STATISTICAL REPORTING AND ANALYSIS PLAN

A PHOTO-IRRITATION AND PHOTO-SENSITISATION STUDY IN HEALTHY SUBJECTS FOR THREE DEVELOPMENTAL COSMETIC FACIAL PRODUCTS

Protocol Number: 212378

Phase: N/A

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	28-Jun-2019	Not applicable
RAP Amendment 1	28-Aug-2019	Reference to amended protocol V2.0, dated 08 August 2019. Section 5 "Changes to the Protocol Defined Statistical Analysis Plan" updated to reflect no changes or deviations to the originally planned statistical analysis specified in the protocol, dated 08 August 2019.

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Abbreviation

Abbreviation	Term
AEs	Adverse Events
ANVISA	Agência Nacional de Vigilância Sanitária (The National Health Surveillance Agency)
BDRM	Blinded Data Review Meeting
eCRF	Electronic Case Report Form
cm^2	Centimeter squared
GSKCH	Glaxo SmithKline Consumer Healthcare
ICDRG	International Contact Dermatitis Research Group
ICF	Informed Consent Form
MED	Minimal Erythemal Dose
MedDRA	Medical Dictionary for Regulatory Activities
MFG	Manufacturing Code
mL	Milliliter
N/A	Not Applicable
PD	Protocol Deviation
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Events
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UVR	Ultraviolet Radiation

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 212378 v2.0, dated 08 August 2019.

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. As a general requirement, the safety and compatibility of a new formulation should be confirmed before it is commercialized.

Compatibility studies, performed as patch tests, aim to confirm the local tolerance of topical cosmetic products during the first application to the skin, therefore providing assurance that the product is safe for use under maximized conditions.

Photo-irritation assessments aim to demonstrate the absence of irritation potential of a product when applied to the skin and exposed to ultraviolet radiation (UVR). Photo-sensitization assessments aim to demonstrate the absence of allergic potential of a product applied to the skin when exposed to UVR.

The objective of this clinical study is to assess the photo-irritation and photo-sensitization potential of three developmental cosmetic formulations compared to a reference product (negative control) after duplicate, repeated semi-occlusive patch applications to healthy human subjects by following a conventional photo-irritation and photo-sensitization methodology under supervision of a dermatologist.

Photo-irritation potential will primarily be evaluated through the repeated occluded application and UV exposure of the study products over 3 weeks (induction phase). Photo-sensitization potential will primarily be evaluated through a subsequent semi-occluded application and UV exposure (challenge phase) after a 2-week rest period.

1.1 Study Design

This will be a single-center, randomized, evaluator (single) blind study in healthy adult subjects aged 18 to 65 years with no dermatological disorders and with a Fitzpatrick skin phototype II to IV to evaluate the cutaneous photo- irritation and photo- sensitization potential of three cosmetic facial skincare products. Approximately 80 healthy subjects will be screened to randomize at least 40 subjects to ensure at least 25 evaluable subjects complete the entire study.

The study will consist of three phases, a 3-week induction phase consisting of two parallel repeated 24 hour patch applications on the backs of healthy subjects (one of which is subsequently exposed to UV radiation upon patch removal, and evaluation of cutaneous responses of both sites after each patch removal); a 2 week rest phase; and a final challenge phase, consisting of two parallel 24 hour patch applications to naive sites (one set of which is subsequently exposed to UV radiation upon patch removal, and evaluation of cutaneous responses of both sites 24, 48 and 72 hours after patch removal).

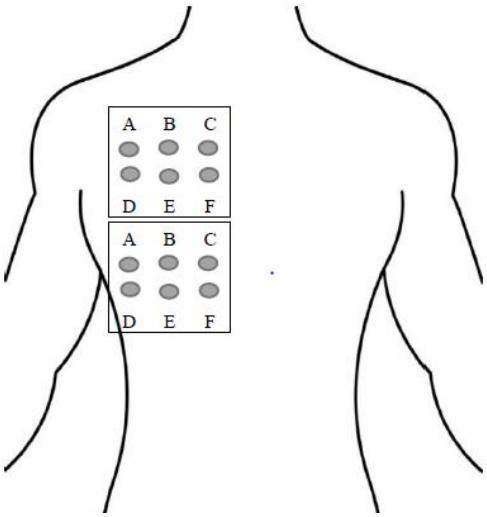
The sequence of each of the test products to the cells within the patch system for each subject will be randomly assigned per the randomization sequences provided. The sequence of the products to the cells for each subject will remain the same throughout the induction phase, and a different sequence per the randomization provided will be provided for each subject for the challenge phase.

There will be a total of 5 different test areas, located on the back of each subject, which will be used in this study across the screening, induction and challenge phases:

- 1 test area to determine the provisional MEDu in screening;
- 2 test areas for test products and reference product (saline solution) in the induction phase (1 series will be exposed to UV radiation, the other series will not);
- 2 test areas for test products and reference product (saline solution) in the challenge phase (1 series will be exposed to UV radiation, the other series will not).

The 4 test areas in the induction and challenge phases will each undergo applications of an adhesive patch system. Within each patch system, there will be 6 circular cells, of which 4 will be used to host the study products and 2 will be left blank. In this study, each of the study products will be dispensed into 4 adjacent cells, in two duplicate series of patches, as per the randomization schedule. Three cells will be used for the test products (serum, lotion and cream) and a fourth for the reference product (saline solution).

Figure 1-1 Example layout of the patch on the dorsum (shown adhesive side down)



Two semi-occlusive patches with 6 cells labelled A-F will be used. Four cells (A-D) will be used in this study (1 for each test product and 1 for the saline solution). Two cells (E-F) will remain empty.

1.2 Study Objectives

The study objectives are as follows:

Objectives	Endpoints
Primary Objective	Primary Endpoint
To evaluate the cutaneous photo-Sensitization potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a potential sensitization reaction which is considered photo-initiated.
Secondary Objectives	Secondary Endpoints
To evaluate the cutaneous photo-irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a photo-initiated reaction score of '+' or greater which not considered a potential sensitization reaction.
To evaluate the cutaneous sensitization potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a potential sensitization reaction which is not considered photo-initiated.
To evaluate the cutaneous irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a non-photo-initiated reaction score of '+' or greater which is not considered a potential sensitization reaction.
Safety	
To evaluate the general safety of three cosmetic facial skincare products	Frequency and severity of Adverse Events

Success criteria:

A test product will be considered to have low photo-sensitization potential if the proportion of subjects with a potential photo-sensitization reaction are comparable for the test product and saline.

The hypothesis is that the study products will have low photo-sensitization potential. Therefore, it is expected that the vast majority of responses will be negative. No formal statistical comparison between product groups shall be made.

1.3 Treatments

	Test Product 1	Test Product 2	Test Product 3	Reference product (Negative Control)
Product Name	Developmental Serum	Developmental Lotion	Developmental Cream	Saline Solution: Sodium Chloride (NaCl; 0.9%)
Pack Design	40 mL Pump Pack	50 mL Tube	50 mL Tube	500 mL
Product Manufacturing Code (MFC)	CCI [redacted]	CCI [redacted]	CCI [redacted]	N/A – Commercial Product
Application quantity	Dose: 0.02 mL/cm^2 Each product will be dispensed into an individual cell within the patch system according to the randomization sequence for the induction phase and the challenge phase and removed/reapplied as per study schedule.			
Route of administration	Topical dermal application via semi-occlusive patch to the dorsum.			
Application Instruction	Applied on-site by technician			

1.4 Sample Size Calculation

Approximately 80 healthy subjects will be screened to randomize at least 40 subjects to ensure at least 25 evaluable subjects complete the entire study. No formal power calculations have been performed on this study. This sample size is standard in clinical testing practices and is consistent with the guidelines the National Health Surveillance Agency, 2012 (ANVISA).

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final planned 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

Baseline grading of naïve test sites will be performed prior to the patch application at Visit 4 Day 1 (induction phase) and Visit 19 Day 36 (challenge phase) using the scoring system detailed in grading scale Table 4-2.

3.2 Subgroups/Stratifications

No subgroups or stratification factors are defined in this study.

3.3 Centers Pools

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

3.4 Timepoints and Visit Windows

The time points and visits for this study are defined in the section "Schedule of Activities" of the protocol. Any deviation from the study schedule may be reviewed on case-by-case basis at 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 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. An enrolled subject is a subject who has signed informed consent and is eligible to proceed beyond the screening visit. There are two randomizations; one is at Visit 4 for the induction phase and one at Visit 19 for the challenge phase. The number of subjects screened, enrolled and randomized in induction and challenge phase will be presented in Table 14.1.1.

Table 14.1.1 will also display the number and percentage of screen failure subjects (subjects not randomized in induction phase) with reasons why subjects are not randomized in induction phase. Percentages for screen failure subjects will be based on the total number of

subjects screened. The number and percentage of subjects not randomized in challenge phase will be displayed and percentages based on the number of subjects randomized in induction phase.

Subjects who complete the study (complete both induction and the challenge phases) and who discontinue during the challenge phase will be broken down by reason for discontinuation. The percentages will be based on the total number of subjects randomized in challenge phase.

The number and percentage of subjects in the safety population will also be summarized and percentages based on the number of subjects randomized in induction phase. The summary will be presented for all subjects (overall).

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

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), displaying subject number, demographic information (age, sex and race), screening date, reason for screen failure and any further details of reason for screen failure.

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 may include, but will not be necessarily be limited to the following:

- Consent procedures
- Inclusion/exclusion criteria
- Non-compliance with product application
- Study procedures

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 will be presented overall and by type of deviation (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form page 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 defined for this study are as follows:

Population	Definition / Criteria	Analyses Evaluated
Safety	The Safety population includes all randomized subjects who received at least one dose of any study product. This population will be based on the product sequence the subject received.	Primary endpoint, Secondary endpoints Safety
Randomized	All subjects randomized in induction phase regardless of whether they received study product. Any subject who receives a treatment randomization number will be considered to have been randomized.	Protocol deviations, disposition and medical history listings

NOTES :

- To be randomized into the challenge phase, a subject must have been already randomized in the induction phase. Therefore, the randomization status in challenge phase won't be considered to define the randomized population. Only the randomization in induction phase status will be used to define this population.
- Please refer to Attachment 1: List of Data Displays which details the population to be used for each of the displays being generated.

Listing 16.2.3.1 will display all randomized subjects (induction phase) included and excluded from the safety 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 for all subjects (overall). These variables include age, gender, race and Fitzpatrick skin type will be presented for the safety population (Table 14.1.3).

Table 4-1 Fitzpatrick Skin Type

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

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

Mean Individual typology angle (ITA), Mean L and b, and Provisional Minimal Erythemal Dose (MED) will be listed for each subject Listing 16.2.4.3.

4.2.2 General Medical History

Medical history data will be listed (Listing 16.2.4.2) with start date and end date or ongoing at the start of the study.

4.2.3 Characteristics of Disease

N/A

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

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

4.3.1 Study Drug Compliance and Exposure

Product application will be conducted at study site. Any protocol deviation associated with product applications will be reviewed during Blind Data Review Meeting prior to database lock.

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.

Prior medication will be listed by subject, with drug name, GSK drug synonym, dose, dose form, frequency, route, start date, study day relative to study product administration and end date (Listing 16.2.4.4). Prior medications are defined as those which stopped before the start date of study product. If the stop date is unknown or incomplete and the medication cannot be

considered as stopped prior to the start date of study product then the medication will be considered as a concomitant medication.

Concomitant medications will be listed similarly (Listing 16.2.4.5) with either ongoing or end date displayed. Concomitant medications are defined as medications that are ongoing or started on or after the start date of study product.

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 Endpoints

The primary and secondary endpoints will be derived based on the International Contact Dermatitis Research Group (ICDRG) scores at the UV-exposed and non-UV-exposed sites during the induction and/or challenge phase and the investigator assessment of potential sensitization at the final visit in the challenge phase (Visit 23, Day 40).

Positive reactions are defined as a score of '+' or higher (that is, '+', '++', '+++') on the ICDRG scale:

Table 4-2 Scoring of patch cells according to ICDRG

-	Negative reaction
+?	Doubtful reaction; faint erythema only
+	Weak (non-vesicular) positive reaction; erythema, infiltration and possibly papules
++	Strong (vesicular) positive reaction; erythema, infiltration, papules and vesicles
+++	Extreme positive reaction; bullous reaction, intense erythema and infiltration, coalescing vesicles
IR	Irritant reaction
NT	Not tested

The following order will be used to determine severity of ICDRG scores for classification of photo-initiated:

- "-" < "+?" < "+" < "++" < "+++"

"IR" has no impact on the severity of a score and IR can be selected by the investigator in addition to a positive reaction. Possible selections will be:

- either "-", "+?", "+", "++", "+++"
- either "+?", "+", "++", "+++" and "IR"
- "NT" only

A subject (with at least one positive reaction) is classified as having experienced a photo-initiated reaction if the maximum score at the UV-exposed site for that subject is greater than the maximum score of the non-UV-exposed site for that subject.

Maximum score refers to the maximum across all visits for which a subject has data available during the relevant phase/phases as described in the individual endpoint definitions.

If "NT" is selected it will be handled in the same way as missing data. Only non-missing data will be considered in the determination of photo-initiated. If a subject discontinues prematurely, data up to the point of discontinuation will be used.

The assessment of positive reactions as potential sensitization reactions in the challenge phase will be determined by the blinded dermatologist and reported as:

- Yes
- No
- Unable to Determine

If "Unable to determine" is reported, it will not be counted as a potential sensitization reaction.

If a subject discontinues prior to the last visit the subject will not be considered for endpoints of sensitization or photo-sensitization, the subject can still be included in endpoints of irritation or photo-irritation based on ICDRG scores.

4.4.1 Primary Endpoint

4.4.1.1 Primary Endpoint Definition

The primary analysis will be based on safety population.

The primary analysis will be based on the number of subjects with potential sensitization reactions considered photo-initiated (i.e. potential photo-sensitization reactions).

Potential photo-sensitization reactions are defined as a positive reactions meeting both of the following requirements:

- sensitization reported as "yes" at final visit of challenge phase (sensitization box ticked "yes" on eCRF)
- the maximum score of the UV-exposed site (across all visits) during the challenge phase > maximum score of the non-UV exposed site (across all visits) during the challenge phase

The number and percentage of subjects with potential sensitization considered photo- initiated reactions will be presented by product group in Table 14.2.2.1. No formal statistical inference will be performed.

All potential sensitization reactions considered photo-initiated will be listed (Listing 16.2.6.3) for the safety population.

A frequency table will be presented for potential sensitization reactions (Sensitization (Yes), non-sensitization (No) and Unable to determine) regardless of photo initiation status by product group in Table.14.2.1.1.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

No formal statistical inference is planned for primary endpoint.

4.4.1.3 Supportive Analyses

N/A

4.4.2 Secondary Efficacy Variables

Secondary endpoint variables are defined in Section 4.5.

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 Endpoints

The secondary analysis will be based on safety population. The secondary endpoints will be derived based on the ICDRG scores and the investigator assessment of potential sensitization as described in Section 4.4.

4.5.1 Secondary Endpoint

Evaluation of the cutaneous photo-irritation potential:

- Potential photo-irritation reactions (photo-initiated reactions that are not considered a potential sensitization reaction) are defined as positive reactions meeting both of the following requirements: sensitization reported as “No” or “Unable to determine” or missing at final visit of challenge phase (sensitization box ticked “No” or “Unable to determine” or missing on eCRF)
- the maximum score of the UV-exposed site (across all visits) during the induction and challenge phase > maximum score of the non-UV exposed site (across all visits) during the induction and challenge phase

The number and percentage of subjects with photo-initiated reaction that is not considered a potential sensitization reaction will be presented by product group in Table 14.2.2.1. No formal statistical inference will be performed.

All photo-initiated reactions that are not considered as potential sensitization reactions, will be Listed (Listing 16.2.6.4) for the safety population.

Evaluation of the cutaneous sensitization potential:

Potential sensitization reactions not considered photo-initiated are defined as positive reactions meeting both of the following requirements:

- sensitization is equal to "Yes" at final visit of challenge phase (sensitization box ticked "Yes" on eCRF)
- the maximum score of the UV-exposed site (across all visits) during the challenge phase ≤ maximum score of the non-UV-exposed site (across all visits) during the challenge phase

The number and percentage of subjects with potential sensitization not considered photo-initiated will be presented by product group in Table 14.2.2.1 using the maximum score. No formal statistical inference will be performed.

All potential sensitization reactions that are not considered photo-initiated will be listed (Listing 16.2.6.5) for the safety population.

Evaluation of the cutaneous irritation potential

Positive reactions not considered potential sensitization and not considered as photo-initiated are defined as positive reactions meeting both of the following requirements:

- sensitization reported as to "No" or "Unable to determine" or missing at final visit of challenge phase (sensitization box ticked "No" or "Unable to determine" or missing on eCRF)
- the maximum score of the UV-exposed site (across all visits) during the induction and challenge phase ≤ maximum score of the non-UV exposed site (across all visits) during the induction and challenge phase

The number and percentage of subjects with positive reactions not considered potential sensitization and not considered as photo-initiated will be presented by product group in Table 14.2.2.1 using the maximum score. No formal statistical inference will be performed.

All positive reactions not considered potential sensitization and not considered as photo-initiated, will be listed (Listing 16.2.6.6) for the safety population.

A listing will be presented for all the ICDRG grades in Listing 16.2.6.1 and all positive reactions will be listed in Listing 16.2.6.2.

Narrative descriptions of all positive reactions (scores of + or greater), in the challenge phase, will be provided in Listing 16.2.6.7 for the safety population.

4.5.2 Pharmacokinetic (Secondary)

N/A.

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 products will be assessed with respect to 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).

AEs will be classified as skin and non-skin on the AE page of eCRF.

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

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

- Table of treatment emergent AEs by system organ class (SOC) and Preferred Term (PT) (Table 14.3.1.1). 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.
- Table of treatment-related treatment emergent AEs by SOC and PT (Table 14.3.1.3)
- Table of treatment emergent AEs by Skin/Non-Skin and PT (Table 14.3.1.2)
- Table of treatment-related treatment emergent AEs by Skin/Non-Skin and PT (Table 14.3.1.4)
- Table of treatment emergent serious adverse events (SAEs) by SOC and PT (Table 14.3.1.5) [only produced if there are more than 5 SAEs].
- Table of treatment emergent AEs by SOC, PT, and severity (Table 14.3.1.6)
- Table of treatment-related treatment emergent AEs by SOC, PT, and severity (Table 14.3.1.7)
- 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 drug withdrawal (Listing 14.3.2.3)
- Listing of treatment-emergent AEs by Skin/Non-Skin (Listing 14.3.2.4)

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

4.7 Analysis of Other Variables

N/A.

5 Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol, dated 08 August 2019.

Attachment 1: List of Data Displays

GSK_CH 212378 List of TLF's Final v1.0 03