Statistical Analysis Plan for Protocol 212383

A Human Repeat Insult Patch Test (HRIPT) in Healthy Subjects to Assess the Cutaneous Irritation and Sensitization Potential of Three Developmental Cosmetic Facial Products.

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STATISTICAL REPORTING AND ANALYSIS PLAN

A HUMAN REPEAT INSULT PATCH TEST (HRIPT) IN HEALTHY SUBJECTS TO ASSESS THE CUTANEOUS IRRITATION AND SENSITIZATION POTENTIAL OF THREE DEVELOPMENTAL COSMETIC FACIAL PRODUCTS.

Protocol Number: 212383

Phase: N/A

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	16-Jul-2019	Not applicable (N/A)

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Abbreviation

Abbreviation	Term
AE	Adverse Event
BDRM	Blinded Data Review Meeting
CH	Consumer Healthcare
CI	Confidence Interval
cm^2	Centimeter squared
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HRIPT	Human Repeated Insult Patch Test
ICDRG	International Contact Dermatitis Research Group
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Product Master Formulation Code
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Milliliter
N/A	Not Applicable
NaCl	Sodium chloride
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
TEAEs	Treatment emergent adverse events
US	United States

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 212383 version 1.0 dated 25-Mar-2019.

1 Summary of Key Protocol Information

A cosmetic product that is freely available to the consumer must be safe and must not cause damage 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.

The human repeated insult patch test (HRIPT) is a long standing, standard method to determine whether exposure to a topical product will elicit a cutaneous (dermal) irritant or allergic response under exaggerated (occluded) conditions. It is also routinely used and accepted as an appropriate methodology to establish the sensitization potential of topical medicated products by health authorities, including the United States (US) Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA). The HRIPT requires approximately 6 weeks and involves 3 phases: induction, rest and challenge, and is based on the modified Draize test.

1.1 Study Design

This will be a randomized, evaluator-blind, single-center, HRIPT study in healthy adult subjects aged 18 to 65 years to evaluate the cutaneous irritation and contact sensitization potential of three cosmetic facial skincare products compared to saline solution. Subjects will be exposed to repeated cutaneous (dermal) semi-occlusive application of 3 cosmetic facial skincare products and a negative control (saline solution).

The study will consist of three phases, a 3-week induction phase, a 2-week rest phase; and a final challenge phase.

During induction phase, the subjects will undergo repeated adhesive patch application for 3 weeks. There will be a total of 9 patch applications over 3 consecutive weeks, with patches applied to the same location on alternate weekdays each week (Monday, Wednesday, and Friday). Patches will remain affixed to the skin for 48 (weekdays) or 72 (weekends) hours during the induction phase, after which they will be removed, the skin evaluated for signs of reactions, and new adhesive patches with all the test products applied to the same site on the dorsum.

After the induction phase is complete, subjects will enter a 2-week rest phase, during which no patches or products will be applied. Subjects will be reminded to continue to follow the Lifestyle Considerations throughout the rest phase.

After the rest phase is complete, subjects will return to the clinical site for the challenge phase. In this phase, a new adhesive patch containing all the products will be affixed to virgin

skin (i.e. previously unpatched) for 48 hours. The patch will then be removed, and the skin assessed for any signs of reactions shortly after patch removal, and the area assessed again after a further 24 and 48 hours.

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

The schedule of activities table (Table 1-1) provides an overview of the subject visits and study procedures.

Table 1-1 Schedule of Activities

	Screening	Induction									Rest	Challenge			
Study Week	-	Week 1			Week 2			Week 3			Week 4-5	Week 6			
Study Day / Procedure/ Assessment	VISIT 1 DAY -14 to DAY 0	VISIT 2 DAY 1	VISIT 3 DAY 3	VISIT 4 DAY 5	VISIT 5 DAY 8	VISIT 6 DAY 10	VISIT 7 DAY 12	VISIT 8 DAY 15	VISIT 9 DAY 17	VISIT 10 DAY 19	VISIT 11 DAY 22	VISIT 12 DAY 36	VISIT 13 DAY 38	VISIT 14 DAY 39	VISIT 15 DAY 40
Day of Week	-	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Mon	Wed	Thu	Fri
Informed Consent *(date and time captured)*	X														
Demographics	X														
Medical History	X														
Current/Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fitzpatrick Skin Type Assessment	X														
Inclusion/Exclusion Criteria	X	X [a]													
Dermatologist Assessment [b]	X											X	X	X	X

	Screening	Induction									Rest	Challenge			
Study Week	-	Week 1			Week 2			Week 3			Week 4-5	Week 6			
Study Day / **Procedure/ Assessment**	VISIT 1 DAY -14 to DAY 0	VISIT 2 DAY 1	VISIT 3 DAY 3	VISIT 4 DAY 5	VISIT 5 DAY 8	VISIT 6 DAY 10	VISIT 7 DAY 12	VISIT 8 DAY 15	VISIT 9 DAY 17	VISIT 10 DAY 19	VISIT 11 DAY 22	VISIT 12 DAY 36	VISIT 13 DAY 38	VISIT 14 DAY 39	VISIT 15 DAY 40
Day of Week	-	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Wed	Fri	Mon	Mon	Wed	Thu	Fri
Subject Eligibility	X														
Continued Eligibility		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization *(sequence of products to cells within the patch)*		X										X			
Patch (product) Application [c]		X	X	X	X	X	X	X	X	X		X [g]			
Patch Removal [d]			X	X	X	X	X	X	X	X	X [h]		X [j]		
Assessment of the test sites [e]		X [f]	X	X	X	X	X	X	X	X	X	X [i]	X [k]	X [l]	X [l]
Adverse Events [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Conclusion/ Discharge from Study															X

Notes:

- Visit 1 and Visit 2 could occur on the same day but Visit 2 must be within 14 days of Visit 1.
- A 'patch' contains individual cells, each of the test products and the saline solution (reference product) will be applied into separate single cells. The order of application of the products into the cells will be randomized for each subject. The same sequence within each subject will be used throughout the induction phase. But the sequence will change for each subject for the challenge phase.
- Subjects should avoid missing the first day of application during the Induction Phase, or the day of application during the Challenge Phase.
- Subjects should avoid missing 2 or more consecutive visits or more than 2 alternate visits.

Footnotes:

a. Only inclusion criterion 6 will be assessed (by a qualified dermatologist) if visits are not combined.
b. A blinded dermatologist will review overall subject eligibility at the screening visit and the final visit and review any evaluator reaction score that is '+' or greater in the challenge phase to provide a narrative and classification as a potential sensitization reaction.
c. Patch Application; Patches will remain in place on the back for 48 (±4) hours during the week. If a patch is applied on a Friday it will remain in place for approximately 72 (±4) hours until Monday.
d. Patch Removal; Approximately 15-30 (maximum 1 hour) minutes following patch removal, subjects will rest in standard room conditions (18-26°C) prior to the test area assessment. Approximately 30 minutes up to 1 hour after each patch is removed, a trained, blinded evaluator will evaluate the test sites for visual signs of reactions using the scoring system detailed in Appendix 2 of Protocol.
e. Patch Assessment - A trained blinded evaluator will perform assessments of all test site areas (where each cell was in contact with the skin) for reactions using the scoring system detailed in Appendix 2 of Protocol.
f. Visit 2 (Day 1) - Baseline assessments of the proposed induction phase area on the subjects back will be made prior to product application.
g. Visit 12 (Day 36) - Challenge Phase patch application (after a 2-week Rest Phase of no patch /product application). The challenge patch will be applied to a naïve site on the subjects back and remain in place for 48 (±4) hours.
h. Visit 11 (Day 22) will be the final induction phase patch removal and test site area assessment.

i. Visit 12 (Day 36) - Baseline assessments of the proposed challenge phase area on the subjects back will be performed prior to the challenge patch (product) application.
j. Challenge patch removal.
k. Approximately 15-30 minutes (maximum 1 hour) following challenge patch removal, subjects will rest in standard room conditions (18-26°C) prior to the test area assessment. Approximately 30 minutes up to 1 hour following naïve site challenge patch removal a trained blinded evaluator will perform an assessment of the challenge test site areas (where each cell was in contact with the skin) for reactions using the scoring system detailed in Appendix 2 of Protocol.
l. Further challenge phase test site assessments will take place 24 (±4) and 48 (±4) hours after challenge patch removal.
m. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides written consent to participate in the study by completing the Informed Consent Form (ICF).

1.2 Study Objectives

The study objectives are as follows:

Objective(s)	Endpoint(s)
Primary	
To evaluate the cutaneous sensitization potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects potentially sensitized, as assessed by a dermatologist.
Secondary	
To evaluate the cutaneous irritation potential of three cosmetic facial skincare products compared to saline solution.	Proportion of subjects with a positive reaction (score of '+' or greater) as assessed by a trained evaluator.
Safety	
To evaluate the general safety of three cosmetic facial skincare products	Frequency and severity of Adverse Events

1.3 Treatments

The 3 test products are developmental cosmetic moisturizers (a serum, lotion, and cream), intended to be used topically by healthy individuals with dry facial skin. A fourth reference product will be used as a negative control; saline solution.

A controlled quantity (0.02 mL/cm^2) of each of the study products will be applied to a cell contained within an adhesive semi-occlusive patch system. The number of cells available in the patch system will be 6, of which 4 will be used for the products and 2 will be left blank. Each of the study products will be dispensed into 4 adjacent cells, per the randomization schedule. Three cells will be used for the test products (serum, lotion, and cream) and a fourth for the negative control (saline solution). No other products will be applied to subjects enrolled in this study.

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

Table 1-2 Study Products

	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	500ml
Product Master Formulation Code (MFC)	CCI	CCI	CCI	N/A Commercial Product
Application Quantity	0.02 mL/cm^2 Each product will be dispensed into an individual cell within the adhesive 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 cutaneous (dermal) application via semi-occlusive adhesive patch to the dorsum.			
Application Instruction	Applied on-site by technician			

1.4 Sample Size Calculation

Approximately 470 healthy subjects will be screened to randomize at least 280 subjects to ensure 200 evaluable subjects complete the entire study. If no reaction is observed in 200 subjects, the 95% exact confidence interval (CI) (Clopper-Pearson method for binomial proportions) for the true of rate of positive reactions (in the general population) would be [0, 1.83%].

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned for this study.

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 2 (induction phase) and Visit 12 (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 a single center study, pooling of centres is not applicable.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the Section 1-1 "Schedule of Activities" of the protocol and in Table 1-1 of this document. Any deviation from the study schedule may be reviewed on case-by-case basis at the Blinded Data Review Meeting (BDRM). A time window non-compliance listing will be produced for the 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 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 in induction phase of the study. An enrolled subject is a subject

who has signed informed consent and is eligible to proceed beyond the screening visit. As defined in Section 1.1 of this document, the subjects will be randomized twice during the study - once at Visit 2 (or Visit 1, if combined) for the induction phase and once at Visit 12 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 will be 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 (Table 14.1.1).

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) (Table 14.1.1).

Subject disposition including demographic data (age, sex, and race), screening date, start date and time of study product, last study product administration date and time, duration (in days) of study product usage (defined as: [(last date of study product – start date of study product) + 1]) and subject status (completer, Yes/No) will be listed (Listing 16.2.1.1) separately for induction and challenge phases and overall for both phases, for all randomized subjects. In addition, study completion/withdrawal date, duration (in days) in the study (defined as: [(date of completion or withdrawal – start date of study product) + 1], and the primary reason for withdrawal will be listed (Listing 16.2.1.1), by overall for all 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 categorized.

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

- Consent procedures
- Inclusion/Exclusion criteria
- 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 with reasons for deviations will be presented by reason (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 population defined for this study is as follows:

Population	Definition / Criteria	Analyses Evaluated
Randomized	All subjects randomized in induction phase regardless of whether they received study product. Any subject who receives a randomization number will be considered to have been randomized.	Protocol deviations, disposition and medical history listings
Safety	The Safety population will comprise of all randomized subjects who receive any application of the study products.	Primary endpoint, Secondary endpoint, Safety

NOTE:

- 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 status in induction phase will be used to define both populations.
- Please refer to Attachment 1: List of Data Displays which details the population to be used for each of the displays being generated.

This safety study is designed to evaluate cutaneous irritation (local tolerance) and sensitization potential. There are no efficacy outcomes. Therefore, analyses will be conducted only on the Safety population.

Subjects who are randomized in the study, but did not receive any application of the study products, will not be part of safety population. Exclusion of these subjects (if any) from the safety population will be reviewed during the BDRM prior to database lock and approved prior to unblinding. Listing 16.2.3.1 will display the subjects excluded from analysis population of all randomized subjects.

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 and frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for demographic variables by overall. These variables include age, gender, race, and Fitzpatrick skin type and will be presented for the Safety population (Table 14.1.3).

The Fitzpatrick scale is a numerical classification that is widely used by dermatologists to classify a person's skin type by their response to sun exposure.

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.

4.2.2 General Medical History

Medical history data will be listed (Listing 16.2.4.2) for all randomized subjects 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 Product, 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 and corresponding planned study product and actual study product received for all randomized subjects.

4.3.1 Study Product Compliance and Exposure

Product application will be conducted at study site. Any protocol deviations associated with product applications or patch adherence will be reviewed during BDRM prior to database lock.

In addition, product and patch application details will be listed (Listing 16.2.5.3) for all randomized subjects.

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, reason for medication, dose, frequency, route, start date, end date, and corresponding study days relative to first study product administration in the study (i.e. in the induction phase) in Listing 16.2.5.1 for all randomized subjects.

Prior medications are defined as those which stopped before the start date of first study product administration in the study (i.e. in the induction phase). If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to the start date of first study product administration in the study (i.e. in the induction phase), then the medication will be considered as concomitant medication.

Concomitant medications and concomitant non-drug treatments will be listed similarly (Listing 16.2.5.2) with either ongoing or end date displayed for all randomized subjects. Concomitant medications are defined as medications that are ongoing or started on or after the start date of first study product administration in the study (i.e. in the induction phase).

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 Primary Objectives

4.4.1 Primary Endpoint

4.4.1.1 Primary Endpoint Definition

The primary analysis will be based on potential sensitization reactions as assessed by a dermatologist and will be conducted on the Safety population.

For each subject who presents a positive reaction (a score of '+' or greater), a blinded dermatologist will further classify the reaction as potential sensitization (or not) at the final visit and provide a narrative description of the event. The dermatologist will not be scoring the reaction.

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 sensitisation reaction.

The number and percentage of subjects with any potential sensitization reactions versus those without any potential sensitization reactions will be presented by product group in Table 14.2.1 for safety population. In addition, the 95% exact CIs for binomial proportions using the Clopper-Pearson method will be computed for the proportion of subjects with potential sensitization reactions and will also be presented (Table 14.2.1).

Narrative description of all potential sensitization reactions will be provided in Listing 16.2.6.1 for safety population.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

No formal statistical analysis is planned for primary endpoint.

4.4.1.3 Supportive Analyses

N/A

4.4.2 Secondary Variables

There are no secondary variables defined for this study. Analysis of secondary objective/endpoint variables is 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 Objectives

4.5.1 Secondary Endpoint

The key secondary analysis will be based on the positive reactions scores (scores of '+' or greater) as assessed using the International Contact Dermatitis Research Group (ICDRG) scale described in Table 4-2 and will be conducted on the Safety population.

Any skin response at a patched site will be clinically assessed by a trained blinded evaluator using the scale recommended by ICDRG.

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:

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

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

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

The following ICDRG scores will be considered as negative reaction scores:

- "-"
- "+?"

In addition, the following ICDRG scores will be considered as positive reaction scores:

- "+"
- "++"
- "+++"

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 skin response at a patched site. If a subject discontinues prematurely, data up to the point of discontinuation will be used.

A trained, blinded evaluator will score the test sites for signs of reactions per ICDRG scale at all timepoints specified in Section 1-1 "Schedule of Activities" of the Protocol and Table 1-1 of this document. The evaluator score will be considered final.

The number and percentage of subjects with each category of score will be presented by phase, visit, and product group in Table 14.2.2 for Safety Population. All patch site assessments will be listed in Listing 16.2.6.2.

The number and proportion of subjects with any positive reactions scores (scores of '+' or greater) will be summarized in Table 14.2.3 for safety population by phase and across both

phases by product group using the maximum score. The 95% exact CIs for binomial proportions using the Clopper-Pearson method will be computed in Table 14.2.3 as well.

Narrative descriptions of all positive responses (scores of + or greater), in the challenge phase, will be listed (Listing 16.2.6.1) for 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 in skin health study.

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 Electronic Case Report Form (eCRF).

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the start date of first study product 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 study product application will be considered as non-treatment emergent.

The following summary tables and listings will be presented by study product and overall:

- Table of TEAEs by SOC and PT (Table 14.3.1.1).
- Table of TEAEs by Skin/Non-Skin and PT (Table 14.3.1.2).
- Table of treatment-related TEAEs by SOC and PT (Table 14.3.1.3).
- Table of treatment-related TEAEs 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 TEAEs by SOC, PT, and severity (Table 14.3.1.6).
- Table of treatment-related TEAEs 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 TEAEs leading to study or product discontinuation (Listing 14.3.2.3).
- Listing of TEAEs classified as 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

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**
• 6.8 Current and Concomitant Medication/Treatments(s): Medication or treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications or treatments taken after signing the informed consent, will be documented as concomitant medication/treatments.	• 4.3.2 Prior and Concomitant Medications: Prior medications are defined as those which stopped before the start date of first study product administration in the study (i.e. in the induction phase). If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to the start date of first study product administration in the study (i.e. in the induction phase), then the medication will be considered as concomitant medication. … Concomitant medications are defined as medications that are ongoing or started on or after the start date of first study product administration in the study (i.e. in the induction phase).	• Definition of Prior and Concomitant Medications was updated in order to keep consistent across other GSK CH studies.
• 12.2.5 Primary Analysis(es): The number and percentage of subjects with any potential sensitization reactions versus those without any potential sensitization reactions will be presented by visit and treatment group.	• 4.4.1.1 Primary Endpoint Definition The number and percentage of subjects with any potential sensitization reactions versus those without any potential sensitization reactions will be presented by product group.	• Potential Sensitization Reactions assessment performed by a blinded dermatologist will occur at final visit (i.e. Visit 15/Day 40), as defined in Section 4.1 of the Protocol.

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
		Because of this, the proportion of subjects with any potential sensitization reactions cannot be presented by visit, but only by product group.

Attachment 1: List of Data Displays

GSKCH_212383_TFL List_FinalV1.0_16Jul20´