STATISTICAL REPORTING AND ANALYSIS PLAN

A Clinical Study to Assess the Local Cutaneous and Ocular Tolerance of a Developmental Cosmetic Facial Serum Formulation in Healthy Females with Sensitive Skin

Protocol Number: 209442

Phase: Not Applicable

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	21-Sep-2018	Not applicable

Table of contents

List of tables

Abbreviation

Abbreviation	Term
AEs	Adverse Events
ANVISA	Agência Nacional de Vigilância Sanitária
BDRM	Blinded Data Review Meeting
GSKCH	GlaxoSmithKline Consumer Healthcare
LAST	Lactic Acid Sting Test
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RLR	Review Listing Requirement
SAE	Serious Adverse Events
SD	Standard Deviation
SOC	System Organ Class
TEAEs	Treatment Emergent Adverse Events

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 209442.

1 Summary of Key Protocol Information

A cosmetic product that is freely available to the consumer must be safe when applied under normal or reasonably foreseeable conditions of use. Thus, as a general requirement, the safety of a developmental formulation should be confirmed before it is marketed.

Acceptability 'in-use' studies are useful clinical models with which to determine the irritation potential (local tolerance) of a cosmetic formulation to provide confidence the finished product is suitable for general sale.

The objective of this clinical study is to determine the local cutaneous and ocular tolerance of a developmental cosmetic facial serum in healthy females with sensitive facial skin under normal conditions of use.

1.1 Study Design

This is a randomized, evaluator-blind (dermatologist and ophthalmologist), 2-arm, parallel-group, single-center, non-comparative clinical 'in-use' study to determine the local cutaneous and ocular tolerance of a developmental cosmetic facial serum formulation in healthy female subjects aged 18 to 65 years (inclusive) with clinically evaluated sensitive skin, as determined by a positive response to a Lactic Acid Sting Test (LAST), with minimal signs or symptoms of cutaneous irritation and no signs or symptoms of ocular irritation. A reference product, proven to be suitable for use in a sensitive skin population, is included to enable the study to be conducted in a randomized and blinded manner, rather than as a single-arm or open-label study, to minimize bias and ensure a robust outcome.

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study.

At Visit 1 (screening), subjects who agree to participate in the study by signing the informed consent will be assessed by a qualified dermatologist for baseline clinical assessments of the signs and symptoms of cutaneous irritation and by a qualified ophthalmologist for baseline clinical assessments of the signs and symptoms of ocular irritation. Following these assessments, a LAST will be conducted in the nasolabial region to confirm whether the subject has sensitive skin. Subjects will only be considered eligible to continue in the study if they present a positive response to the LAST. Medical history, Fitzpatrick skin type, prior, current and concomitant medication will also be recorded at this visit. Subjects will be asked to self-assess baseline signs and symptoms of cutaneous and ocular irritation prior to the LAST and any product application.

Subjects will only be considered eligible to continue in the study if they have a dermatologist signs and symptoms cutaneous irritation score of greater than or equal to 0.5 (very slight) for erythema and a score of greater than or equal to 0.5 (very slight) for dryness, a score of 0 (none)

or 0.5 (very slight) for scaling and 0 (none) or 0.5 (very slight) for edema. Any subject with a score of 3 (severe) in any cutaneous irritation attribute will exclude the subject from the study, as this does not reflect the target population for the product. Any ophthalmologist signs and symptoms attribute score of greater than 0 (none) will exclude the subject from the study.

For subjects who continue to be eligible to participate in the study, the first application of their assigned product will be at the investigational site, under the supervision of a trained technician. Subjects will be asked to complete further self-assessment questions of the signs and symptoms of cutaneous and ocular irritation they are experiencing, 1 to 2 hours after first application. Subjects will then be instructed to apply their assigned product at home again the same evening and twice-daily for 21 (+2) days as part of their normal skin care routine. A paper diary will be provided to each subject to record the number of daily applications of product, from first application at site to final application at home. The final application of product will be at home on the morning of the final visit (Visit 2).

At Visit 2 (final visit), the dermatologist and ophthalmologist will conduct final clinical assessments of the signs and symptoms of cutaneous and ocular irritation, respectively. Subjects will also be asked to conduct a final self-assessment of the signs and symptoms of cutaneous and ocular irritation. Subjects will return their completed diary and supplied product and will subsequently be discharged from the study.

1.2 Study Objectives

The objectives of this study are as follows:

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To determine the local cutaneous tolerance profile of the investigational product in healthy females with sensitive facial skin under normal conditions of use	Change from baseline (prior to any product application) in dermatologist visual assessment scores of signs and symptoms of cutaneous irritation to 21 (+2) days of product use
Secondary Objectives	**Secondary Endpoints**
To determine the local ocular tolerance profile of the investigational product in healthy females with sensitive facial skin under normal conditions of use	Change from baseline (prior to any product application) in ophthalmologist visual assessment scores of signs and symptoms of ocular irritation to 21 (+2) days of product use
To determine the local cutaneous and ocular tolerance of the investigational product from the perspective of the subject in healthy females with sensitive facial skin under normal conditions of use	Change from baseline in subject self-assessment scores of signs and symptoms of cutaneous and ocular irritation to 1 to 2 hours after first product application and following 21 (+2) days of use

Objectives	Endpoints
Safety Objective	**Safety Endpoint**
To evaluate the general safety of two cosmetic facial serums	Frequency and severity of Adverse Events

1.3 Treatments

The following study products will be supplied by the Clinical Supplies Department, GlaxoSmithKline Consumer Healthcare (GSK CH):

Table 1-1 Details of Study Products

	Investigational Product	Reference Product
Product Name	Developmental Serum	Physiogel Calming Relief Anti-Redness Serum (Korean market place product)
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]
Product Format	30 ml Bottle with piston pump	
Dispensing Details	A kit will be dispensed to each subject containing 2 bottles	
Application Quantity	To be used as per normal home use application	
Route of Administration	Topical dermal (facial) application	
Application Instructions	Apply twice-daily to freshly cleansed skin in place of your current serum and before your moisturizer	
Return Requirements	All used/unused samples to be returned to the study site	

Other items to be supplied by the clinical investigational site:

- Aqueous Lactic Acid solution (10%) – For LAST.
- Saline solution (0.9 Molar) – For LAST.
- Cotton Buds - For LAST.

1.4 Sample Size Calculation

A sufficient number of subjects will be screened (approximately 180) to randomize 90 subjects to ensure that at least 60 subjects (30 per arm) complete the study. It is deemed that 30 subjects per arm are considered sufficient to assess the primary endpoint: dermatologist assessment of

signs and symptoms of cutaneous irritation total score. The sample size for this study has been selected based on clinical considerations and to ensure compliance with the Agência Nacional de Vigilância Sanitária (ANVISA) Guideline for the Safety Evaluation of Cosmetic Products (ANVISA, 2012) which mandates an investigational product be tested on at least 30 subjects.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned for this study.

2.2 Final Analyses

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

1. All subjects have 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

For all endpoints, the baseline value will be the (non-missing) value obtained prior to any product application.

3.2 Subgroups/Stratifications

There are no subgroup/stratifications for this study.

3.3 Center Pools

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

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 identify any major deviations. A listing of subjects who are non-compliant with the protocol specified time-window for study visits will be produced for the Blinded Data Review Meeting (BDRM).

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, during 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

Tables described in this section will be produced for all randomized subjects.

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A summary will be provided for the number of subjects screened and the number and percentage of screen failures with reasons why subjects are not randomized (PPD). Percentages for screen failure subjects will be based on number of screened subjects. The number of subjects enrolled for this study will also be presented. A subject who has signed informed consent and is eligible to proceed beyond the screening visit is considered to be enrolled.

Subject disposition will be summarized by the number and percentage of subjects (out of the number of randomised subjects), who complete the study and those who discontinue the study (broken down by reason for discontinuation, if any) (PPD). The table will also summarize the number and percent of subjects assigned to the Safety Population. The percentages will be based on the total number of subjects randomized.

Subject disposition including the subject status (completed study, Yes/No), demographic data (age, gender and race), screening date, date of study completion or withdrawal, study product start date and time, duration (in days) in the study (defined as [(date of completion or withdrawal – start date of study product) + 1], and primary reason of discontinuation (further details if any) will be listed by product group (PPD).

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

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 categorised.

Important deviations of the protocol procedures identified as liable to influence the primary tolerability outcome may include, but will not necessarily be limited to:

- Violation of inclusion or exclusion criteria at screening that may affect primary tolerability.
- Non-compliance with product application.
- Use of prohibited treatment or medication before or during the study which will affect the primary tolerability.
- Violation of the visit window.

Further deviations liable to influence the primary tolerability will be given in the Review Listing Requirement (RLR) document where important deviations will be identified at the BDRM.

The number and percentage of subjects with an important protocol deviation (overall and by type of deviation) will be presented by product group (PPD) and listed in PPD .

All protocol deviations captured on the case report form will be listed in PPD . The listing will present date of deviation, deviation type and deviation description.

4.1.3 Analysis Populations

The analysis population in this study is defined as the follows

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprise of all subjects who receive at least one dose of study product. • This population will be based on the product the subject actually received.	• Tolerability and Safety

Exclusion of any subjects from the safety population will be reviewed during a BDRM prior to database lock and approved prior to unblinding. PPD will display all randomised subjects included and excluded from the safety population.

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the Safety Population and the listing will be produced on all randomized subjects.

4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects (n), mean, standard deviation (SD), median, minimum and maximum) for continuous variables and frequency count (n) and percentage (%) of subjects for categorical variables will be presented for demographic variables by product group and overall. Continuous variable will include age (in years) and categorical variables include gender and race. All demographic information will be tabulated in PPD and listed in PPD .

4.2.2 General Medical History

Medical history data will be listed (PPD) with start date and end date (or ongoing at the start of study product). A data listing will also be produced for the evaluation of protocol violations at the BDRM.

4.2.3 Characteristics of Disease

Fitzpatrick skin type and the baseline data of primary and secondary variables will be summarised by the number and percentage of subjects (by product group and overall) in PPD and listed in PPD .

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

4.3.1 Study Product Compliance and Exposure

Compliance data (based on the subject diary data) will also be summarized for the Safety Population as the percentage of subjects in each study product group who took 80% ~ 120% of the number of prescribed uses of study product group (PPD).

The 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 the two visits;

Actual number of product use = expected number of product use − missed product use + additional product use.

Study product compliance will be listed (PPD). Supervised product application (subject number, date of visit and time of the supervised procedure) will be listed (PPD).

The randomization information will be listed in PPD . Kit list allocation will be listed in PPD .

4.3.2 Prior and Concomitant Medication

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

As justified within Section 5, the current analysis standards for defining concomitant medications will be used rather than those provided in the protocol (which defined concomitant based on the timing of providing informed consent):

- Prior medications are defined as those which stopped before the first application of the study product.

- Concomitant medications are defined as the medication ongoing or started on or after the first application of the study product.

Prior and concomitant medication will be listed (PPD and PPD) by subject, with drug name, GSK drug synonym, dose, dose form, frequency, route, start date/ study day relative to first study product administration, and ongoing or end date/ study day relative to first study product administration.

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

4.4 Analysis of Tolerability

4.4.1 Primary Tolerability Endpoint

4.4.1.1 Primary Tolerability Endpoint Definition

The primary endpoint will be the change from baseline (prior to any product application) in dermatologist signs and symptoms of cutaneous irritation total score following 21 (+2) days of product use.

This study will be considered a success if at least 90% of completed subjects do not have a significant increase (i.e. a unit increase score of 1 in the total score) from baseline in dermatologist assessed signs and symptoms of cutaneous irritation following 21 (+2) days of investigational product use.

Calculation of dermatologist assessment of signs and symptoms of cutaneous irritation total score and change from baseline in total score:

The cutaneous irritation total score will be calculated in the following way:

Cutaneous irritation total score = dermal response score of erythema + dermal response score of dryness + dermal response score of scaling + dermal response score of edema

Where, the dermal response score is described in Table 4-1.

Table 4-1 Dermatological Evaluation

Attribute	Description (Score)				
Erythema	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Dryness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Scaling	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Edema	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

For example, if the dermal responses score of erythema = 2, dermal responses score of dryness = 0.5, dermal responses score of scaling = 1 and dermal responses score of edema = 0.5.

Then the cutaneous irritation total score will be:

Total score = 2 + 0.5 + 1 + 0.5 = 4.

Change from baseline in dermatologist signs and symptoms of cutaneous irritation total score = total score at day 21 − total score at baseline.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The dermatologist signs and symptoms of cutaneous irritation total score will be calculated as the sum of the individual dermal response attributes (erythema, dryness, scaling, and edema). The change from baseline in the total score will be summarised by number and percentage of subjects by visit for each product group (PPD). Additionally the change from baseline score greater than 1 will be summarised by number and percentage of subjects by visit for each product group. No formal statistical inference will be performed.

The individual attribute responses, total score and change from baseline in total score will be listed for each subject by visit and by product group (PPD).

4.4.2 Secondary Tolerability Variables

4.4.2.1 Secondary Tolerability Variable 1

The key secondary endpoint will be the change from baseline (prior to any product application) in the ophthalmologist signs and symptoms of ocular irritation total score following 21 (+2) days of product use.

Calculations of ocular irritation total score and change from baseline in total score:

The ocular irritation total score will be calculated in the following way:

Ocular irritation total score = ocular response score of eczema of the eyelid + ocular response score of conjunctivitis + ocular response score of follicles + ocular response score of chemosis conjunctivae

Change from baseline in ocular irritation total score = total score at day 21 − total score at baseline.

Where, the ocular response score is described in the Table 4-2.

Attribute	Description (Score)				
Eczema of the eyelid	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Conjunctivitis	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

Follicles	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Chemosis conjunctivae	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

Table 4-2 Ophthalmological Evaluation

4.4.2.2 Secondary Tolerability Variable 2

The other secondary endpoints will be change from baseline in subject self-assessment scores of signs and symptoms of cutaneous and ocular irritation to 1 to 2 hours after first product application and following 21 (+2) days of product use.

Calculations of subject self-assessment of cutaneous irritation total score and change from baseline in total score:

Subject self-assessment of cutaneous irritation total score = redness + dryness + itching + stinging/burning + tightness

Change from baseline in subject self-assessment of cutaneous irritation total score = total score at 1 to 2 hours (and day 21) − total score at baseline

Calculations of subject self-assessment of ocular irritation total score and change from baseline in total score:

Subject self-assessment of ocular irritation total score = redness + dryness + stinging/ burning + Itching

Change from baseline in subject self-assessment of ocular irritation total score = total score at 1 to 2 hours (and day 21) − total score at baseline

Where, the subject self-assessment of cutaneous irritation score is as described in the

Table 4-3, and the subject self-assessment of ocular irritation score is as described in the Table 4-4.

Table 4-3 Subject Self-Assessment Scale for Sign and Symptoms of Cutaneous Irritation

Attribute	Description (Score)				
Redness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Dryness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Stinging/Burning	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Itching	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Tightness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

Table 4-4 Subject Self-Assessment Scale for Signs and Symptoms of Ocular Irritation

Attribute	Description (Score)				
Redness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Dryness	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Stinging/Burning	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)
Itching	None (0)	Very Slight (0.5)	Slight (1)	Moderate (2)	Severe (3)

4.4.3 Handling of Missing Values/Censoring/Discontinuations

Missing data will not be replaced or imputed. Subjects who withdraw from the study prematurely will be included in the statistical analyses up to the point of discontinuation.

4.5 Analysis of Secondary Objectives

4.5.1 Tolerability (Secondary)

The ophthalmologist assessment of signs and symptoms of ocular irritation total score will be calculated as the sum of the individual ocular response scores (eczema of the eyelid, conjunctivitis, follicles, chemosis conjunctivae). The change from baseline in the total score will be summarised by number and percentage of subjects by visit for each product (PPD). Additionally the change from baseline score greater than 1 will be summarised by number and percentage of subjects by visit for each product. No formal statistical inference will be performed.

The individual attribute responses, total score and change from baseline in total score will be listed for each subject by visit and by product group (PPD).

The subject self-assessment on Visit 1 will be measured twice: once prior to the LAST and product application and once 1 to 2 hours after first supervised product application. Also Subject self-assessment will be measured on Day21 as well. The change from baseline in the total subject self-assessment scores for signs and symptoms of cutaneous irritation and ocular irritation score at 1 to 2 hours after first product application and following 21 (+2) days of use

will be summarized by number and percentage of subjects by visit for each product (PPD).

The individual attribute responses, total score and change from baseline in total score will be listed for each subject by visit and by product group (PPD).

All secondary analyses will be performed using the Safety Population.

4.5.2 Pharmacokinetic (Secondary)

Not Applicable.

4.6 Analysis of Safety

All safety data will be reported for the Safety Population as per actual product received. The safety profile of the study product 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 product application. Adverse events with an onset date/time prior to the first product application will be considered as non-treatment emergent.

Treatment emergent adverse events will be summarized by the number and percentage of subjects having any AE, an adverse event in each System Organ Class, and each Preferred Term. The following summary tables and listings will be presented by product:

- Table of TEAEs by SOC and PT (PPD).
- Table of TEAEs by SOC, PT and severity (PPD).
- Table of TEAEs by skin/non-skin and PT (PPD).
- Table of treatment emergent treatment-related AEs by SOC and PT (PPD).
- Table of treatment emergent treatment-related AEs by SOC, PT and severity (PPD).
- Table of treatment emergent treatment-related AEs by skin/non-skin and PT (PPD).
- Table of treatment emergent treatment-related serious adverse events (SAEs) by SOC and PT (PPD) [only produced if there are more than 5 treatment emergent SAEs].
- Table of treatment emergent treatment-related non-serious SAEs by SOC and PT (PPD) [only produced if there are more than 5 treatment-emergent SAEs].
- Listing of all AEs (PPD for all randomized subjects; PPD for non-randomized subjects).

- Listing of deaths (PPD).
- Listing of non-fatal SAEs (PPD).
- Listing of treatment emergent AEs leading to study or product discontinuation (PPD).
- Listing of treatment-emergent AEs classified as skin (PPD).

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

4.7 Analysis of Other Variables

No other analyses will be performed for this study.

5 Changes to the Protocol Defined Statistical Analysis Plan

Any 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**
• Section 6.8: Medication/treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after signing the informed consent form will be documented as concomitant medication/treatments.	• The current standard definition of the prior medication and concomitant medications has been used in the Reporting and Analysis plan: Prior medications are defined as those which stopped before the first application of the study product. Concomitant medications are defined as the medication ongoing or started on or after the first application of the study product.	• To maintain the current standard definition of prior medication and concomitant medications • Importantly, all medications/therapies concomitant to study participation will be provided. • For this study, signing the informed consent form and the first application of the study product will be on the same day. Thus, the variance in definitions will not impact the overall analysis of the prior and concomitant medications.