by the parameters of skin redness and dryness (Lukacocvic, 1987).

Transepidermal water loss (TEWL) is the rate at which water permeates the stratum corneum and evaporates from the skin surface and qualifying TEWL can be used to support the examiner 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 is included to provide an instrumental measurement of skin moisturisation to support the examiner assessments.

Clinical studies which are designed to evaluate the irritation and sensitisation potential of a product must take into account a number of variables including the components used in the formulation and their concentration, absorption, amount applied, skin condition, application directions and frequency, as well as the cumulative effect (Dooms-Goossens, 1993).

The objective of this clinical study is to assess the relative mildness of a cosmetic facial cleanser in comparison to water through repeated application to the volar forearm using the FCAT wash procedure. A positive control has been included in the design to help validate the trial results. Specifically, Imperial Leather Original bar soap has been selected as the positive control as CCI [redacted] CCI [redacted]. An area that will remain unwashed is also included in the study as a reference for the treated areas.

2. OBJECTIVE(S) AND ENDPOINT(S)

Objective(s)	Endpoint(s)
Primary	
To compare change from Baseline in examiner rating of dryness to 3 hours following last wash procedure on Day 5, for the test product versus water in the skin of healthy subjects.	Examiner assessment of dryness (Lukacovic, 1987) as per Appendix 2 at Day 5, 3 hours post last wash procedure.
Secondary	
To compare change from Baseline in the examiner rating of redness to 3 hours following last wash procedure on Day 5 for the test product versus water in the skin of healthy subjects.	Examiner assessment of redness (Lukacovic, 1987) as per Appendix 2 at Day 5, 3 hours post last wash procedure.

To compare change from Baseline in the examiner rating of dryness and redness each day for test product and the positive control versus water in the skin of healthy subjects.	Examiner assessment of redness and dryness (Lukacovic, 1987) as per Appendix 2 at Day 2, 3, 4 and 5, 3 hours post last wash procedure.
To assess change from Baseline in skin barrier function following the FCAT wash procedure for test product and positive control versus water.	TEWL measurements on Day 5, 3 hours post last wash procedure.
To assess change from Baseline skin moisturisation following the FCAT wash procedure for test product and positive control versus water.	Corneometer measurements on Day 5, 3 hours post last wash procedure.
To evaluate the general safety of the test product.	Assessment of frequency and severity of Adverse Events

3. STUDY PLAN

3.1. Study Design

Overall Design
This is a test site randomised, examiner blinded, positive and negative-controlled, single-center; Forearm Controlled Application Technique clinical study in healthy subjects to assess the mildness potential of a cosmetic facial cleansing product. Subjects will give their written consent prior to any study procedures taking place. Visual assessments of dryness and redness will be conducted (by a trained blinded examiner). Each subject should have a score of zero for dryness and zero for redness on each volar forearm to be eligible for inclusion in the study. Eligible subjects will undergo a 5 to 7-day washout period, during which only the provided standard soap (Simple Soap®) will be used. This standard soap will also be used throughout the study in place of current cleansing product(s), but subjects should avoid using anything other than water on the volar forearms throughout the study, including the washout period. A qualified dermatologist will assess subjects at Screening (Visit 1) for eligibility and again at Visit 2 for continued eligibility, to ensure the subjects are free of any

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clinically-relevant dermatological conditions. At the Baseline Visit (Visit 2, Day 1) examiner assessment of the dryness and redness of each proposed test site on each volar forearm will be performed prior to any wash application using the scoring system detailed in Appendix 2. Each subject should have a score of zero for dryness and zero for redness to be considered eligible to continue in the study. Prior to any wash procedure, subjects will be acclimatized to the environment of controlled temperature and humidity room and instrumental measurements of skin barrier function (measured with a Tewameter) and skin moisturisation (measured with a Corneometer) will be performed at Baseline (Visit 2 (AM)) in addition to the Baseline examiner ratings of dryness and redness at each forearm test site. This will be followed by 5 days of repeated FCAT wash procedure where subjects will be instructed to attend the site for two wash visits per day for the first 4 days (Visits 2-5, AM and PM) and one wash visit on Day 5 (Visit 6, AM only). The AM and PM wash procedures on any given day will be separated by a minimum of 3 hours. Visual assessment of dryness and redness will be conducted (by a trained, blinded examiner) prior to each PM wash procedure for Days 1-4 (Visits 2-5). The final examiner assessment of dryness and redness will be conducted on Day 5 (Visit 6), a minimum of 3 hours following the final Day 5 AM wash procedure. A trained technician will perform each wash procedure to ensure consistency and eliminate the risk of cross-contamination of the study test sites. The technician will wash each of the 4 designated sites with one of the randomly allocated products; test product, positive control (Imperial Leather bar soap), negative control (sterile water only) or unwashed. On Day 5, 3 hours after the last wash procedure, examiner ratings of dryness and redness and final instrumental measurements of skin barrier function and skin moisturisation will be performed. Additionally, a final clinical assessment by a qualified dermatologist will be performed to ensure that it is medically appropriate to discharge each subject from the study.
Visit 1 - Screening Visit (Day -7 to 0)
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 Assessment (Appendix 3)
6. Examiner assessment of dryness and redness (Inclusion criteria 4b)
7. Inclusion/Exclusion criteria
8. Dermatologist assessment for eligibility to participate in the study (including visual examination of the volar forearm region)
9. Subject Eligibility
10. Dispense standard soap and instructions for use
11. Adverse events will be reported following first use of the Standard soap.

Visit 2 - Baseline Visit - Day 1 AM & PM (FCAT Wash Period)

The following assessments will be conducted:

12. Current/Concomitant Medications review (AM only)
13. Compliance Check (for standard soap use – AM only)
14. Continued eligibility check (AM only)
15. Test Site allocation on each volar forearm (AM only)
16. Examiner assessment of dryness and redness AM (prior to AM wash procedure) and PM (3 hours post AM wash procedure and prior to Day 1 PM wash procedure).

    NOTE: To continue in the study subjects should have a dryness score of zero and a redness score of zero at each of the proposed test sites (Inclusion criteria 4b) at Baseline (AM only).
17. Inclusion criteria 3c and 4b review - AM only
18. Dermatologist determination for continued eligibility to participate in the study (AM only)
19. Subject acclimatised to standard room conditions (AM only)
20. Baseline TEWL and Corneometer assessments (AM only)
21. Randomisation (AM only)
22. Controlled wash procedure by trained technician (AM and PM)
23. Adverse event assessment

Visit 3 to Visit 5 / Day 2 to Day 4 AM & PM (FCAT Wash period)

The following assessments will be conducted:

1. Current/Concomitant Medications review (AM only)
2. Continued eligibility check (AM only)
3. Compliance Check (for standard soap use – AM only)
4. Examiner assessment of dryness and redness (PM only prior to PM wash procedure)
5. Controlled wash procedure by a trained technician (AM and PM)

1. Adverse event assessment
Visit 6 - Day 5 AM (Final Test Product Application)
The following assessments will be conducted: 1. Current/Concomitant Medications review 2. Continued eligibility check 3. Compliance Check (for standard soap use) 4. Controlled wash procedure by a trained technician 5. Adverse event assessment
Visit 6 - Day 5 PM (Final Assessments) Exit from Study
The following assessments will be conducted: 1. Examiner assessment of dryness and redness 2. Subject acclimatised to standard room conditions 3. TEWL and corneometry assessments 4. Return Standard soap 5. Adverse event assessment 6. Dermatologist final assessment 7. Study discharge from the study site following completion of all study procedures.

3.2. Subject Restrictions

Lifestyle/ Dietary
During the entire study (Screening – Last Subject Last Visit (LSLV)) the following should be avoided: 1. Applying any product to the forearms (other than water during bathing) except during the wash procedure. 2. Changing any cosmetic habits, including personal hygiene. 3. Changing dietary habits. 4. Wearing tight or restrictive clothing that could cause friction or cause redness to the forearms. 5. Exposure to artificial ultraviolet (UV) light or cosmetic procedures (includes tanning beds, Intense Pulsed Light (IPL), etc.) on the test areas. 6. Introduction of new products during the study including but not limited to;

soap, laundry detergent, or fabric softener.

7. Use of self-tanning products 2 weeks prior to screening and for the duration of the study

8. Crossing or folding of arms throughout the duration of each of the visits (AM and PM) in order to reduce the risk of product cross-contamination.

9. Contact between clothing and the test sites during a Visit period (AM and PM) (sleeves rolled up if required).

Medications and Treatments

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

1. Having any body aesthetic or dermatological treatments performed.

2. Changing hormone treatment.

3. Changing contraceptive method.

4. Use of the following medications:

    a) Systemic or topical corticosteroids

    b) Systemic or topical immunosuppressive drugs

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

    d) Concomitant topical treatment at test sites

3.3. Type and Planned Number of Subjects

A sufficient number of healthy male and female volunteers aged 18 to 65 with no dermatological disorders, with Fitzpatrick skin phototype I to IV and a trained blinded examiner assessment of dryness score of zero and redness score of zero will be screened in order to randomise approximately 45 subjects to ensure that at least 40 subjects complete the study.

3.4. Study Design and Application Amount Justification

This will be a single centre, randomised, positive and negative-controlled, examiner-blinded study in healthy subjects aged 18-65 years. Subjects will be exposed to a repeated wash procedure method which will be conducted for the test product, a positive control (Imperial Leather bar soap), and a negative control (sterile water) for 5 days. A fourth unwashed site will be included as a reference.

The study will be conducted under the supervision of a qualified dermatologist. Prospective subjects will be assessed by the dermatologist as a prerequisite to enrollment, and again at study end.

During screening subjects will sign an informed consent document and then a dermatological assessment will be conducted to ensure subjects have no dermatological conditions on their forearms that might impact subject safety or study results and to ensure subjects are classified as Fitzpatrick Phototype I to IV. A trained, blinded examiner will assess the dryness and redness of each volar forearm and only subjects with a score of zero for dryness and zero for redness will be enrolled into the study. Each subject's medical and medication history will be reviewed, in addition to the inclusion/exclusion criteria. Subsequently, site staff will review lifestyle guidelines and directions with eligible subjects.

A standard soap to be used in place of subjects' normal cleansers will be provided for use during the washout period and study treatment phase. Subjects will be instructed to avoid using any products, including the supplied cleanser, on their forearms throughout the washout and study treatment phase.

Consented eligible subjects will undergo a one-week washout period (5-7 days) prior to first wash procedure, during which the use of any skin cleansing products, including the standard soap, and any other topical products on the forearms will be prohibited.

On Day 1 (Visit 2, AM), eligible subjects will return to the study site and another dermatological assessment will be conducted, as will a review of any concomitant medications used since screening to ensure subject continued eligibility. Compliance concerning correct use of the standard soap will also be checked.

Each subject will have two test sites (3x3 cm) marked out on each volar forearm. The distance between the two sites should be at least 1 cm to prevent either the test product, positive control product (Imperial Leather Original bar soap) or negative

control (sterile water) applications from spreading over and influencing neighbouring test sites. A trained, blinded examiner assessment (Baseline; Day 1 - AM) of dryness and redness will be conducted at each marked site to ensure the dryness score is zero and the redness score is zero for each site for continued eligibility. The site on each forearm for each wash procedure (or unwashed) will be determined according to the provided randomisation schedule. The randomisation schedule will determine the allocation of the 4 test sites for the test product, positive control and negative control wash applications and the site to be left unwashed. A trained technician will perform product application to ensure consistency and eliminate the risk of cross-contamination of the study test sites.

Subjects will be acclimatised to the environment of a temperature (20-22ºC) and humidity (40-60% RH) controlled room for a period of at least 30 minutes before instrumental measurements of TEWL and corneometry at Baseline (Day 1 - AM) are taken, prior to any wash procedures and additionally at the final visit (Day 5 - PM) following the final wash procedure (Day 5 – AM). (EEMCO, 1997).

The treatment period will consist of 5 days of FCAT wash procedure where subjects will be instructed to come to the site for two wash procedures per day for the first 4 days (AM and PM) and one wash procedure on Day 5 (AM only). Each wash procedure will consist of two washings of each test site AM and PM. The AM and PM wash procedures on any given day will be separated by a minimum of 3 hours.

Further visual assessments of dryness and redness will be performed prior to each PM wash procedure on Days 1 to 4 and again at Day 5 (PM) following the final Day 5 AM wash procedure (Appendix 2). The visual assessments of dryness and redness will be performed prior to subject acclimatisation, TEWL and corneometry measurements on Day 1 and Day 5.

The FCAT generally produces only mild to moderate skin irritation, however, if any site reaches a dryness or redness score of ≥ 5.0 at any time during the study, treatment of all sites on that subject will be immediately discontinued, all test sites will be scored and these will be recorded as an Adverse Event and the subject will be withdrawn from the study.

<u>FCAT *Wash Procedure*:</u>

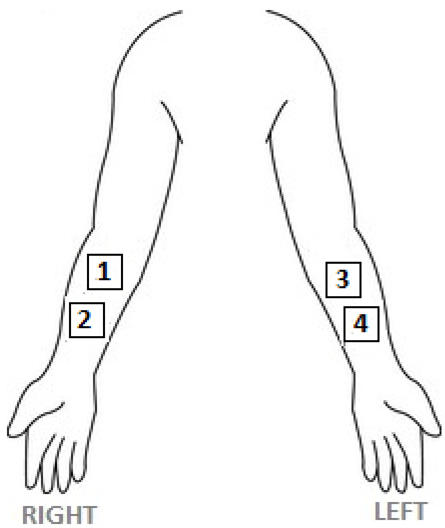
The wash procedure has been derived from consumer habit and general use practices and is therefore considered to be reflective of realistic conditions of product exposure.

Generally, people will use a cleanser once or twice a day for between 6 and 10 seconds (Lukacovic, 1987).

Each subject will have 2 test sites (3x3 cm) marked out on each volar forearm (Figure 1). The distance between sites will be at least 1 cm to prevent products from spreading over and influencing neighbouring test sites.

The randomisation schedule will identify the test sites for the test product, positive control and water (negative control) wash applications and the unwashed site.

Figure 1.



All washings will be performed at the study site by a trained technician to ensure consistent washing and correct product usage. The technician will adhere to the following instructions:

1. Wet the forearm liberally with warm (32-37ºC) tap water.

2. Soak a piece of Masslinn® (or equivalent non-woven towel) with sterile water, and then squeeze to remove excess water.

    a. <u>For the test product:</u> Dispense 0.09ml of the test product via pipette onto the moistened towel.

® Masslinn Towel is a registered trademark of Chicopee Mills, New Brunswick

b. For the positive control: Rub the moistened towel in a circular motion on the Imperial Leather Original soap bar for 6 seconds to generate a lather.

c. For the negative control: Dispense 0.09ml of sterile water onto the moistened towel.

d. For the un-washed site: no further action.

3. Rub the towel in a circular motion on the allocated site for 10 seconds.

4. Wait 90 seconds.

5. Rinse the application site with warm (32-37ºC) tap water for 15 seconds and pat dry.

6. Repeat this procedure for each test applicable product application.

7. After each forearm has been washed once with test product, positive control, and sterile water, and is patted dry, repeat this procedure a second time - i.e. each test site is to be washed twice at the AM and PM time points.

During the study, each subject will have the wash procedure completed four times daily at each application site as per the randomisation schedule, two wash procedures in the morning (AM) and two wash procedures in the afternoon (PM) on Days 1, 2, 3 and 4. On Day 5, each subject will have the wash procedure performed twice only in the morning (AM).

This study aims to determine whether the test product is no more drying to the skin than water. The study design is based on the published FCAT method (Ertel, 1995) which was developed to assess the cutaneous compatibility of personal cleansers.

Assessments:

The same experienced trained blinded examiner will assess the dryness and redness of all test sites for the duration of the study according to the scoring scale (Appendix 2). A Baseline assessment will be carried out at Visit 2, prior to any wash procedure. Baseline scores of dryness and redness must be zero for each proposed test application site on each forearm for subjects to be considered eligible to continue in the study.

Additionally, dryness and redness assessments will be performed for each test site prior to each PM wash procedure on Days 1 to 4 and following the final AM wash procedure on Day 5 (Final assessment).

Transepidermal water loss (TEWL) is the rate at which water permeates the stratum corneum and evaporates from the skin surface and qualifying TEWL can be used to support the examiner assessments. TEWL measurements will be taken at baseline (Day 1) and on Day 5 PM, 3 hours post AM application.

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 is included to provide an instrumental measurement of skin moisturisation to support the examiner assessments. Corneometer measurements will be taken at baseline (Day 1) and on Day 5 PM, 3 hours post AM application.

Application Quantity Justification:

The application regimen and study duration are consistent with the methodology published by Ertel (Ertel, 1995). The application quantity of study product has been selected based on the assumption that, typically, 4ml of a cleansing product will be applied to a facial area of approximately 400cm^2, as consistent with the average amount of non-lathering cleanser reported in the literature (Loretz, 2008). This equates to 0.09ml on a 9cm^2 area of the volar forearm.

A positive control has been included in the design to help validate the trial results. Specifically, Imperial Leather Original bar soap has been selected as the positive control [redacted] An area that will remain unwashed is also included in the study as a reference for the treated areas.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or

subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

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

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

2. AGE
Aged between 18 and 65 years inclusive.

3. GENERAL HEALTH
a.) Good general and mental health with, in the opinion of the investigator or medically qualified designee no clinically significant and relevant abnormalities in medical history or upon physical examination. b.) Intact skin at the proposed application site; volar forearm. c.) Clinical assessment for eligibility by a dermatologist to ensure subject is free of clinically relevant dermatological conditions (Visit 1 and Visit 2(AM)).

4. SKIN TYPE
a) Fitzpatrick phototype I to IV (see Appendix 3). b) Trained examiner scores of zero for dryness and redness for each volar forearm at Screening visit (Visit 1) and each allocated test site on each forearm at Baseline visit (Visit 2, AM).

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

4.2. Exclusion Criteria

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

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

2. BREAST-FEEDING
Women who are breast-feeding

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
a) Any history of significant dermatological diseases or conditions or medical conditions known to alter skin appearance or physiologic response (e.g. diabetes,) which could, in the opinion of the Investigator, preclude topical application of the investigational products and/or interfere with the evaluation of the test site reaction. b) Presence of open sores, pimples, or cysts at the application site. c) Active dermatosis (local or disseminated) that might interfere with the results of the study. d) Considered immune compromised. e) History of diseases aggravated or triggered by ultraviolet radiation. f) History of atopic dermatitis. g) Participants with dermatographism. h) 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. i) Use of the following topical or systemic medications: immunosuppressants, antihistamines, non-hormonal anti-inflammatory drugs, and corticosteroids up to 2 weeks before screening visit. j) Oral or topical treatment with vitamin A acid and/or its derivatives up to 1 month before the screening visit.

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 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 30 days of the screening visit. b) Previous participation in this study.

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

7. DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
a) Intense sunlight exposure or sun tanning sessions, including use of self-tanning products on the test areas up to 14 days before the Screening evaluation. b) Intention of bathing (in the sea or pool), sauna, water sports, or activities that lead to intense sweating. c) Any Subject who, in the judgment of the Investigator and Dermatologist, should not participate in the study. d) Any skin marks on the test site that might interfere with the evaluation of possible skin reactions (e.g. pigmentation disorders, vascular malformations, scars, tattoos, excessive hair, numerous freckles).

e) Prisoner or involuntary incarcerated subject.

f) Subject from an indigenous tribe.

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

4.3. Screening/ Baseline Failures

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

4.4. Withdrawal/ Stopping Criteria

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

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

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

1. The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
2. The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. 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.

3. 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:

	Test Product	Positive Control	Reference Product
Product Name	Micellar Cleanser	Imperial Leather Original Bar Soap	Baxter Sterile Water
Product Formulation Code (MFC)	CCI [redacted]	N/A Market Place product	N/A Market Place product
Product Format	200ml Clear PET bottle	100g Bar	1000ml bottle
Application Quantity	0.09ml onto a Moistened Towel *(with sterile water)*	Moistened Towel *(with sterile water)* rubbed onto soap for 6 seconds to generate a lather	0.09ml onto a Moistened Towel *(with sterile water)*
Route of Administration	Topical dermal application		
Application Instructions	Applied on-site by technician		

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

Name of Item	Purpose
Simple Soap	Standard soap for use as during the washout period and for standard use at home during the study period.
Soap holder	To contain the subject standard soap between uses. Additional soap holders for use at the study site as require.
Baxter Sterile Water	Additional supplies for general use during the wash procedure to moisten the non-woven towels

5.2. Application Schedule

Each subject will have four test sites; two test sites (3x3 cm) marked out on each volar forearm (Figure 1, Section 3.4). The distance between different application sites must be at least 1 cm to prevent either the test product, positive control (Imperial Leather bar soap) or negative control (sterile water) wash from spreading over and influencing neighbouring test sites. The site on each forearm for each wash application (or unwashed) will be determined according to the provided randomisation schedule. The randomisation schedule will identify the test sites for the test product, positive control and water (negative control) wash applications, and the unwashed site.

A trained technician will wash each marked site with the appropriate product.

All wash procedures will be performed at the study site by a technician to ensure consistent wash application and correct product usage.

During the study, subjects will have the wash procedure completed four times daily at each allocated site, two wash applications in the morning (AM) and two wash applications in the afternoon (PM) on Days 1, 2, 3 and 4. On Day 5, subjects will have the wash procedure completed twice in the morning (AM) only. Each AM and PM wash procedure will be separated by a minimum of 3 hours.

5.3. Product Assignment

Each subject will have the test product, positive control (Imperial Leather Original bar soap), negative control (sterile water) and an unwashed site randomly assigned to sites on each volar forearm. The specific site locations will be assigned to subjects in

accordance with the randomisation schedule generated prior to the start of the study, using validated software.

5.3.1 Randomisation

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomized according to the randomisation schedule, which will be prepared to achieve balance between each forearm and upper and lower forearm. Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

The study site will receive two versions of the randomisation schedule, each in a sealed envelope and clearly marked as either “For Dispensing” or “Emergency Use Only”. The “For Dispensing” schedule will contain the list of randomisation numbers and the test site location (1 to 4) a letter code A, B, C or D will be used to determine which product is to be applied to which site.

The ‘Emergency Use Only’ randomisation schedule will only be removed from the sealed envelope in an emergency situation. This schedule will have a randomisation number followed by the letter. The schedule will have a footnote with a key for the letters identifying the treatments.

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

5.3.2 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation/test site location. Site staff dispensing and carrying out the wash procedures will be aware of each subject’s test location and must not divulge information to other study staff or the examiners. The examiners performing the measures of dryness and redness will be blinded to wash procedure and locations.

5.3.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Wherever

possible the Investigator (or designee) must contact the Sponsor prior to breaking the blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

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

5.4. Packaging and Labelling

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

The test product; facial micellar cleanser (CCI [redacted]) will be supplied in 200 ml bottles which will have a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number, product code letter and directions for storage.

The positive control product; Imperial Leather Original bar soap will be supplied in market place packaging in a labelled soap holder. Each study label will contain, but not be limited to, protocol number, product code letter and directions for storage.

The negative control product; Baxter sterile water will be supplied in market place packaging. Each study label will contain, but not be limited to, protocol number, product code letter and directions for storage.

Additional sterile water will be supplied for use to moisten the non-woven towels for product wash procedures. This will also be supplied in market place packaging. Each study label will contain, but not be limited to, protocol number, and directions for storage.

The standard soap (Simple) will be supplied in a market place packaging 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 on the standard soap.

5.4.1. Accountability of Product

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

The investigator or designee will maintain a full record of study product accountability.

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

5.4.2. Storage of Product

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

6. STUDY ASSESSMENTS AND PROCEDURES

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

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

6.1. Visit 1 - Screening Visit

6.1.1 Telephone Screening

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

6.1.2. Informed Consent

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

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

the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly after the subject has signed. The subject will be provided with a copy of their signed and dated consent form and any other written information which they will be instructed to retain.

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

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

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, Fitzpatrick skin type (skin phototype classification, according to the Fitzpatrick classification, per Appendix 3), gender and race.

6.1.4 Dermatologist Assessment

For products with specific safety appeals, the study must be followed up by a specialist (ANVISA, 2012). A qualified dermatologist will assess overall subject eligibility at the Screening Visit (Visit 1) and their continued eligibility at Baseline (Visit 2) to ensure that the subject is free of any pre-existing dermatological conditions. Additionally, a final assessment at Visit 6 by a qualified dermatologist will be performed to confirm whether it is medically appropriate to exit the subject from the study (Edward & Robillard, 2008).

6.1.5. Medical History and Concomitant Medication

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

All eligible subjects will be provided with a standard soap to use for the washout period and during the study. However, no products other than water (for bathing) should be applied to the forearms from completion of the Screening visit.

6.1.6. Examiner Assessment of Redness and Dryness

Mildness is defined by the parameters of skin dryness and redness (Lukacocvic, 1987). An experienced, trained and blinded examiner will assess the dryness and redness according to the scale defined in Appendix 2. To be considered eligible to join the study, the volar forearm of each subject must have overall dryness and redness scores of zero.

6.2. Visit 2 – Day 1 - Baseline Visit to Visit 6 (AM)

At Visit 2, any current and concomitant therapy taken will be reviewed and the eligibility of each subject to continue in the study will be checked by a qualified dermatologist prior to randomisation. Continued eligibility will be reviewed at each subsequent visit by a member of study staff. Subject adherence to correct usage of the standard soap will be checked at all visits.

6.2.1. Examiner Assessment of Redness and Dryness

An experienced, trained and blinded examiner will assess the redness and dryness of all skin sites for the duration of the study according to the scoring scale defined in Appendix 2. A Baseline assessment will be carried out at Visit 2 prior to any wash procedure. The dryness and redness scores of each proposed test application site on each volar forearm must be zero for dryness and redness for the subject to continue in the study.

Additionally, redness and dryness assessments will be performed at each test site prior to each PM wash procedure on Days 1-4 and following the final wash procedure on Day 5 (Final assessment). The examiner visual assessments of dryness and redness will be performed prior to subject acclimatisation and TEWL and corneometry assessments on Day 1 and Day 5.

The FCAT procedure generally produces only mild to moderate skin irritation, however, if any test site reaches a dryness or redness score of ≥ 5.0 at any time during the study, treatment of all sites on that subject will be immediately discontinued, all test sites will be scored and these will be recorded as an Adverse Event and the subject will be withdrawn from the study.

The examiner visual grading of dryness and redness will be performed prior to subject acclimatisation and TEWL and corneometry assessments on Day 1 and Day 5.

6.2.2. Corneometry

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). Corneometer measurements are included to provide support for examiner assessments. Corneometry will be initially measured at Baseline visit (Visit 2) prior to any study product application on both volar forearms at each designated test site. It will then be measured at the final visit (Day 5 - PM), at least 3 hours following the final wash procedure completed at that AM visit.

CCI

[redacted]

6.2.3. Transepidermal Water Loss (TEWL)

TEWL is a non-invasive method to measure the integrity of stratum corneum barrier function. This measurement has been included to provide support for the examiner assessments. TEWL will be initially measured at the Baseline visit (Visit 2) prior to any study product application on both forearms at all the designated sites. It will then be measured again at the final visit (Day 5 – PM), at least 3 hours following the final wash procedure completed at that AM visit.

CCI [redacted]

[redacted]

[redacted]

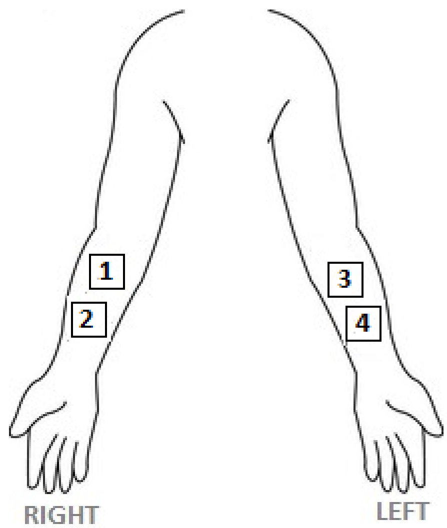
6.2.4. FCAT Wash Procedure

The wash procedure has been derived from consumer habit and general use practices and is therefore considered to be reflective of realistic conditions of product exposure. Generally, people will use a cleanser once or twice a day for between 6 and 10 seconds (Lukacovic, 1987).

Each subject will have 2 test sites (3x3 cm) marked out on each volar forearm (Figure 1). The distance between sites will be at least 1 cm to prevent products from spreading over and influencing neighboring test sites.

The randomisation schedule will identify the test sites for the test product, positive control and water (negative control) wash applications and the unwashed site.

Figure 1.



All washings will be performed at the study site by a trained technician to ensure consistent washing and correct product usage. The technician will adhere to the following instructions:

1. Wet the forearm liberally with warm (32-37ºC) tap water.

2. Wet a piece of Masslinn® (or equivalent non-woven towel) with sterile water, then squeeze to remove excess water.

    a. <u>For the test product:</u> Dispense 0.09ml of the test product via pipette onto the moistened towel.

    b. <u>For the positive control:</u> Rub the moistened towel in a circular motion on the Imperial Leather Original soap bar for 6 seconds to generate a lather.

® Masslinn Towel is a registered trademark of Chicopee Mills, New Brunswick

c. For the negative control: Dispense 0.09ml of sterile water onto the moistened towel.

d. For the un-washed site: no further action.

3. Rub the towel in a circular motion on the allocated site for 10 seconds.

4. Wait 90 seconds.

5. Rinse the application site with warm (32-37ºC) tap water for 15 seconds and pat dry.

6. Repeat this procedure for each test applicable product application.

7. After each forearm has been washed once with test product, positive control, and sterile water, and is patted dry, repeat this procedure a second time - i.e. each test site is to be washed twice at the AM and PM time points.

During the study, each subject will have the wash procedure completed four times daily at each application site as per the randomisation schedule, two wash procedures in the morning (AM) and two wash procedures in the afternoon (PM) on Days 1, 2, 3 and 4. On Day 5, each subject will have the wash procedure performed twice only in the morning (AM).

6.3. Visit 6 - Day 5 (PM) and Study Conclusion

Subjects will return to the study site on the final day (Day 5, Visit 6) and will undergo the FCAT wash procedure at the AM visit as per Section 6.2.4. A minimum of 3 hours following the final wash procedure, final examiner assessments of redness and dryness (per Section 6.2.1) and final instrumental measures of corneometry (per Section 6.2.2) and TEWL (per Section 6.2.3) will be performed.

6.3.1. Study Conclusion

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

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up

4. Protocol Violation
5. Withdrawal of Consent
6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

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

Events meeting AE definition include:
1. Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator. 2. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. 3. New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study. 4. Signs, symptoms, or the clinical sequelae of a suspected interaction. 5. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:
1. Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. 2. The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. 3. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. 4. Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). 5. Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. 6. The FCAT generally produces only mild to moderate skin irritation; however, if a treated site reaches a dryness or redness score of ≥ 5.0 at any time during the study, treatment of all sites on that subject will be immediately discontinued and all test sites will be scored and these will be recorded as an Adverse Event. Subjects will be discontinued.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:
A. Results in death
B. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
C. Requires hospitalization or prolongation of existing hospitalization NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills

any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

D. Results in disability/incapacity

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

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

E. Is a congenital anomaly/birth defect

F. Other Situations

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

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

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

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

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

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

submission to GSK.

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

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

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

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

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

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

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

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

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

Assessment of Causality:
1. The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE. 2. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. 3. The investigator will use clinical judgment to determine the relationship. 4. 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. 5. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. 6. 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. 7. 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.** 8. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. 9. 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:
1. AEs will be recorded in the AE section of the CRF. 2. Medical conditions recorded by the subject on a diary card or similar document

that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in the subject's medical history.

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

4. 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.

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

SAE Reporting to GSKCH:

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

1. Protocol and subject identifiers
2. Subject's demography
3. Description of events, with diagnosis if available
4. Investigator opinion of relationship to study product (see section 8.3)
5. Criterion for seriousness.

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

1. Date of onset of AE
2. Date AE stopped, if relevant
3. Study product start date
4. Study product end date if relevant
5. Action taken on study product
6. Outcome if known

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

Study Manager should be notified of the situation by telephone or email.

Serious Adverse Events to:
Brazil Clinical Study Manager PPD
Tel: PPD
E-mail: PPD
Pharmacovigilance (Brazil) Fax Number: PPD

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

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

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

Follow-up of AEs and SAEs:

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

2. 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.

3. 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.

4. 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.

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

Regulatory and ethics reporting requirements for SAEs:

1. 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. 2. GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB and investigators. 3. Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation. 4. An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IRB, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:
Pregnancy information will be collected on all pregnancies reported following administration of any investigational product (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:
1. 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.

2. 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.

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

4. 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

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

8. DATA MANAGEMENT

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

8.1. Source Documents/ Data

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

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

8.2. Electronic Case Report Form

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

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

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

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

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™).

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

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

8.3. Data Handling

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

will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

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

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

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 hypothesis is that the test product is not inferior to water in the change from baseline in the examiner rating of dryness on Day 5. Assuming that the standard

deviation of the within subject treatment difference in change from baseline in examiner rating of dryness is 0.25 (based on previous study CCI [redacted]), a CCI [redacted]

Sufficient number of subjects will be screened in order to randomise 45 subjects and to ensure that at least 40 subjects complete the study.

9.2. General Considerations

The test for non-inferiority between test product versus water in the examiner rating of dryness and redness will be one-sided at the 0.05 level of significance. All other statistical tests will be done at a two-sided 0.05 level of significance.

9.2.1. Definition of Analysis Populations

The ‘Intent-to-treat’ (ITT) population will include all subjects who are randomized, receive at least one wash procedure, including sterile water, and have at least one post-baseline clinical assessment available. The ITT population will be the primary population for all clinical assessed analyses, including dryness and redness.

The Safety population will include all subjects who have received at least one wash procedure. All safety analysis 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 endpoint will be tested for non-inferiority of the test product to water in examiner rating of dryness. The test will be carried out as follows: within subject treatment difference (test to water) in change from Baseline to 3 hr following last application on Day 5 will be estimated. To test the hypothesis that the difference has a mean 0.25 or greater at 0.05 level of significance, a one-sided upper 95% confidence limit will be estimated for the test product to water mean difference. If the upper 95% confidence limit is below 0.25, it will be concluded that the test product is not inferior to water in the examiner rating of dryness.

The criteria for non-inferiority of 0.25 on mean dryness score is considered clinically relevant after consideration of mean differences seen between positive control (bar soap) and water in previous studies (Ertel, 1995 and GSK Clinical Study CCI [redacted]

9.2.4. Criteria for Assessing Safety and Tolerability

Adverse events will be tabulated according to the version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current at the time of analysis.

9.2.5. Handling of Dropouts and Missing Data

Missing data will not be replaced or imputed. Dropouts will be included in analyses up to the point of discontinuation. Sensitivity analyses may be conducted if substantial number of subjects have discontinued from the study.

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.

Selected raw data may be listed as defined in the SAP

9.3.1. Demographic and Baseline Characteristics

Age will be summarised using descriptive statistics such as the number of non-missing observations, mean, and standard deviation, median, minimum, and maximum. Gender, race and Fitzpatrick skin type will be summarized using frequency counts and percentages.

9.3.2. Primary Analysis(es)

The primary endpoint will be tested for non-inferiority of the test product to water in change from baseline on Day 5 in examiner rating of dryness, using treatment estimates derived from an ANCOVA with subject (random effect), treatment and site as factors with baseline value as a covariate. The LSMeans will be presented for each treatment. The treatment difference (test product to water) and upper one-sided 95% confidence limit will be presented. If this upper confidence limit is below 0.25, it will be concluded that the test product is not inferior to water in the examiner rating of dryness.

This will be corroborated by using a one-sided 0.05 level of significance Wilcoxon sign rank test performed on the adjusted difference (within subject change from Baseline subtracted by 0.25) on Day 5 to test the hypothesis that the mean change from baseline for the test product is not greater than the change for water by 0.25 or more. The interpretation of this analysis will be assessed with caution as the non-

inferiority margin of 0.25 is based on mean dryness score with assumption of normal rather than discreet distribution.

For individual subjects an increase in dryness score from baseline of 1 or more with treatment is considered as a clinically relevant irritation response, so additional analysis will be performed based on subjects with this response, with more details provided in the SAP.

9.3.3. Secondary Analysis(es)

The non-inferiority analyses performed for primary endpoint will also be performed for the secondary endpoint based on examiner rating of redness on Day 5.

For secondary endpoints based on examiner rating of dryness and redness on Day 5 to compare positive control versus water, the same ANCOVA model as above will be used and the treatment difference (positive control to water), p-value and 95% confidence interval will be presented. Also for information, the treatment difference (positive control to test product) and treatment difference (water to unwashed), p-value, and 95% confidence interval will be presented.

For the other secondary endpoints of redness and dryness each day, TEWL and corneometer, the change from baseline will be analysed using ANCOVA with subject (random effect), treatment and site as factors with baseline value as a covariate. LSMeans for each treatment will be presented. The treatment differences (test product to water and positive control to water), p-value and 95% confidence intervals will be presented. Also for information, the treatment difference (positive control to test product) and treatment difference (water to unwashed), p-value, and 95% confidence interval will be presented.

If data are sufficiently non-normal in distribution, the non-parametric Wilcoxon signed ranks test will be used with median differences and 95% confidence interval presented based on the Hodges-Lehmann method.

Redness and dryness scores, TEWL and corneometer measurements at each time point and change from baseline in these scores and measurements at each time point will also summarized for test product, water, positive control and unwashed site using descriptive statistics such as the number of non-missing observations, mean, standard deviation, median, minimum, and maximum.

No adjustment will be made for multiplicity testing for the secondary endpoints, however consistency of effects will be taken into consideration in interpreting the results.

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 overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AE's, treatment-related AE's, and AE's leading to discontinuation, and serious AE's will be completed. For treatment-related AE's, these will also be presented by treatment/test site.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

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

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

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

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

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

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

10.3. Quality Control (Study Monitoring)

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

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

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

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

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

10.4. Quality Assurance

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

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the

conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

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

10.5. Conditions for Terminating the Study

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

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

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

In addition:

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

10.6. Records Retention

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

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

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

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

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

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

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

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

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

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

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

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

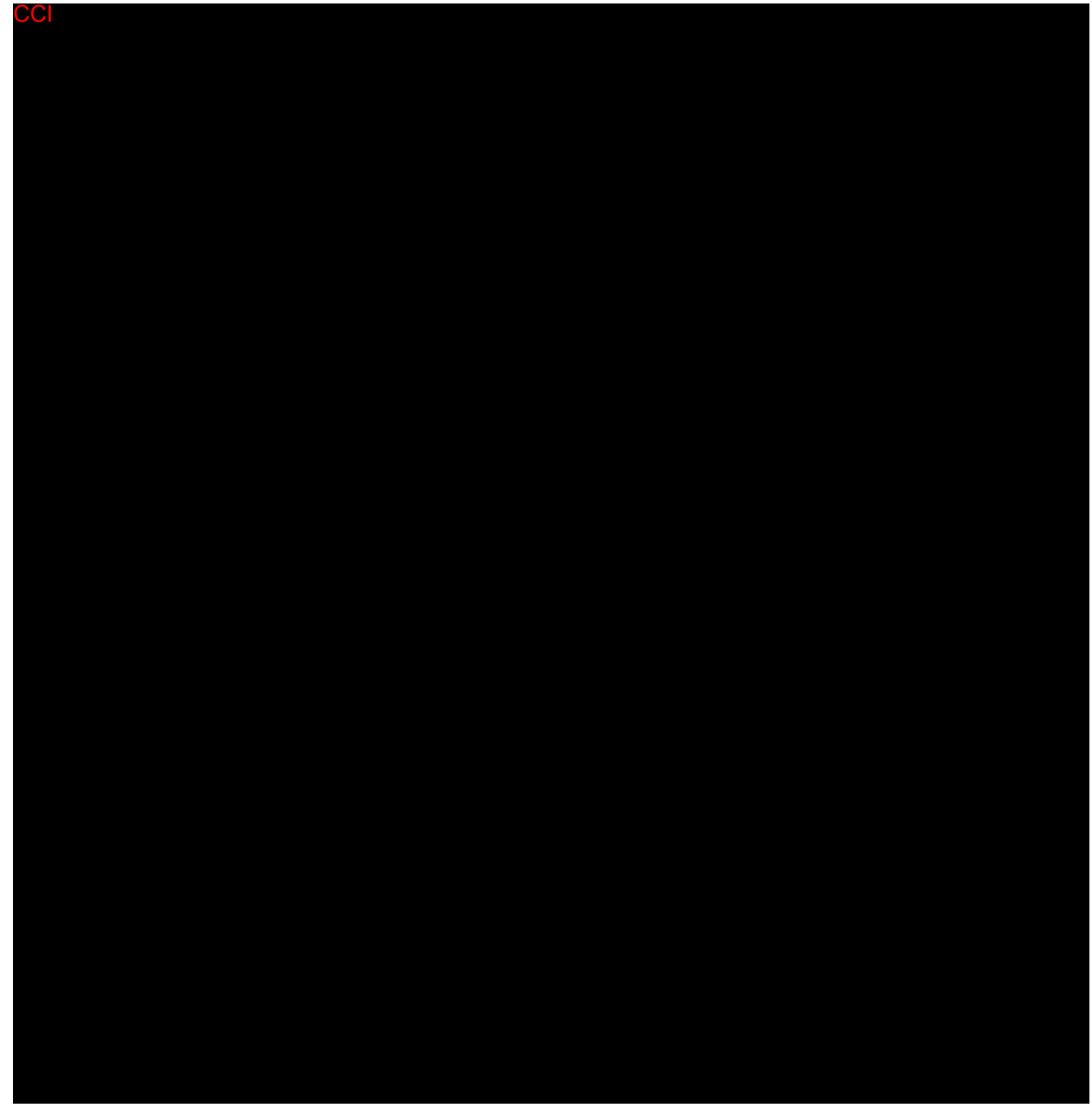
µl	Microliters
AE	Adverse Event
ANCOVA	Analysis of Covariance
aq	Aqueous
AUC	Area under Curve
CD	Compact Disc
cm^2	Centimetre squared
CRF	Case Report Form
DVD	Digital Versatile Disc
EDC	Electronic Data Capture
EEMCO	European Group for Efficacy Measurements on Cosmetics and Other Topical Products
FSFV	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^2	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
TEWL	Transepidermal Water Loss
w/w	Weight by Weight

12.2. Appendix 2 – CCI

CCI

CCI



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