STATISTICAL REPORTING AND ANALYSIS PLAN

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

Protocol Number: 209638

Phase: Not applicable

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan Text	07-Feb-2019	Not applicable (N/A)

Amendments incorporate all revisions to date.

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Abbreviation

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BDRM	Blind Data Review Meeting
CI	Confidence Interval
CRF	Case Report Form
GSKCH	GlaxoSmithKline Consumer Healthcare
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-To-Treat
PT	Preferred Term
SAE	Serious adverse event
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
TEWL	Trans-epidermal Water Loss

The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 209638 v1.0 dated 05 Sep 2018.

1 Summary of Key Protocol Information

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

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

1.1 Study Design

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

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

- Treatment Regimen 1 = Test Product 1 + Standard cleanser soap vs. Standard cleanser soap, and
- Treatment Regimen 2 = Test Product 2 + Standard cleanser soap vs. Standard cleanser soap.

A subject will be in 4 possible treatment combinations as follows:

Table 1-1 Treatment Combinations

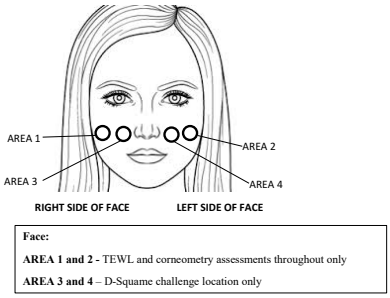
Right side of the body	Left side of the body
Test Product 1 + Standard cleanser soap	Standard cleanser soap
Standard cleanser soap	Test Product 1 + Standard cleanser soap
Test Product 2 + Standard cleanser soap	Standard cleanser soap
Standard cleanser soap	Test Product 2 + Standard cleanser soap

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

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

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

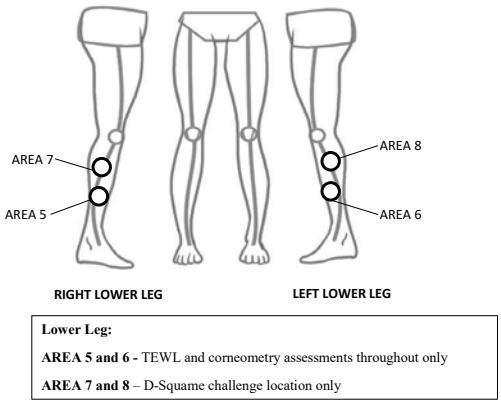
Figure 1-1 Layout of Test Areas (Face)



Two areas on the outside of each lower leg assigned below each knee and above each ankle will be assigned as close together as possible, without overlap, for all leg measurements of TEWL and moisturization as indicated in Figure 1-2.

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

Figure 1-2 Layout of Test Areas (Leg)



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

1.2 Study Objectives

The objectives and endpoints of this study are as follows:

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

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

1.3 Treatments

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

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

- Treatment Regimen 1 = Test Product 1 + Standard cleanser soap; and Standard cleanser soap
- Treatment Regimen 2 = Test Product 2 + Standard cleanser soap; and Standard cleanser soap

To ensure balance across each side of face and legs, each eligible subject will be randomized to one of the following four arms:

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

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

1.4 Sample Size Calculation

The sample size is determined with the success criteria of the study in mind that each developmental product will be significantly beneficial on change from baseline in TEWL measurements, following 4 weeks of twice-daily use on the face.

The distributional assumptions underlying the calculations are taken from the pilot study 207451 (GSK data on file) for which change from baseline in TEWL for the face is used. The leg responses for this study are secondary and not considered in the sample size estimation. From the pilot study, it is expected that leg treatment effects will be larger and also variability reduced compared to face values.

In the pilot study the mean change from baseline between active (test moisturizers) and control (soap only) groups in terms of face TEWL at Day 29 was -1.24. Each subject will receive a pair of products to be applied randomly to Left/Right or Right/Left sides consistently throughout the trial. The primary response will therefore be a pair of changes from baseline in face TEWL for each test product vs. a control (soap only). The square root of the Mean Square Error (MSE) from the analysis of the pilot study (207451) is estimated as 2.199, with 60 subjects directly comparing test product with control with a mean difference in change from baseline face TEWL of -1.24. The power to detect such a difference at the two-sided 5% significance level is approximately 86%. Via a simulation study (50,000 simulated studies) we can allow each group of 60 subjects receiving a test product to be compared to 120 subjects who receive control (soap only), 60 who received the test product, and 60 who got the other test product, so some contributions are within subject and some between. This results in an estimated power for any single test product versus control (soap only) of approximately 89.2% and for both test products to achieve significance of 80%.

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

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final analyses will be performed after the completion of the following sequential steps:

1. All subjects completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

Baseline value is defined as the latest assessment prior to product application.

For TEWL and Corneometer variables, the baseline value will be value obtained on Day 1 (Visit 2) before study product application.

For endpoints of D-Squame Challenge, the baseline value will be value obtained prior to D-Squame Challenge on Day 29.

3.2 Subgroups/Stratifications

No subgroups or stratification factors are defined in this study.

3.3 Centers Pools

Since this is single center study, pooling of centres is not applicable for this study.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the section “Schedule of Activities” of the protocol.

Any deviation from the study schedule will be reviewed on case-by-case basis to determine whether the data should be excluded from the Per-Protocol (PP) population. A time window non-compliance listing will be produced for the Blind Data Review Meeting (BDRM).

All data included will be by nominal visits and visit windows will not be considered.

4 Data Analysis

Data analysis will be performed by Syneos Health. The statistical analysis software used will be SAS (Studio) version 9.4 or higher.

Prior to database closure, a BDRM will be conducted in which various aspects of the trial will be discussed and agreed.

Unless otherwise described, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. Enrolled subjects are defined as subjects who have signed the informed consent and are eligible to proceed beyond the screening visit.

A summary (Table 14.1.1) will be provided for number of subjects screened, number and percentage of screen failures with reasons why subjects are not randomized and number of subjects enrolled. Percentages for screen failure subjects will be based on total number of screened subjects.

Subject disposition will also summarize number and percentage of subjects in each of the defined analysis populations, who complete the study and who discontinue the study broken down by reason for discontinuation. The summary will be presented by treatment regimens [treatment regimen 1 (test product 1 + standard cleanser soap vs standard cleanser soap only), treatment regimen 2 (test product 2 + standard cleanser soap vs standard cleanser soap only)] and overall. The percentages are based on the total number of subjects randomized in each treatment regimen.

Subject disposition including the subject status (completer, Yes/No), demographic data (age, gender, and race), screening date, study product application start date and time, duration (in days) in the study (defined as [(date of completion or withdrawal – start date of study product application) + 1]), duration (in days) of study product (defined as: [(date/time of last product application - date of first product application) + 1]) and the specific reason for discontinuation, will be listed (Listing 16.2.1.1) by treatment regimen.

Subject disposition information for non-randomized subjects will include subject number, demographic information (age, gender, and race), screening date, reason for screen failure and details if any regarding the reason for screen failure (Listing 16.2.1.2).

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with important protocol deviations liable to influence the key efficacy outcomes will be excluded from the PP population. Subjects may

also be identified as having important protocol deviations not leading to exclusion from the PP population.

Important deviations of the protocol procedures may include, but will not be necessarily limited to, the following:

- Consent procedures
- Inclusion/Exclusion criteria
- Concomitant Medication/Therapy
- Study procedures
- Randomization procedures
- Study product compliance
- Visit schedule

The specific details of the important protocol deviations and how these will be assessed will be specified in the Blind Data Review Plan and subjects with important protocol deviations will be identified at the BDRM.

The number and percentage of subjects with at least one important protocol deviation, important protocol deviations not leading to exclusion from PP population with reasons for deviations, and subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations will be presented by treatment regimens (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation page of case report form (CRF) will be listed in Listing 16.2.2.2. The listing will present date of deviation, type of deviation, and deviation description.

4.1.3 Analysis Populations

The analysis populations are defined as follows:

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprise all randomized subjects who receive at least one dose of the study product. • This population will be based on the product the subject actually received.	• Study Population • Demographic and Baseline Characteristics • Safety Analysis
Modified Intent-To-Treat (MITT)	• All subjects in safety population. • Have at least one post-randomized assessment of efficacy. • This population will be based on the study product to which the subject was randomized.	• Demographic and Baseline Characteristics • Efficacy Analysis
PP	• All subjects in MITT population. • All subjects comply with all study procedures and restrictions that may affect the interpretation of primary efficacy response. • Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters	• Primary Efficacy Analysis

NOTES :

- Please refer to Attachment 1: List of Data Displays which details the population to be used for each displays being generated.

Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1.

The primary population for assessment of efficacy will be the MITT Population. A PP analysis will be performed only on primary endpoint only if 10% or more MITT subjects are excluded from the PP Population.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; frequency count (n) and percentage (%) of subjects for categorical variables) will be presented for demographic variables (age, gender, race, and Fitzpatrick skin type grading) by treatment regimen and overall for all subjects in safety (Table 14.1.3.1), MITT (Table 14.1.3.2), and if applicable, PP (Table 14.1.3.3) population.

Demographic information will be listed (Listing 16.2.4.1) for all randomized subjects.

4.2.2 Baseline Characteristics

The summary of dryness assessment for face and legs will be presented by treatment regimen for the safety (Table 14.1.4.1), MITT (Table 14.1.4.2), and if applicable, PP (Table 14.1.4.3) population. The table will summarize self-assessment of feeling of tightness on both the sides of face and dermatologist assessment of dullness, scaling, and roughness on both the sides of face and legs by number of subjects (n) and percentages (%). The total score of assessment of face and legs for each side will be summarized descriptively (n, mean, SD, median, minimum, and maximum).

The dryness assessment of face (Listing 16.2.4.2.1) and legs (Listing 16.2.4.2.2) will be listed for all randomized subjects.

4.2.3 General Medical History

Medical history data will be listed (Listing 16.2.4.3) with start date and end date or ongoing at the start of study product for all randomized subjects.

4.3 Treatments (Study Product, Rescue Medication, other Concomitant Therapies, Compliance)

The study product kits allocation will be listed (Listing 16.1.6.1), including container number and study product information.

Randomization details will be listed (Listing 16.1.7.1), including the planned randomized study product, the actual study product received, and the randomization date.

4.3.1 Study Product Compliance and Exposure

In this study, subjects will apply the study products (test product 1 and test product 2, along with standard cleanser soap) to the randomly designated side of the face and the lower leg, and standard cleanser soap only on the other side of the face and lower legs, twice-daily (in the morning and evening, approximately 8-12 hours apart), for 4 weeks (28±2 days) treatment period.

The number of any missed or additional applications of above study products will be captured on CRF at each visit.

Study Product Compliance (%) will be calculated as [(actual number of product use ⁄ expected number of product use) × 100],

Where,

Expected number of product use = 2 × [(number of days between Visit 2 and Visit 5) – 1]

Actual number of product use = expected number of product use – total number of missed applications + total number of additional applications.

The overall compliance (%) will be summarized descriptively (n, mean, SD, median, minimum, and maximum) by study products (test product 1 + standard cleanser soap and test product 2 + standard cleanser soap) for safety (Table 14.2.1.1) and MITT (Table 14.2.1.2) population.

Subjects are said to be study product compliant, if the study product compliance (%) will be in range of 80% - 100%. The number (n) and the percentage (%) of compliant subjects will be presented for safety (Table 14.2.1.1) and MITT (Table 14.2.1.2) population.

The study product compliance will be listed (Listing 16.2.5.1) for all randomized subjects. This listing will display information of date and time of product application at each visit in treatment phase, number of missed product uses since the last visit at each treatment site and side, number of additional product uses since the last visit at each treatment site and side, expected number of product use, actual number of product use and overall compliance (%).

4.3.2 Prior and Concomitant Medication

Prior or concomitant medication taken by or administered to a subject will be recorded in the CRF. The prior and concomitant medications will be coded using an internal validated medication dictionary, GSKDrug.

Prior medication will be listed by subject, with drug name, GSK drug synonym, reason, dose, frequency, route, start date, study day relative to study product administration and end date (Listing 16.2.5.2). Prior medications are defined as those which stopped prior to signing the informed consent form. If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to signing the informed consent form then the medication will be considered as a concomitant medication.

Concomitant medications and significant non-drug therapies taken during treatment will be listed similarly (Listing 16.2.5.3) with either ongoing or end date displayed. Concomitant medications are defined as medications that are ongoing or started on or after signing the informed consent form.

Unknown dates will not be imputed, however if the start or stop date is unknown, then it will be assumed to be concomitant medication unless the partial start date or stop date indicates differently.

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is change from baseline in TEWL (face) of each of the two developmental products, compared to the standard cleanser soap use only, at Day 29.

4.4.1.1 Primary Efficacy Endpoint Definition

TEWL (face) measurements will be taken on different parts of each designated area on each location (face and legs) so the measured parts do not overlap.

Each TEWL measurement is targeted to take 40 seconds and will yield 40 data values (1 value per second of measurement). However, practically it is expected that TEWL measurements will vary by several seconds.

- If ≤37 values are collected, no TEWL value will be calculated and the data will be considered as missing and entered into the CRF as a missing value.
- If >37 values are collected, TEWL will be calculated as the mean of final 10 values.

TEWL measurements will be taken in triplicate for Area 1 and 2 of the face. The average (mean) TEWL value will be calculated from all valid TEWL measurements for each area and each time point.

The mean TEWL value will be recorded on CRF and will be used for analysis.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The MITT population will be considered primary for this analysis.

The observed and change from baseline in TEWL measurements (Area 1 and 2 on the face) will be summarized descriptively (n, mean, SD, Standard Error [SE], median, minimum, and maximum) at each visit by treatment arms (test product 1 + standard cleanser soap, test product 2 + standard cleanser soap, and standard cleanser soap alone) for all the subjects in the MITT population (Table 14.2.2.1.1.1).

The primary analysis will compare change from baseline in TEWL (face) in each of the two developmental products and standard cleanser soap use only, at Day 29.

The null hypothesis for the primary endpoint is that the mean change from baseline TEWL (face) measurements is equal between the two groups.

H_0: $\mu_1 = \mu_2$

The alternative hypothesis for the primary endpoint is that the mean change from baseline TEWL (face) measurements is not equal between the two groups.

H_0: $\mu_1 \neq \mu_2$

There will be two primary comparisons, 1 for each test product + standard cleanser soap versus standard cleanser soap. For success, both the comparisons have to achieve statistical significance; hence no correction to the testing level is required for multiple comparisons.

The change from baseline in TEWL (face) measurements at Day 29 (Table 14.2.2.1.1.2) will be analysed by mixed model analysis of covariance (ANCOVA) with change from baseline as a response variable, treatment arm and side of the face (right, left) as factors and baseline TEWL (for that side of the face) value as covariate. Subject will be included as a random effect.

The adjusted mean change from baseline, SE, 95% CI, and p-value for each treatment arm will be presented. The adjusted mean difference between each test product + standard cleanser soap and standard cleanser soap (only) along with, SE, 95% CI for difference from standard cleanser soap, and p-value will be presented. All statistical tests of hypothesis will be two-sided and will employ a level of significance of $\alpha = 0.05$.

The assumptions underlying ANCOVA analysis will be checked and in case of any deviation from them, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In the case of a non-parametric analysis, median differences will be presented, together with 95% CIs based on the Hodges-Lehmann method.

The effect size presented will be calculated as adjusted mean difference from standard cleanser soap divided by pooled standard deviation.

The percentage difference between each test product + standard cleanser soap and standard cleanser soap (only) for TEWL of will be presented at each visit. The percentage difference will obtained using following formulae:

100* [Adjusted mean difference in each test product + standard cleanser soap and standard cleanser soap (only)]/Adjusted Mean of TEWL for standard cleanser soap (only).

The denominator of above formulae will be obtained by mixed model ANCOVA with absolute value as response variable and baseline TEWL value as covariate.

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

The plot (Figure 14.2.1.1) of mean TEWL will be presented with visits on x-axis and the mean value on y-axis. Separate colour codes will be used for each treatment arm. This plot will include all the visits from baseline until visit 10 (day 34). The post baseline visits, with statistically significant p-value of mean difference between each test product + standard cleanser soap and standard cleanser soap (only) obtained from ANCOVA model defined above will be indicated in this plot.

The listing of TEWL measurements (Listing 16.2.6.1) by visit will be presented for all randomized subjects. This listing will include subject number, treatment regimen, date of TEWL assessment, TEWL measurement mean values at each visit, and change from baseline at each post-baseline visits.

4.4.1.3 Supportive Analyses

If there is more than 10% difference in the overall number of subjects between PP and MITT populations, a summary of the primary efficacy variable will be presented for all the subjects in the PP population (Table 14.2.2.1.2.1) and will be analyzed similar to primary analysis (Table 14.2.2.1.2.2). The summary and analysis of PP population will be presented only for TEWL (face) at Day 29.

4.4.2 Secondary Efficacy Variables

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

TEWL measurements will be obtained as described in Section 4.4.1.1 of the RAP.

Corneometer measurements will be taken 5 times and an average (mean) will be calculated for each site and time point. While the target is to take exactly 5 measurements, it is possible that the number of measurements may vary (e.g. due to human error or machine malfunction).

- If <4 measurements are taken, no mean Corneometer value will be calculated and the data will be considered as missing, and entered into the CRF as a missing value.
- If ≥4 measurements are taken, the mean Corneometer value will be calculated from all available measurements.

The mean Corneometer value will be recorded on the CRF and will be used for analysis.

4.4.2.1 Secondary Efficacy Variable 1

Change from baseline in TEWL (legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at Day 29.

4.4.2.2 Secondary Efficacy Variable 2

Change from baseline in TEWL (face and legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at Day 15.

4.4.2.3 Secondary Efficacy Variable 3

Change from baseline in Corneometer measurements (face and legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at following time-points:

- Day 1: 30 minutes after first supervised application;
- Day 1: 6 hours after first supervised application;
- Day 2: 24 hours after first supervised application.

4.4.2.4 Secondary Efficacy Variable 4

Change from baseline in Corneometer measurements (face and legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at following time-points:

- Day 15;
- Day 29.

4.4.2.5 Secondary Efficacy Variable 5

Change from baseline in TEWL (face and legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at following time-points:

- Day 30;
- Day 31;
- Day 32;
- Day 33;

- Day 34.

4.4.2.6 Secondary Efficacy Variable 6

Change from baseline in Corneometer measurements (face and legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at following time-points:

- Day 30;
- Day 31;
- Day 32;
- Day 33;
- Day 34.

4.4.2.7 Secondary Efficacy Variable 7

Change from pre-challenge TEWL (face and legs) of each of the two test products + standard cleanser soap, compared to the standard cleanser soap only, at Day 29 to the following time-points:

- Removal of 3 tape strips (face: area 3 compared to area 4) and 4 tape strips (legs: area 7 compared to area 8);
- Removal of 6 tape strips (face: area 3 compared to area 4) and 8 tape strips (legs: area 7 compared to area 8);
- Removal of 9 tape strips (face: area 3 compared to area 4) and 12 tape strips (legs: area 7 compared to area 8).

4.4.2.8 Secondary Efficacy Variable 8

Total protein content extracted from all tape strips using each of the two test products + standard cleanser soap, compared to the standard cleanser soap (face: area 3 compared to area 4; leg: area 7 compared to area 8).

4.4.3 Handling of Missing Values/Censoring/Discontinuations

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

4.5 Analysis of Secondary Objectives

All secondary analyses will be conducted only on MITT population.

No alpha adjustments will be made for multiple secondary endpoints due to the exploratory nature of the inferences. All statistical tests of hypothesis will be similar to that mentioned for primary analysis and will be two-sided with 0.05 level of significance.

4.5.1 Efficacy (Secondary)

The analysis of each secondary endpoint is as follows:

Change from baseline in TEWL (legs) at Day 29

For TEWL (legs) endpoint, the comparison will be performed on area 5 and area 6.

The summary (Table 14.2.2.2.1) and statistical analysis (Table 14.2.2.2.2) of this endpoint will be performed in a similar fashion to the primary analysis.

The TEWL (legs) measurements at Day 29 will be listed in Listing 16.2.6.1.

Change from baseline in TEWL (face and legs) at Day 15

The summary (Table 14.2.2.1.1.1 for face and Table 14.2.2.2.1 for legs) and statistical analysis (Table 14.2.2.1.1.2 for face and Table 14.2.2.2.2 for legs) of this endpoint will be performed in a similar fashion to the primary analysis.

The TEWL (face and legs) measurements at Day 15 will be listed in Listing 16.2.6.1.

Change from baseline in Corneometer measurement (face and legs) at Day 1: 30 minutes, 6 hours, and Day 2: 24 hours after the first supervised application

The summary (Table 14.2.3.1.1 for face and Table 14.2.3.2.1 for legs) and statistical analysis (Table 14.2.3.1.2 for face and Table 14.2.3.2.2 for legs) of these endpoints will be performed in a similar fashion to the primary analysis.

The percentage difference between each test product + standard cleanser soap and standard cleanser soap (only) for Corneometer measurements will be presented at each timepoint. The percentage difference will obtained using following formulae:

100* [Adjusted mean difference in each test product + standard cleanser soap and standard cleanser soap (only)]/Adjusted Mean of Corneometer measurements for standard cleanser soap (only).

The denominator of above formulae will be obtained by mixed model ANCOVA with absolute value as response variable and baseline Corneometer measurements as covariate. This model will be fitted for standard cleanser soap (only).

The plot (Figure 14.2.2.1.1 for face and Figure 14.2.2.1.2 for legs) of mean Corneometer measurements will be presented with various timepoints (30 minutes, 6 hours, and 24 hours) of Day 1 on x-axis and corresponding mean value on y-axis. Separate colour codes will be used for each treatment arm. The post baseline timepoints, with statistically significant p-value of mean difference between each test product + standard cleanser soap and standard cleanser soap (only) obtained from ANCOVA model defined in primary analysis section will be indicated in this plot.

The listing of Corneometer measurements at various timepoints on Day 1 and Day 2 will be listed in Listing 16.2.6.2 for all randomized subjects.

Change from baseline in Corneometer measurements (face and legs) at Day 15 and Day 29

The summary (Table 14.2.3.1.1 for face and Table 14.2.3.2.1 for legs) and statistical analysis (Table 14.2.3.1.2 for face and Table 14.2.3.2.2 for legs) of these endpoints will be performed in a similar fashion to the primary analysis.

The percentage difference between each test product + standard cleanser soap and standard cleanser soap (only) for Corneometer measurements will be presented at each visit. The percentage difference will obtained using following formulae:

100* [Adjusted mean difference in each test product + standard cleanser soap and standard cleanser soap (only)]/Adjusted Mean of Corneometer measurements for standard cleanser soap (only).

The denominator of above formulae will be obtained by mixed model ANCOVA with absolute value as response variable and baseline Corneometer measurements as covariate. This model will be fitted for standard cleanser soap (only).

The plot (Figure 14.2.2.2.1 for face and Figure 14.2.2.2.2 for legs) of mean Corneometer measurements will be presented with visits on x-axis and the mean value on y-axis. Separate colour codes will be used for each treatment arm. This plot will include all the visits from baseline until Visit 10 (Day 34). The post baseline visits, with statistically significant p-value of mean change from baseline difference between each study product + standard cleanser soap and standard cleanser soap (only) obtained from ANCOVA model defined above will be indicated in this plot.

The listing of Corneometer measurements at Day 15 and Day 29 will be listed in Listing 16.2.6.2 for all randomized subjects.

Change from baseline in TEWL (face and legs) at Day 30, 31, 32, 33, and 34

The summary (Table 14.2.4.1.1 for face and Table 14.2.4.2.1 for legs) and statistical analysis (Table 14.2.4.1.2 for face and Table 14.2.4.2.2 for legs) of this endpoint will be performed in a similar fashion to the primary analysis.

The TEWL (face and legs) measurements at Day 30, 31, 32, 33, and 34 will be listed in Listing 16.2.6.1.

Change from baseline in Corneometer measurements (face and legs) at Day 30, 31, 32, 33, and 34

The summary (Table 14.2.5.1.1 for face and Table 14.2.5.2.1 for legs) and statistical analysis (Table 14.2.5.1.2 for face and Table 14.2.5.2.2 for legs) of this endpoint will be performed in a similar fashion to the primary analysis. The analysis will be performed separately at each visit.

The listing of Corneometer measurements at Day 30, 31, 32, 33, and 34 will be listed in Listing 16.2.6.2 for all randomized subjects.

Change from pre-challenge TEWL (face and legs) at Day 29

The change in TEWL values from pre- to post D-Squame challenge on Day 29 will be summarized descriptively (Table 14.2.6.1.1 for face and Table 14.2.6.2.1 for legs) and statistically analyzed (Table 14.2.6.1.2 for face and Table 14.2.6.2.2 for legs) similar to the primary analysis, with baseline value as the pre- D-Squame value. Summarization and analyses will be for values after 3, 6, and 9 discs removed from the face and 4, 8, and 12 discs removed from the legs.

The percentage difference between each test product + standard cleanser soap and standard cleanser soap (only) for TEWL value will be presented at removal of 3, 6 and 9 discs. The percentage difference will obtained using following formulae:

100* [Adjusted mean difference in each test product + standard cleanser soap and standard cleanser soap (only)]/Adjusted Mean of TEWL value for standard cleanser soap (only).

The denominator of above formulae will be obtained by mixed model ANCOVA with absolute value as response variable and pre- D-Squame TEWL value as covariate. This model will be fitted for standard cleanser soap (only).

The listing of pre-challenge and post-challenge TEWL measurements at Day 29 will be listed in Listing 16.2.6.3.1 for face and Listing 16.2.6.3.2 for legs for all randomized subjects.

Total protein content

The protein content of each D-Squame disc and the total value of all the discs together (area 3 and 4 on the face and area 7 and 8 on the legs) will be summarized descriptively (n, mean, SD, SE, median, minimum, and maximum) by treatment arm (Table 14.2.7.1.1 for face and Table 14.2.7.2.1 for legs).

The total protein content (Table 14.2.7.1.2 for face and Table 14.2.7.2.2 for legs) will be analysed by mixed model analysis of variance (ANOVA) with observed value as a response variable, treatment arm and side of the face or leg (right, left) as factors. Subject will be included as a random effect.

The adjusted mean for each treatment arm will be presented along with SE, 95% Confidence Interval (CI) for the adjusted mean, and p-value. Also, the adjusted mean difference between each test product + standard cleanser soap and standard cleanser soap (only) along with SE, 95% CI of the difference from standard cleanser soap, and p-value will be presented.

The assumptions underlying ANOVA analysis will be checked and in case of any deviation from them, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. In the case of a non-parametric analysis, median differences will be presented, together with 95% CIs based on the Hodges-Lehmann method.

The percentage difference between each test product + standard cleanser soap and standard cleanser soap (only) for total protein content will be presented. The percentage difference will obtained using following formulae:

100* [Adjusted mean difference in each test product + standard cleanser soap and standard cleanser soap (only)]/Adjusted Mean of total protein content for standard cleanser soap (only).

The denominator of above formulae will be obtained by mixed model ANCOVA with absolute value as response variable and baseline total protein content as covariate. This model will be fitted for standard cleanser soap (only).

The listing (Listing 16.2.6.4.1 for face and Listing 16.2.6.4.2 for legs) of protein measurement at Day 29 or any other unscheduled visits will be presented for all randomized subjects.

4.6 Analysis of Safety

All safety data will be reported for the safety population as per the actual treatment received. The safety profile of the study treatment will be assessed with respect to adverse events (AEs).

4.6.1 Adverse Events and Serious Adverse Events

All AEs will be reviewed by the Clinical Research Scientist or Designee prior to database lock and will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorized as skin or non-skin.

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the first treatment application (if this date is missing a suitable alternative will be used e.g., date of randomization). AEs with an onset date/time prior to the first treatment application will be considered as non-treatment emergent.

Summary of the number and percentage of subjects with at least one AE, total number of AEs, number and percentage of AEs within each SOC and PT will be displayed.

The treatment-related AE tables will be summarized by treatment arms (test product 1 + standard cleanser soap, test product 2 + standard cleanser soap, and standard cleanser soap alone); whereas, all other AE tables will be summarized by treatment regimen.

The listing of AEs will be provided by treatment regimen.

The following summary tables and listings will be presented by test product.

- Table of TEAEs by SOC and PT (Table 14.3.1.1.1).
- Table of TEAEs by Skin or Eye/Non-Skin or Non-Eye and PT (Table 14.3.1.1.2)
- Table of TEAEs by SOC, PT, and severity (Table 14.3.1.1.3)
- Table of treatment-related TEAEs by SOC and PT (Table 14.3.1.2.1)
- Table of treatment-related TEAEs by Skin or Eye/Non-Skin or Non-Eye and PT (Table 14.3.1.2.2)
- Table of treatment-related TEAEs by SOC, PT, and severity (Table 14.3.1.2.3)

- Table of treatment-emergent serious adverse events (SAEs) by SOC and PT (Table 14.3.1.3) [only produced if there are more than 5 SAEs]
- Table of treatment-emergent non-serious AEs by SOC and PT (Table 14.3.1.4) [only produced if there are more than 5 SAEs]
- Table of TEAEs leading to study or treatment discontinuation by SOC and PT (Table 14.3.1.5).
- Listing of all AEs (Listing 16.2.7.1 for all randomized subjects; Listing 16.2.7.2 for non-randomized subjects)
- Listing of deaths (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of treatment-emergent AEs leading to study or treatment discontinuation (Listing 14.3.2.3)
- Listing of treatment-emergent AEs classified as skin or eye (Listing 14.3.2.4)

In the event that there is nothing to report, a null table or listing will be produced.

4.6.2 Other Safety Variables

No other safety variables are applicable for this study.

4.7 Analysis of Other Variables

No other analysis will be performed in this study.

5 Changes to the Protocol Defined Statistical Analysis Plan

The changes from the originally planned statistical analysis specified in the protocol are outlined in Table 5-1.

Table 5-1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
12.2.1 Definition of Analysis Populations PP Population The PP population includes all MITT subjects who fully comply with all study procedures and restrictions. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters	4.1.3 Analysis Population PP Population All subjects in MITT population. All subjects comply with all study procedures and restrictions that may affect the interpretation of primary efficacy response. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters	The definitions PP population in protocol was generalized. The definitions have been clarified and are now more study specific.

Attachment 1: List of Data Displays

GSKCH_209638_List of TFLs v1.0_07Feb2