GlaxoSmithKline
Consumer Healthcare

STATISTICAL REPORTING AND ANALYSIS PLAN

A Clinical Study to Assess the Local Cutaneous and Ocular Tolerance of Three Developmental Cosmetic Facial Skin Care Formulations in Healthy Females with Clinically Assessed Sensitive Skin

Protocol Number: 213059

Phase: N/A

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	18-Sep-2020	Not applicable (N/A)

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Abbreviations

Abbreviation	Term
AEs	Adverse Events
ANVISA	Agência Nacional de Vigilância Sanitária
BDRM	Blinded Data Review Meeting
COVID-19	Coronavirus Disease of 2019
eCRF	Electronic Case Report Form
GSK CH	GlaxoSmithKline Consumer Healthcare
ICF	Informed Consent Form
LAST	Lactic Acid Sting Test
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAEs	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 213059 version 1.0, dated 10-Mar-2020.

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, which determine the irritation potential (local tolerance) of cosmetic formulations to provide confidence the finished products are suitable for general sale.

The objective of this clinical study is to determine the local cutaneous and ocular tolerance of three developmental cosmetic facial skin care products (a serum, a lotion and a cream) in healthy females with clinically assessed sensitive facial skin, under normal conditions of use.

1.1 Study Design

This is a randomized, evaluator-blind (dermatologist and ophthalmologist), 3-arm, parallel-group, single-center, clinical 'in-use' study to determine the local cutaneous and ocular tolerance of 3 developmental cosmetic facial skin care formulations (a serum, a lotion and a cream) in healthy female subjects aged 18 to 65 years (inclusive) with clinically evaluated sensitive facial skin, as determined by a positive response to a Lactic Acid Sting Test (LAST).

A sufficient number of subjects will be screened (approximately 350) to randomize approximately 150 subjects to ensure that at least 135 subjects (45 per arm) complete the study.

Subjects will be clinically assessed by a qualified dermatologist for a baseline clinical assessment of signs and symptoms of facial cutaneous irritation and by a qualified ophthalmologist for a baseline clinical assessment of the signs and symptoms of ocular irritation. Subjects will be asked to answer a series of self-assessment questions on the facial cutaneous and ocular signs and symptoms of tolerance prior to any product application.

Site personnel involved in any clinical assessments will not be involved in the dispensing of test products and will be blind to product allocation. All reasonable efforts will be made to ensure the same assessors evaluate the same subject. Subjects will be required not to divulge the identity of the test products they have been using to any assessor, unless required for adverse event reporting or other medical or safety reason.

For eligible subjects, 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 answer the same series of self-assessment questions again on the facial cutaneous and ocular signs and symptoms of tolerance 1-2 hours after first product application.

Subjects will then be instructed to apply their assigned product at home again the same evening and twice-daily for a total of 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 the study site to final application at home. The final application of product will be at home on the morning of the final visit (Visit 3).

At the final visit (Visit 3), the dermatologist and ophthalmologist will conduct final clinical assessments of the signs and symptoms of cutaneous and ocular irritation, respectively. The dermatologist will determine whether any subject with an increase in total dermatologist score at final visit versus baseline experienced a clinically relevant positive reaction, or not. Similarly, a total ophthalmologist score will be calculated as the sum of the eczema of the eyelid, conjunctivitis, follicles and chemosis conjunctivae scores for the baseline visit and final visit. The ophthalmologist will determine whether any subject with an increase in total ophthalmologist score at final visit versus baseline experienced a clinically relevant positive reaction, or not.

Subjects will also be asked to conduct final self-assessment of the signs and symptoms of facial cutaneous and ocular irritation. Subjects will return their completed diary, supplied product and will then be discharged from the study.

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening	Randomization	Final Visit
	Visit 1 Day – 6 to 0	Visit 2 Baseline/Day 1[a]	Visit 3 Day 21 (+ 2)
Informed Consent (date and time captured)	X		
Demographics	X		
Medical History	X		
Medications Review (current/concomitant)	X	X	X
Inclusion/Exclusion Criteria	X [b]	X [c]	
Lactic Acid Sting Test (LAST)	X		
Fitzpatrick Skin Type Assessment	X		
Subject Eligibility for Enrolment	X		
Clinical Assessment by Dermatologist		X	X
Clinical Assessment by Ophthalmologist		X	X
Subject Continued Eligibility		X	X
Subject Self-Assessment		X [d]	X
Randomization		X	

Product and Diary Dispensing		X	
Supervised Product Application		X [e]	
Adverse Events (AEs) Review [f]	X	X	X
Product and Diary Return (Diary review)			X
Study Conclusion/Subject Exit from Study			X

Footnotes:

a. Visit 1 and Visit 2 may be combined. If Visit 1 and Visit 2 are not combined, then Visit 2 must occur within 7 calendar days of Visit 1

b. Inclusion criteria 1-5 and exclusion criteria 1-17 to be assessed at Visit 1

c. Inclusion criteria 6-10 and exclusion criteria 18-23 to be assessed at Visit 2 (if Visit 2 is not combined with Visit 1)

d. Subject self-assessment on Visit 2 will occur prior to randomization and product application (baseline) and 1-2 hours after first supervised product application

e. If Visit 2 is combined with Visit 1, there should be a minimum of 30 minutes after the LAST has completed before the supervised product application.

f. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by completing the Informed Consent Form (ICF).

1.2 Study Objectives

The study objectives and endpoints are defined in Table 1-2

Table 1-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate the local cutaneous tolerance profile (dermatologist assessed) of the 3 investigational products in healthy females with sensitive facial skin under normal conditions of use after 21 days.	Proportion of subjects determined by a dermatologist to have a clinically relevant positive outcome for cutaneous irritation after 21 (+2) days of product use.
Secondary Objectives	**Secondary Endpoints**
To evaluate the local ocular tolerance profile (ophthalmologist assessed) of the 3 investigational products in healthy females with sensitive facial skin under normal conditions of use after 21 days.	Proportion of subjects determined by an ophthalmologist to have a clinically relevant positive outcome for ocular irritation after 21 (+2) days of product use.

Objectives	Endpoints
To evaluate the local cutaneous tolerance profile (subject assessed) of the 3 investigational products in healthy females with sensitive facial skin under normal conditions of use.	• Change from baseline (prior to any product application) in subject self-assessment scores of signs and symptoms of cutaneous irritation 1-2 hours after first product application. • Change from baseline (prior to any product application) in subject self-assessment scores of signs and symptoms of cutaneous irritation after 21 (+2) days of product use.
To evaluate the local ocular tolerance profile (subject assessed) of the 3 investigational products in healthy females with sensitive facial skin under normal conditions of use.	• Change from baseline (prior to any product application) in subject self-assessment scores of signs and symptoms of ocular irritation 1-2 hours after first product application. • Change from baseline (prior to any product application) in subject self-assessment scores of signs and symptoms of ocular irritation after 21 (+2) days of product use
Safety	
To evaluate the general safety of the 3 investigational products.	Frequency and severity of Adverse Events.

The objective of this clinical study is to evaluate the local tolerance profile of 3 developmental skin care products; a serum, a lotion and a cream, in healthy females with clinically assessed sensitive facial skin under normal conditions of use.

Cosmetic manufacturers, even those with basic toxicologic testing and epidemiologic feedback on their products, are aware that l to 10% of all cosmetic users note and often complain of discomfort, primarily on the face. Therefore, if 10% or less of subjects in each treatment arm experience a significant increase in clinical signs of irritation as determined by a dermatologist, the product will be considered to have comparable tolerability to other commercially available cosmetic skin care products.

1.3 Treatments

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

Table 1-3 Study Product Supplies

	Investigational Product 1	Investigational Product 2	Investigational Product 3
Product Name	Developmental Serum	Developmental Lotion	Developmental Cream
Product Formulation Code (MFC)	CCI	CCI	CCI
Product Format	40 mL pump pack	50 mL tube	50 mL tube
Dispensing Details	A kit will be dispensed to each subject containing 2 bottles/tubes		
Application Quantity	To be used as per normal home use application in place of the current facial skin care product.		
Route of Administration	Topical dermal (facial) application		
Application Instructions	Apply twice daily to freshly cleansed skin, continue with your normal moisturizing routine.	Apply twice daily to freshly cleansed skin.	Apply twice daily to freshly cleansed skin.
Return Requirements	All used/unused samples to be returned to the study site		

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

Opaque bags will be supplied by the Clinical Supplies Department, GSKCH for dispensing of the kits to subjects.

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 tipped swabs - For LAST
- Paper towels

Supplies provided by the clinical investigational site must also be stored in compliance with the label requirements in a secure place with limited or controlled access.

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSK CH during the study in time for study close out visit.

1.4 Sample Size Calculation

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.

A sufficient number of subjects will be screened (approximately 350) to randomize approximately 150 subjects to ensure that at least 135 subjects (45 per arm) complete the study.

It is deemed that 45 subjects per arm are considered sufficient to assess the primary endpoint of the dermatologist assessment of signs and symptoms of cutaneous irritation total score. With 45 subjects completing each treatment arm and under an assumption of 4% incidence of clinically evaluated intolerance, each group has a 96.68% probability of observing less than 10% events in the study. All the groups are independent hence, the probability that all three groups individually result in less than 10% events is 0.9668^3. Which equates to 0.9037, or a power of 90.4% that the study will result in all three groups having less than 10% of subjects with clinical intolerance.

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

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

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.

3.4 Time Points and Visit Windows

The time points and visits for this study are defined in the section "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).

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 with oversight from GSK CH. 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. Also, the assessment of the number of subjects who have dropped or discontinued from the study due to COVID-19 (Coronavirus Disease of 2019) pandemic related events and the potential need of a sensitivity analysis will be discussed during BDRM. Any major changes to planned analyses will need an amendment to RAP (Reporting and Analysis Plan).

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.

The number of subjects screened, enrolled and randomized will be presented in PPD .

The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized will be displayed. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of randomized subjects who complete and discontinue the study, broken down by reason for discontinuation, by study product and overall will be displayed. The percentages will be based on the number of subjects randomized.

PPD will also summarize the number and percent of subjects assigned to the Safety Population. The summary will be presented by study product and overall. The percentages are based on the total number of subjects randomized.

Subject disposition including demographic data (age, sex and race), screening date, study product start date and time, study product end date and time, duration of study product in days (defined as [(last date of study product application - start date of study product) + 1] for all subjects completing the study as per protocol, and [(date of withdrawal - start date of study product) + 1] for all subjects dropping out of the study), subject status (completer, Yes/No), study completion/withdrawal date, duration in the study in days (defined as [(date of completion or withdrawal - start date of study product) + 1], and the primary reason for withdrawal will be listed (PPD) by study product.

Subject disposition information will be listed for non-randomized subjects (PPD), 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 limited to the following:

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

The specific details of the important protocol deviations will be listed in Protocol Deviation Management Plan and assessment process will be specified in the Blind Data Review Plan. 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 summarized in PPD by study product and listed in PPD .

All protocol deviations collected on the protocol deviation electronic case report form (eCRF) will be listed in PPD . 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	Comprise of all randomized subjects who receive at least one application of study product (serum, lotion, or cream). This population will be based on the study product the subject actually received.	Primary endpoint, Secondary endpoints, Safety
Randomized	This population will be based on the study product to which the subject was randomized, regardless of whether they received study product. Any subject who receives a study product randomization number will be considered to have been randomized.	Protocol deviations, Disposition and medical history, Prior and concomitant, Primary and Secondary listings

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

PPD will display all randomized subjects included and excluded from the safety population.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic and Baseline 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 by study product and overall. These variables include age, gender, race and Fitzpatrick skin type and will be presented for the safety population (PPD).

Table 4-1 Fitzpatrick Skin Type Grading

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 and baseline characteristics information will be listed (PPD) for all randomized subjects.

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 the study.

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

Randomization details will be listed, including the randomization number, the planned randomized study product, the actual randomized study product and the randomization date (PPD).

The study product kit allocations will be listed (PPD), including kit number and study product information.

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 who took 80% ~ 120% of the number of prescribed uses of study product (PPD).

The compliance (%) will be calculated as [(actual number of study product applications/ expected number of study product applications) × 100],

Where,

Expected number of study product applications = twice daily application for a total of 21 (+2) days;

Actual number of study product applications = expected number of study product applications − missed study product applications + additional study product applications.

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

Also, the number of missed and additional study product application will be summarized 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.

Prior medication will be listed by subject, with drug name, GSK drug synonym, reason, route, dose, frequency, start date and end date both relative to study product start date (PPD). Prior medications are defined as those, which stopped before the first application of the study product. If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to the first application of study product then the medication will be considered as a concomitant medication.

Concomitant medications and concomitant non-drug treatments/procedures taken during study product application will be listed similarly (PPD) with either ongoing or end date

displayed. Concomitant medications are defined as medications that started or stopped on or after the first application of the 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

4.4.1 Primary Endpoint

This is a non-comparative study and the three, separate, within group, assessments will form the primary analysis. No comparison between groups will be made. No formal statistical inference will be performed. The primary analysis will be performed using the safety population.

4.4.1.1 Primary Endpoint Definition

The primary endpoint within each group will be the proportion (number and percentage) of subjects determined by the study dermatologist to have a clinically relevant positive outcome for cutaneous irritation after 21 (+2) days of study product use, which is defined as an increase in total cutaneous irritation score at Day 21 (+2) versus baseline and dermatologist characterization of this as a clinically- relevant positive outcome (recorded as Yes/No on in the CRF). It will be presented in PPD by study product and overall.

The dermatologist signs and symptoms of cutaneous irritation total score will be calculated as the sum of the individual cutaneous response attributes (erythema, dryness, scaling, and edema). Additionally the change from baseline in the total score will be summarized by number and percentage of subjects by visit for each study product and overall (PPD).

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 = cutaneous response score of erythema + cutaneous response score of dryness + cutaneous response score of scaling + cutaneous response score of edema

Change from baseline in cutaneous irritation total score = total score at day 21(+2) – total score at baseline

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

Table 4-2 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 cutaneous response score of erythema = 3, cutaneous response score of dryness = 0.5, cutaneous response score of scaling = 2 and cutaneous response score of edema = 0.5.

Then the cutaneous irritation total score will be:

Total score = 3 + 0.5 + 2 + 0.5 = 6.

In addition, the individual attribute responses, total score, change from baseline, clinical relevance and narratives will be listed (PPD) for each subject by visit and by study product.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

This is a non-comparative study and the three, separate, within group assessments will form the primary analysis. No formal statistical inference is planned for primary endpoint.

4.4.1.3 Supportive Analyses

N/A

4.4.2 Secondary Endpoint 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. Subjects who withdraw from the study prematurely will be included in analyses up to the point of discontinuation.

4.5 Analysis of Secondary Endpoints

4.5.1 Secondary Endpoints

All secondary analyses will be performed using the safety population and no formal statistical inference will be performed.

4.5.1.1 Secondary Endpoint Variable 1

The key secondary endpoint will be the proportion (number and percentage) of subjects determined by the study ophthalmologist to have a clinically relevant positive outcome for ocular irritation after 21 (+2) days of study product use, which is defined as an increase in total ocular irritation score at Day 21 (+2) versus baseline and ophthalmologist characterization as a clinically-relevant positive outcome (recorded as Yes/No on in the CRF). It will be tabulated in PPD by study product and overall.

The ophthalmologist signs and symptoms of ocular irritation total score will be calculated as the sum of the individual ocular response attributes (eczema of the eyelid, conjunctivitis, follicles, and chemosis conjunctivae). Additionally the change from baseline in the total score will be summarized by number and percentage of subjects by visit for each study product and overall (PPD)

Calculations of ophthalmologist assessment of signs and symptoms 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 (+2) − total score at baseline.

Where, the ocular response score is described in the Table 4-3

Table 4-3 Ophthalmological Evaluation

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)

For example, if the ocular response score of eczema of the eyelid = 0.5, ocular response score of conjunctivitis = 0.5, ocular response score of follicles = 2 and ocular response score of chemosis conjunctivae= 0.5.

Then the ocular irritation total score will be:

Total score = 0.5 + 0.5 + 2 + 0.5 = 3.5.

In addition, the individual attribute responses, total score, change from baseline, clinical relevance and narratives will be listed (PPD) for each subject by visit and by study product.

4.5.1.2 Secondary Endpoint Variable 2

The other secondary endpoints will be change from baseline (prior to any product application) in the total subject self-assessment scores for signs and symptoms of cutaneous irritation at 1 to 2 hours after first product application and 21 (+2) days of twice daily product use. It will be summarized by number and percentage of subjects by visit for each study product and overall in PPD .

Calculations of subject self-assessment of sign and symptoms of cutaneous irritation total score and changes from baseline in total score:

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

Change from baseline in subject self-assessment of sign and symptoms of cutaneous irritation total score at 1 to 2 hours = total cutaneous score at 1 to 2 hours − total cutaneous score at baseline

Change from baseline in subject self-assessment of sign and symptoms of cutaneous irritation total score at Day 21(+2) = total cutaneous score at day 21 (+2) − total cutaneous score at baseline

Where, the subject self-assessment of cutaneous response score is described in the Table 4-4

Table 4-4 Subject Self-Assessment Scale for Signs 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)

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

4.5.1.3 Secondary Endpoint Variable 3

The last secondary endpoint will be change from baseline (prior to any product application) in the total subject self-assessment scores for signs and symptoms of ocular irritation at 1 to 2 hours after first product application and 21 (+2) days of twice daily product use. It will be

summarized by number and percentage of subjects by visit for each study product and overall in PPD .

Calculations of subject self-assessment of sign and symptoms of ocular irritation total score and changes from baseline in total score:

Subject self-assessment of sign and symptoms of ocular irritation total score = ocular response score of redness + ocular response score of dryness + ocular response score of stinging/ burning + ocular response score of itching

Change from baseline in subject self-assessment of sign and symptoms of ocular irritation total score at 1to 2 hours = total ocular score at 1 to 2 hours − total ocular score at baseline

Change from baseline in subject self-assessment of sign and symptoms of ocular irritation total score at Day 21(+2) = total ocular score at day 21 (+2) − total ocular score at baseline

Where, the subject self-assessment of ocular response score is described in Table 4-5

Table 4-5 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)

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

4.5.2 Pharmacokinetic (Secondary)

N/A

4.6 Analysis of Safety

All safety data will be reported for the Safety Population as per actual study product received. The safety profile of the study products 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).

AEs will be classified as Skin (Face/Non-Face) 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 first treatment application (if this date is missing a suitable alternative will be used eg date of

randomization). Adverse events 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 treatment.

- Table of TEAEs by SOC and PT (PPD).
- Table of TEAEs by Skin(Face/Non-Face)/Non-Skin and PT (PPD)
- Table of TEAEs by SOC, PT and severity (PPD)
- Table of treatment-related TEAEs by SOC and PT (PPD)
- Table of treatment-related TEAEs by Skin(Face/Non-Face)/Non-Skin and PT (PPD)
- Table of treatment-related TEAEs by SOC, PT and severity (PPD)
- Table of treatment-related treatment-emergent serious adverse events (SAEs) by SOC and PT (PPD) [only produced if there are more than 5 SAEs]
- Table of AEs related to COVID-19 by SOC and PT (PPD)
- Listing of all AEs (PPD for all randomized subjects; PPD for non-randomized subjects)
- Listing of all AEs related to COVID-19 Subjects (PPD for all screened subjects)
- Listing of deaths (PPD)
- Listing of non-fatal SAEs (PPD)
- Listing of TEAEs leading to study product discontinuation (PPD)
- Listing of TEAEs classified as skin(Face/Non-Face) (PPD)

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

4.6.2 Other Safety Variables

Other safety variables are listed below:

- COVID-19 infection diagnosis and assessment
- COVID-19 infection diagnosis and assessment – symptoms for symptomatic subjects

COVID-19 diagnosis and assessment and the symptoms for symptomatic subjects data will be listed (PPD and PPD , respectively) for all screened subjects.

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 the first supervised test product application (serum, lotion or cream) 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.
• Section 12.3.7: • Prior medications, concomitant medications and significant non-drug therapies taken during treatment will be listed for the safety population.	• Prior medications, concomitant medications and concomitant non-drug treatments/procedures taken during treatment will be listed for the Randomized population.	• To maintain the current listing presentation
• N/A	• Section 4.6: Safety analysis for COVID subjects added	• This is not part of the protocol and covered under RAP

Attachment 1: List of Data Displays

PPD