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CLINICAL STUDY PROTOCOL

Protocol Status	Final
Version	2.0
Protocol Date	27 September 2021
Protocol Number	PPD
PPD	PPD
Study Title	A Clinical Study to Evaluate the 8-Hour Moisturization Efficacy of an Over-The-Counter Sunscreen Lip Balm After a Single Application
GSK CH Study Number	218006
Sponsor	GSK Consumer Healthcare Holdings (US) LLC (GSK CH) PPD
Sponsor Representative	PPD Sr. Clinical Study Manager
Test Material	ChapStick Active Performance UnScented CCI
Principal Investigator	PPD Manager, Bioinstrumentation
Sub-Investigator	PPD Diplomate, American Board of Dermatology
Clinical Site	PPD
Institutional Review Board	Advarra IRB PPD

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1.0 OBJECTIVE

The objective of this clinical study is to evaluate the 8-hour moisturization efficacy of an over-the-counter (OTC) sunscreen lip balm after a single treatment application.

2.0 CLINICAL STUDY PRODUCT

A single sunscreen lip balm will be evaluated - ChapStick Active Performance UnScented CCI

The test material will be supplied labelled with the GSK CH study number (218006) and product identifier.

Prior to study start, and for the duration of the study, the test material will be stored securely at ambient conditions. Unused test material will be returned to the Sponsor.

The Sponsor assumes responsibility for the purity, stability, characterization and adequate preservation of the test products. The Sponsor assumes responsibility for determining the test material is safe for use in humans as described in this protocol.

3.0 STUDY DESIGN/RANDOMIZATION

This is a randomized, controlled, open label clinical study in healthy adult volunteers designed to evaluate the 8-hour moisturization efficacy of the test material using corneometry.

Skin hydration ('moisture') will be assessed before and after a single treatment with test material (2, 4, 6, and 8 hrs post-treatment), compared to 'no treatment' as control. A 1-week (7 days ± 2 days) skin conditioning phase will precede the test day (Visit 2), during which study participants will use only the soap provided for personal washing. No other products will be applied to the skin of the test sites for the duration of the study.

Each participant will have 2 test sites delineated on the skin of their volar forearm (one per arm). Eligible participants will be assigned to treatment based on the randomization schedule at the start of the test day (Visit 2). Assignment of study treatments shall follow the randomization schedule generated by PPD n accordance with SOP CCI The test material and untreated control sites will be randomized between the right and left volar forearms in accordance with the computer-generated randomization table. The randomization table will be generated prior to the study start date using analysis software SAS Version 9.4 or higher. The statistician responsible for data analysis will not have access to the randomization code until after the database has been locked.

The Clinical Research Coordinator (CRC) will record corneometer readings on paper score sheets. The raw data will be transcribed into an Excel spreadsheet; Transcription review/ database release for statistical analysis will be performed in accordance with SOP CCI

Given the likely visual/textural differences between the treated and untreated test sites (test material is a waxy solid), the corneometer operator cannot be blinded. To help minimize bias, the corneometer operator will not participate in treatment application and the technician(s) responsible for treatment application will not be present for, or influence, the corneometer assessments. In addition, the randomization table and the seed will be kept in a secure location; the statistician responsible for data analysis will remain blinded to the treatment allocation until after the database has been locked. After the database lock, the statistician will unblind the study by assigning the treatment codes for the analysis.

Study duration is expected to be 5-10 days.

4.0 STUDY POPULATION

Approximately 38 participants will be enrolled in this study with the goal to complete with at least 30 subjects. Potential study participants will be recruited from PPD Volunteer Database as described in SOP CCI

Study participants will be healthy male and female volunteers of any ethnicity/skin type. No discrimination of any kind (e.g. social class, gender, skin color, ethnicity) should preclude eligible participants from participating in the study.

Eligible participants must satisfy the following inclusion and exclusion criteria. Current and historical medical conditions, medications and treatments will be self-reported by study participants.

4.1. INCLUSION CRITERIA

a) Participant must provide a signed and dated, legally effective, informed consent document, which indicates they have been informed of, and understand, all pertinent aspects of the study, before any study procedures are performed (in conformance with 21 CFR Part 50: 'Protection of Human Subjects.');

b) Participant must be 18-70 years old inclusive at the time of consent;

c) Participant must provide relevant details of their medical history and current/recent medications and treatments;

d) Participant has completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;

e) Participant must have completed a Photo Release Form;

f) Participant must be able to read, write, speak and understand English;

g) Participant must be in good general health;

h) Participant must have a valid form of personal identification (photo ID, driver's license, passport, permanent resident card, military ID card; forms cannot be expired);

i) Male and female participants of child-bearing potential must agree to use a highly effective method of contraception for the duration of the study and for 14 days after treatment application;

Note: A participant is considered to be of child-bearing potential if, in the opinion of the PI, they are biologically capable of having children and sexually active.

j) Participant must agree to be sequestered in a temperature/humidity monitored test room at the clinical site (temperature 21°C ± 2°C, relative humidity (RH) 50% ±10%) for the duration of the test day (Visit 2), approximately 9.5 hours;

k) Participant must agree to bring their own food (dry) and beverages to be consumed on the test day (Visit 2);

l) Participant must agree not to consume hot or very cold food/beverages on the test day (Visit 2);

m) Participant must agree to use the non-moisturizing soap provided for all personal washing during the conditioning phase of the study;

n) Participant must agree to wear loose clothing for ease of access to the test sites (arms) and/or sleeves that can be easily rolled up;

o) Participant must agree not to introduce any new cosmetic/toiletry products into their personal care regimen during the study;

p) Participant must agree to refrain from any physical effort which might result in thermal regulation by sweating (e.g., exercise class, rapid climbing of flights of stairs, jogging, cycling, brisk walking) for at least 2 hours prior to arriving the test day (Visit 2);

q) Participant must agree to refrain from prolonged or excessive UV exposure (e.g., sun-bathing, tanning beds) for the duration of the study;

r) Participant should be dependable and able to follow directions as outlined in the protocol and ICF.

4.2. EXCLUSION CRITERIA

a) Participant with scheduled or planned Covid-19 vaccination during likely dates of study participation;

b) Female participant who is pregnant, planning to become pregnant during the study, or breastfeeding (self-reported);

c) Participant with a history of sensitivity to any ingredient of the test material or skin marker pen, or latex; or any known sensitivities/allergies, including but not limited to cosmetic/toiletry products and topically applied skin treatment products/drugs;

d) Participant with a history of an acute or chronic dermatologic, medical and/or physical condition that would, in the opinion of the investigator, confound study outcomes or increase the risk associated with participation;

Note: dry skin is not an exclusion per se; however, a participant with a level of dryness on the skin of the volar forearms that would, in the opinion of the investigator, confound study outcomes or increase the risk associated with participation should be excluded.

e) Participant with a history of skin cancer, or currently undergoing treatment for active cancer of any kind;

f) Participant with diabetes;

g) Participant with a planned medical treatment/vaccination (other than the Covid-19 vaccination) during the study that would, in the opinion of the investigator, confound study outcomes or increase the risk associated with participation;

h) Participant with a planned hospitalization during the study;

i) Participant who is currently using, or has used in the past week, any systemic or topical corticosteroid, non-steroid anti-inflammatory drug, antihistamine, sympathomimetic, and/or vasoconstrictor or any other medication that would, in the opinion of the investigator, confound study outcomes or increase the risk associated with participation;

j) Participant who is unwilling to cease use of *personal care products (e.g. moisturizers, lotions, sunscreens, sunless tanners) and/or topical medications at the test sites* for the duration of the study;

k) Participant who has had extensive UV exposure within 3 weeks of Screening (Visit 1);

l) Participant with visual signs of irritation, sunburn, rashes, scratches, burn marks, scarring at the test sites that would interfere with corneometry measurements;

m) Participant with excessive hair at the test sites that would interfere with corneometry measurements;

n) Participant who has participated in a study involving the arms as a test site, or any other type of clinical study, within three weeks of screening (Visit 1);

o) Participant who is an employee/contractor or immediate family member of the PI, study site or Sponsor.

4.3. PARTICIPANT RESPONSIBILITIES

Lifestyle Considerations:

For the duration of the study, participants should be:

- Dependable, willing and able to keep all study appointments, and follow study instructions.
- Willing to not begin another clinical study while participating in current study.
- Willing to wear loose-fitting clothing to facilitate access to the forearms during study visits.
- Willing to continue with use of their current personal care products and avoid use of any new personal care products (e.g., makeup, cleanser).
- Willing to cease use of any personal care products (e.g., moisturizers, lotions, sunscreens, sunless tanners) and topical medications on the test areas.
- Willing to avoid prolonged or excessive UV exposure (e.g., sun-bathing, tanning beds).
- Willing to inform study staff about any side effects, changes in their health/medications, pregnancy and study-related problems.

Contraception:

All male participants able to father children and female participants who are of child-bearing potential, sexually active and at risk of pregnancy must agree to use a highly effective method of contraception, consistently and correctly, for the duration of the study and for 14 days after their last assigned treatment (recommendation/discretion of the volunteer). This requirement does not apply to females of child-bearing potential with same sex partners or to participants who are, and will continue to be, abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

The PI, or CRC, will discuss the need to use highly effective contraception, consistently and correctly, with the participant; the conversation will be documented. In addition, the PI, or CRC, will instruct the participant to call the site immediately if their contraception method is discontinued or if pregnancy is known, or suspected, in either the participant or the participant's partner.

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The following is an all-inclusive list of female contraceptive methods that meet the GSK definition of highly effective for avoiding pregnancy (i.e., have a failure rate of less than 1 % per year when used consistently and correctly and, when applicable, in accordance with the product label). Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the trial, and this male is the sole partner of the female participant. The documentation on male sterility can come from site personnel review of medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Male participants with female partners of child-bearing potential must comply with the following contraception requirements for the duration of the study and for 14 days after their last assigned test treatment.

- Vasectomy with documentation of azoospermia. The documentation on male sterility can come from site personnel: review of the participant's medical records, medical examination and/or semen analysis, or medical history interview.
- Male condom plus partner use of one of the contraceptive options below that meets the effectiveness criteria including a less than 1% rate of failure per year, as stated in the product label:
    - Contraceptive subdermal implant
    - IUD or intrauterine system
    - Combined estrogen and progestogen oral contraceptive
    - Injectable progestogen
    - Contraceptive vaginal ring
    - Percutaneous contraceptive patches

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The PI, or CRC, will confirm the participant has had instruction in how to properly use their method of contraception from an appropriately trained health care professional and will document this conversation.

4.4. PARTICIPANT DISCONTINUATION AND WITHDRAWAL

A participant may be discontinued or withdraw from study participation at any time if the participant or the PI (or CRC) feels it is not in their best interest to continue. The following is a list of possible reasons for study discontinuation.

- Participant develops a condition listed in the exclusion criteria or hypersensitivity or takes a contra-indicated medication/treatment.
- Non-compliance with the requirements of the protocol.
- Failure to follow site staff instructions.
- Failure to attend scheduled study visits.
- Adverse event (AE) that, in the opinion of the PI, means it would be in the participant's best interest to discontinue study participation.
- Protocol violation requiring documentation of deviation.
- Sponsor request for early termination of study.

Participants are free to withdraw from study participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the PI, or CRC, to ascertain the reason for withdrawal. This will be recorded in source documentation and included in the final report.

4.5. DISPOSITION OF WITHDRAWN PARTICIPANTS

The date a participant is withdrawn from the study and the reason for discontinuation will be recorded in source documentation. If a participant fails to return for scheduled study visits, the PI, or CRC, will make every reasonable effort to contact the participant and determine why they failed to attend. This information will be recorded in source documentation. When a participant is withdrawn (regardless of reason), the PI, or CRC, will encourage the participant to return to site to complete all evaluations which may be necessary to assure that the participant is free of untoward effects, and to seek appropriate follow-up for any unresolved AEs.

4.6. PARTICIPANT REPLACEMENT

Discontinued participants will not be replaced. Any valid data collected for a participant up to the point of discontinuation may be used in the statistical analysis (see Section 7).

5.0 STUDY EVALUATIONS

5.1. CORNEOMETER

Corneometry is a well-established instrumental technique designed to measure changes in the capacitance of the skin resulting from changes in the degree of hydration; it is particularly sensitive to low hydration levels. Corneometry uses a capacitance sensor to measure the dielectric constant of the outer layers of the skin (stratum corneum). The dielectric constant is directly proportional to the water content of the skin (skin hydration. The capacitance of the skin surface is expressed in arbitrary units of skin hydration; the higher the corneometer reading, the more hydrated ('moist') the skin. The corneometer model being used for this study is a Derma Unit SSC 3 Courage + Khazaka (Cologne, Germany). The corneometer will be calibrated at the beginning of each test day in accordance with PPD SOP CCI

5.2. TEMPERATURE/HUMIDITY MONITORED TEST ROOM (VISIT 2)

The temperature/humidity monitored test room will be maintained at a temperature of 21±2°C and 50±10% RH. Temperature and humidity will be recorded/documented on an hourly basis throughout the test day, starting at least an hour before the first subject starts to acclimate and until the last subject exits the facility.

Study participants will acclimate in the temperature/humidity monitored test room for at least 30 mins before their pre-treatment (baseline) corneometer measurement and remain sequestered in the test room for the duration of the test day (Visit 2), approximately 9.5 hours. Participants will take their meals in the test room (hot or very cold food/beverages are not permitted as this can affect corneometry readings). Restroom breaks can be taken as needed. However, subjects must return to the test room at least 30 minutes prior to their next scheduled corneometer measurements. No other breaks outside of the temperature/humidity-controlled test room will be permitted, unless deemed an emergency. The corneometer will be housed in the test room.

5.3. DIGITAL CAMERA

Photographs may be taken of test sites using a Canon DS126621 (or similar system) to document unexpected results/AEs if requested by the PI, CRC, or the Sponsor. Photographs will not reveal participant identity.

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6.0 STUDY PROCEDURES

The study schedule is tabulated below.

Study Procedures and Evaluations	Visit 1 Screening	Conditioning Phase (7±2 days)	Visit 2 Test Day				
			Baseline	2 Hours (±15 mins)	4 Hours (±15 mins)	6 Hours (±15 mins)	8 Hours (±15 mins)
Written Informed Consent Obtained	X						
Collection of Medical History and Concomitant Medications	X						
Skin Examination	X						
Confirm Qualification Against Inclusion/Exclusion Criteria	X						
Provide Eligible Participants with Conditioning Phase Soap, Usage Instructions & Diary	X						
Record Any Changes in Health/ Concomitant Medications			X				
Assess Study Compliance, Including Collection & Review of Conditioning Phase Diary			X				
Participant Enters Temperature/ Humidity Monitored Test Room for Duration of Test Day; Acclimation Begins > 30 minutes (mins) prior to Pre-Treatment (Baseline) Corneometry Measurement			X				
Identify & outline two test sites (one per arm) with skin marker			X				
Pre-Treatment Corneometer Measurements			X				
Apply Test Material to Assigned Test Site According to Randomization Schedule			X				
Post-Treatment Corneometer Measurements				X	X	X	X
Monitor for Adverse Events*	X		X	X	X	X	X
Study Conclusion							X

* Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs will be collected from immediately after the participant provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

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6.1. DAY 1: SCREENING/ENROLLMENT

Written informed consent will be obtained from each potential participant prior to entering the study (Informed Consent of Human Subjects, 21 CFR Part 50). The CRC will ensure the informed consent process is conducted in accordance with applicable local, state, and federal laws and regulations.

Prospective participants will report to the study site and be provided with a copy of the Informed Consent Form (ICF) and a Photo Release Form. Site staff will answer any questions they may have about the study. If they chose to participate, site staff will obtain the applicable signatures on the enrollment documentation, starting with the ICF. Each participant will sign two copies of the ICF, one will be retained in the Investigator Trial Master File, the other will be given to the study participant.

Site staff will then record the participant's relevant Medical History, any concomitant medications/treatments and responses to inclusion/exclusion questions in source documentation. Participant date of birth will not be recorded in study documentation. The skin of the participant's volar forearms will be examined and suitability to participate reviewed against the relevant inclusion/exclusion criteria; findings will be recorded in source documentation. As required, site staff will consult the PI and/or SI (study physician/dermatologist) regarding participant responses and the findings of the skin examination to confirm qualification.

Qualified participants will be enrolled and scheduled for study procedures; ineligible participants will be disqualified.

Each qualifying participant will be assigned a unique identifying screening number (different from the randomization/subject number) in order of enrollment and provided with non-moisturizing soap and a diary; provision of soap and diary will be recorded in source documentation. Participants will be instructed to use the soap provided for all body washing during the conditioning phase (between Visits 1 and 2) and record each soap usage in the diary. Participants will be instructed to refrain from use of moisturization products for the duration of the study.

Enrollment procedures will be completed in a private setting. If the participant has questions about their rights, they may contact the IRB at any time during or after trial participation.

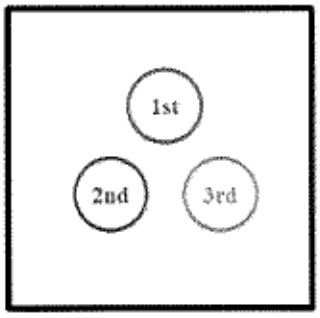
Randomization number assignment will take place prior to study start at Visit 2.

6.2. DAY 2: TEST DAY

Participants will report to the clinical site with clean volar forearms and, as instructed, free from lotions and any other topically-applied products. Each will be questioned non-directively to assess compliance with the requirements of the protocol and to identify changes in health/concomitant medications. Any changes/AEs will be recorded in source documentation. Conditioning phase diaries will be collected and reviewed for study compliance. Randomization/subject number will be assigned.

Participants will enter the temperature/humidity monitored test room and acclimate for at least 30 minutes prior to their baseline corneometry measurements; they will remain in the test room until completion of the '8 hour' corneometer measurements.

Using a skin marker and template, a study technician will identify two test sites (one per arm) for each participant and delineate a 6.3 cm x 6.3 cm square (approximately 40 cm^2 in area) on the skin of each volar forearm. Three corneometer measurements will be taken per test site at each assessment time point (i.e., pre-treatment (baseline) and 2-, 4-, 6- and 8-hours post-treatment). Each measurement will be taken with the corneometer probe tip in contact with the skin; for each test site, the three readings will be taken at different, but nearby locations within the designated test area (see example below). Corneometer readings will be recorded in source documentation.



6.2.1. Study Treatment Application

The study technician will apply 80 ± 2 mg (2.0mg/cm^2 ± 0.05 mg/cm^2) of the test material to its' assigned test site using a fingercot. A double-weighing procedure will be used (weighing boat + test material + fingercot, prior to and after application) to ensure the required quantity of product is delivered. Using the fingercot and light pressure, the test material will be evenly spread over the test site.

No treatment will be applied to the test site on the opposing volar forearm (control site).

7.0 STATISTICAL ANALYSIS

Statistical analyses will be performed by PPD with oversight from GSK CH, using analysis software SAS Version 9.4 or higher. Since all methodologies for the summary and statistical analyses of the data collected in this study are specified in the protocol, a separate Reporting Analysis Plan (RAP) will not be created. Any major modification of the analysis plan will be documented as a protocol amendment.

7.1. SAMPLE SIZE DETERMINATION

Sufficient participants will be screened to enroll approximately 38 healthy adult participants and with the goal of 30 participants to complete all study procedures. The sample size calculation is based on medium to large effect size (standardized effect size = 0.75 or above) for this type of treatment and power = 0.90 at a 0.05 level when comparing difference between treated and untreated groups on primary end point (mean changes from baseline in corneometer measurements).

7.2. ANALYSIS POPULATIONS

The primary analysis population will include all eligible participants (qualified based on the inclusion/exclusion criteria) who were randomized, received study treatment and provided at least one post-treatment efficacy assessment.

The safety population is defined as all randomized participants who received study treatment.

7.3. DATA EXCLUSIONS

Deviations from the protocol will be identified by review of individual participant data; affected data will be excluded from the efficacy analysis prior to database lock, with the agreement of the biostatistician and the CRC. Data exclusions and the reasons for exclusion from the primary analysis population will be provided in the clinical study report (CSR).

7.4. PARTICIPANT DISPOSITION, DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The safety population will be used for participant disposition, demographic characteristics (age, sex) and other baseline characteristics. Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables, and frequency and percentages for categorical variables) will be tabulated and presented.

7.5. EFFICACY ANALYSIS (CORNEOMETER)

The primary analysis population will be used for the efficacy analysis. The primary endpoint is mean changes in corneometry measurements at each timepoint after the baseline.

The mean of the 3 corneometer measurements obtained for each test site at each designated time point (pre-treatment (baseline) and 2-, 4-, 6- and 8-hours post-treatment) will be calculated for each individual participant. An analysis of covariance (ANCOVA) model will be used with treatment, timepoint and subject (random effect) as terms in the model, and baseline value as covariate. The adjusted means of the two treatments, the treatment differences together with the 95% confidence interval (CI) and p-values will be provided.

Change from baseline and percent of participants improved will also be calculated at each post-treatment time point. Change from baseline will be calculated as post-baseline assessment value minus the baseline assessment value. Percent of participants improved will be calculated as number of participants who exhibited an improvement (positive change indicates improvement) divided by the total number of participants included in the statistical analysis. Pairwise comparisons will be applied using the ANCOVA model to determine the differences in corneometer measurements between treated and untreated sites at Baseline and the differences in change from Baseline between treated and untreated sites at each post-treatment interval. A plot of mean corneometer measurements over time will be presented by treatment and assessment time points.

The null hypothesis tested is there is no difference in mean corneometer values between the treatment and no treatment.

- $H_0: \mu_1 = \mu_2$

The alternative hypothesis is there is difference in mean corneometer value between the treatment and no treatment.

- $H_0: \mu_1 \neq \mu_2$

Statistically significant treatment differences will be declared if the probability of random occurrence between the two treatment groups (p) is ≤ 0.05. All tests will be 2-sided.

Individual participant results will be tabulated along with summary statistics, including number of non-missing observations (n), mean corneometer values, standard deviation (SD), median, minimum (Min) and maximum (Max).

Calculations and statistical analyses will be reviewed by PPD Quality Assurance.

7.6. HANDLING OF DROPOUTS AND MISSING DATA

Participants who withdraw from the study or are discontinued will be included in the efficacy analysis up to the point of discontinuation. No data will be imputed in the case of dropouts or missing data.

7.7. SAFETY ANALYSIS

A summary of safety data (AEs/SAEs), or confirmation there were no AEs, will be provided in the CSR; no coding or analysis of safety data will be performed.

8.0 ADVERSE EVENTS

The PI, or designated CRC(s), is responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or a serious adverse event (SAE). Adverse events will be reported for the safety population.

The PI, or designated CRC(s), is responsible for following up SAEs; AEs considered to be test product (or study procedure) related; and AEs that caused the participant to discontinue or be withdrawn from the study.

8.1. DEFINITION OF AN ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a test material, whether or not considered related to the test material. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a test material.

Events Meeting the AE Definition:

- Unexpected or unusual reactions which occur within a test site will be recorded as AEs.
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen after test material administration, considered clinically significant in the medical and scientific judgment of the PI or medically qualified designee (i.e., not related to progression of an underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition after test material administration.
- New conditions detected or diagnosed after test material administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either test material or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- 'Lack of efficacy' per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfil the definition of an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with an underlying disease, unless judged by the PI, or medically qualified designee , to be more severe than expected for the participant's condition.
- A medical or surgical procedure (e.g., endoscopy, appendectomy) is not an AE. The condition that leads to the procedure is the AE (e.g., gastritis, appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations in a pre-existing disease/condition present or detected at the start of the study that did not worsen.

8.2. Definition of a Serious Adverse Event (SAE)

An SAE is a particular category of AE where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of a disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Visit 1 is not considered an AE.
- **Results in persistent or significant disability /incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as an uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

NOTE: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

8.3. EXPECTED EVENTS

There is always the possibility of irritation or reaction to any skin product applied to the skin. Examples of possible skin product reactions are:

- Redness
- Dryness/tightness
- Peeling
- Itching
- Burning/stinging
- Allergic reaction

Any skin reaction associated with the application of the test material to the test site will be considered an AE and documented as such.

8.4. Time Period and Frequency for Collection AE and SAE Information

All AEs, and therefore all SAEs, will be collected immediately after a participant provides consent to participate in the study by the completion (signing) of the ICF and until 14 days following last administration of test material (or last study procedure). Medical occurrences that began before obtaining informed consent will be recorded in the source documentation as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor, or designee, immediately and under no circumstance should this exceed 24 hours. The PI, or CRC, will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The PI is not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the PI learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the test material or study participation, the PI must promptly notify the Sponsor.

8.5. Reporting Procedures

The PI, or medically qualified designee, is responsible for detecting, documenting and reporting all events that meet the definition of an AE and remains responsible for following up on AEs that are serious or considered to be related to a test material, participation in the study or a study procedure, or that caused the participant to discontinue a test material or the study.

Each participant will be questioned about AEs. Spontaneously reported AEs and those elicited by asking non-directive questions (such as "How do you feel?") will be assessed, recorded in AE-specific source documentation and reported appropriately. The PI, or medically qualified designee, is to report all directly observed AEs and all AEs spontaneously reported by a participant.

Each AE should be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate. When an AE occurs, it is the responsibility of the PI, or medically qualified designee, to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The PI, or CRC, will record all relevant information regarding an AE in AE-specific source documentation and all details relating to an SAE on the paper SAE form provided.

It is not acceptable for the PI, or medically qualified designee, to send photocopies of a participant's medical records to GSK CH in lieu of completion of AE-specific source documentation or the SAE form. There may be instances when copies of medical records are requested by GSK CH. In this instance, all participant identifiers, except for the participant number, will be redacted prior to sharing with GSK CH.

The PI, or medically qualified designee, will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis should be the documented as the AE/SAE, where known, and not the individual signs/symptoms (e.q., upper respiratory tract infection, seasonal allergy etc., not cough, runny nose).

AEs elicited by the PI, or medically qualified designee, during study visits should be recorded in AE-specific source documentation and/or using the SAE form, as appropriate. Care will be taken not to introduce bias when questioning a participant about changes in their health. Open-ended and non-directive verbal questioning should be used.

8.5.1. Reporting an Adverse Event

AEs will be reported using AE-specific source documentation by the PI or site staff and the AE form, when appropriate, using concise medical terminology. Where the same data are collected, AE-specific source documentation and the SAE form must be completed in a consistent manner; the same AE terms should be used on both.

8.5.2. Reporting a Serious Adverse Event

In addition to recording the details in AE-specific source documentation, a SAE form should be completed, as fully as possible. Hard copies of the paper SAE form will be provided by the Sponsor for the Investigator Site Master File. Original SAE forms should be retained in the Investigator Trial Master File.

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It is essential to enter the following information:

- Protocol and participant identifiers
- Participant demography
- Description of event(s), with diagnosis if available
- PI opinion of relationship to test material (or study procedure, if appropriate)
- Criterion for seriousness

The following are desirable and are of particular relevance for PI and GSK CH assessment of the SAE report:

- Date of onset of event
- Date event stopped, if relevant
- Test material start date
- Test material end date, if relevant
- Action taken in relation to the test material
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the GSK CH Clinical Operations Safety Reporting email box with the GSK CH study number and participant number in the title field of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The PI will submit any updated SAE data to the sponsor **immediately and under no circumstance should this exceed 24 hours** of it being available. The GSK CH Study Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:
PPD

The GSK CH Study Manager, or CRC, will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD The initial report will be followed up with more information as relevant, or as requested by the GSK CH Study Manager.

8.6. EVALUATING ADVERSE EVENTS

8.6.1. Assessment of Intensity

The PI, or medically qualified designee, will assess intensity for each AE reported during the study and will assign one of the following categories.

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities.

NOTE: An AE classified as 'severe' should not be confused with an SAE.
'Severe' is a category utilized to classify the intensity of an event; both non-serious AEs and SAEs can be classified as 'severe'. For example, a headache may be 'severe' (interferes significantly with the participant's usual function) but would not be classified as 'serious' unless it met one of the criteria for an SAE, as described above (Section 1.2.2.). An event is defined as 'serious' when it meets at least 1 of the pre-defined outcomes as described in Section 1.2.2., not when it is classified as 'severe'.

8.6.2. Assessment of Causality

Causality is one of the criteria used to determine regulatory reporting requirements. For each AE (serious and non-serious), the PI, or medically qualified designee, must provide an assessment of causality in the AE-specific source documentation and, for SAEs, on the SAE form.
The PI, or medically qualified designee, will use clinical judgment to determine causality, having also consulted the Safety Statement provided by the Sponsor for this study. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors and the temporal relationship of the event to test material use will also be taken into consideration and investigated.

There may be situations where an SAE has occurred and the PI has minimal information to include in the initial report to GSK CH. The PI is required to make an assessment of causality prior to the initial transmission of the SAE form to GSK CH; they may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.6.3. Relationship to Test Material

The relationship or association of the AE to test material will be characterized as 'unlikely', 'possible' or 'probable' (Table 10).

A 'reasonable possibility' of relationship conveys there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The facts, evidence and/or arguments which suggest a causal relationship should be provided in the AE report.

Table 10: Causality Assessment

Causality Term	Assessment Criteria
Probable	Event or laboratory test abnormality, with plausible time relationship to test material exposure
	Unlikely to be attributed to condition (or disease) or other products in use by participant
	Response to withdrawal clinically reasonable
	Re-challenqe satisfactory or not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to test material use
	Could also be explained by condition (or disease) or other products in use by participant
	Response to withdrawal unclear or lacking
Unlikely	Event or laboratory test abnormality, with a time to test material use that makes a relationship improbable (but not impossible)
	Condition (or disease) or other products provide plausible explanations

For safety analyses, AEs classified as a 'possible' or 'probable' association to test material shall be considered test material-related AEs.

Follow-up of an AE, after discontinuation of exposure to test material is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the PI and to the Medical Monitor.

8.7. FOLLOW-UP OF AEs AND SAEs

After the initial AE/SAE report, the PI, or medically qualified designee, is required to proactively follow up with each participant and provide further information on the participant's condition. All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained or until the participant is lost to follow-up.

The PI, or medically qualified designee, is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK CH to elucidate as fully as possible the nature and/or causality of an AE. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. New or updated information will be recorded on the AE CRF page and, for SAEs, on the SAE form. The PI, or CRC, will submit updated SAE data to GSK CH within 24 hours of receipt of the information.

The PI is not obliged to actively seek AEs in former study participants. However, if the PI learns of a SAE, including death, at any time after a participant has been discharged from the trial, and considers the event reasonably related to the test material or study participation, they will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD
The GSK CH Study Manager, or CRC, will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD

The PI, or medically qualified designee, will submit any updated SAE data to GSK CH within the designated reporting time frames.

8.8. WITHDRAWAL DUE TO AN ADVERSE EVENT

Withdrawal due to an AE should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded in the appropriate AE-specific source document. When a participant withdraws because of an SAE, the SAE must be reported as already described.

8.9. REGULATORY REPORTING REQUIREMENT FOR SAEs

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a test material under clinical investigation. Prompt notification of SAEs by the PI to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of study participants are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority and IRB, and other investigators if applicable.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators, as required.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE from the sponsor) will review it, file it with the Safety Statement in the Investigator Trial Master File and then notify the IRB, if appropriate, according to local requirements.

8.10. PREGNANCY

8.10.1. Time period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female participant is taking part in the study, from the signing of informed consent until 14 days after last administration of test material.

8.10.2. Action to be Taken if Pregnancy Occurs

The PI, or CRC, will record pregnancy information on the pregnancy form supplied by the Sponsor if reported by a subject during the study. The completed form should be scanned and e-mailed to the GSK CH Clinical Operations Safety Reporting email box (PPD PPD within 24 hours of learning of the pregnancy. The GSK CH Study Manager, or CRC, will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD Original pregnancy information forms should be retained in the Investigator Trial Master File.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE. Any female participant who becomes pregnant during the study will be withdrawn. If a female participant later discovers they were pregnant during the study, i.e., after their participation completed, their data will be considered valid for statistical analysis purposes.

9.0 DATA RECORIDNG AND STUDY RECORD MAINTANCE

Safety/efficacy data and additional clinical observations will be recorded in source documentation (e.g., case report forms [CRFs]) in accordance with the ALCOA+ principles of data integrity; data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available. Correction of data recorded in source documentation will be carried out accordance with PPD SOPs.

Source documents will include completed ICFs, original records of clinical/instrumental observations, test material disposition/product accountability, AE reports, results and activities necessary to reconstruct and evaluate the study. Source documents will be peer-reviewed by the site staff as per PPD standard practice and/or in accordance with PPD SOPs.

Data required for reporting purposes will be transcribed into the study database (Excel spreadsheets), for example, participant disposition, demographics (age, sex), pre- and post-treatment corneometer measurements, with the exception of safety data. AEs will be described for the safety population in the final report; they will not be data-based. All other data collected during the study will be considered source and will not reported or listed.

Source documents and other study records (e.g., protocol, protocol amendments/ deviations, IRB approval(s), correspondence with the Sponsor/IRB, monitor log/reports) will be maintained in the Investigator Trial Master File in accordance with the intent and purpose of GCP guidelines, PPD SOPs and all applicable laws and regulations.

10.0 ETHICAL REVIEW

The Sponsor, Monitor(s) and PI will assure all aspects of the study are conducted in accordance with applicable regulations and laws guiding the protection of human subjects, including regulations requiring informed consent (Informed Consent of Human Subjects, 21 CFR Part 50, Subpart B) and the approval and ongoing review of the research by an IRB (Institutional Review Boards, 21 CFR Part 56). The study will be conducted in accordance with the principles of the Declaration of Helsinki (as amended), the Belmont Report and Good Clinical Practice (GCP).

The PI will submit the protocol for the proposed clinical investigation, the ICF, an ingredients listing for each test product and the SPF standard, the Sponsor-supplied Safety Statement, advertising materials and any other relevant documents, as appropriate, to the following duly constituted Institutional Review Board (IRB) for review. Written IRB approval of each item is required prior to study initiation.

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The PI will assure that all aspects of the IRB review are conducted in accordance with current federal regulations. The letter documenting IRB approval (with the names and titles of the IRB members) will be provided to the Sponsor. Amendments to the protocol or the ICF will be subject to the same IRB review requirements as the original documents.

Should study duration be extended, the PI will submit a progress report, at least annually, to the IRB. This report will include: the test material evaluated; a description of any changes in study procedures or amendments to the protocol; deviations from the protocol; the number and type of participants evaluated; the number of participants who discontinued (and the reasons for discontinuation); the number of participants who completed the trial; a description of any AEs/SAEs.

11.0 PROTOCOL/ICF AMENDMENT

Any change to the approved protocol and/or ICF must be made by formal amendment of the original document. The amended document must be approved in writing by the PI and the Sponsor prior to implementation. Depending on the nature of the change, IRB approval may also be required prior to implementation; administrative changes will be notified to the IRB.

12.0 PROTOCOL DEVIATIONS

Unplanned or unexpected non-compliances with the protocol will be documented as protocol deviations. Protocol deviations should be avoided whenever possible and will be documented in the Investigator Trial Master File and reported to the Sponsor.

The PI and site staff will not deviate intentionally from this protocol for any reason without prior approval of the Sponsor and the IRB, except when the change is necessary to eliminate an apparent immediate hazard to study participants. In that event, the PI must notify the Sponsor and the IRB in writing within 5 working days of the change being implemented.

13.0 CLINICAL STUDY REPORT (CSR)

On completion of the study, the PI will provide the Sponsor with an audited topline, followed by a draft CSR. The CSR will include (but not be limited to): study start and end dates; test material identification; tabulation of participant demographics; corneometer data; descriptive and inferential statistics including mean corneometer values with SD, changes from baseline, 95% CIs and p-values (as described in Section 7); summary of safety data (AEs/SAEs) or confirmation there were no AEs; protocol amendments; protocol deviations; conclusions; identification of the technician who conducted the corneometer measurements. A final signed report will be provided to the sponsor.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under pertinent Good Clinical Practice Guidelines, other applicable regulatory requirements and testing facility Standard Operating Procedures.

14.1. STUDY MONITORING BY THE SPONSOR

In accordance with current FDA regulations and GCP guidelines, study monitors and other Sponsor representatives may periodically inspect study-related data at the study site at pre-agreed, mutually convenient times, during or after completion of the study (Guidance for Industry: Oversight of clinical investigations - A risk-based approach to monitoring, DHHS, FDA, August 2013.). Monitoring provides the Sponsor with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of source documentation, assure all protocol requirements, applicable FDA laws and regulations and the PI's obligations are being fulfilled, and to resolve any issues.

14.2. STUDY REVIEW BY PPD QUALITY ASSURANCE

Study related documents, including source documents, raw data, study database, statistical outputs and the CSR will be examined for completeness, accuracy of transcription and proper documentation practices by PPD Quality Assurance personnel.

15.0 MEDICAL OVERSIGHT

The Sponsor will ensure access to an appropriately experienced GSK CH physician/ clinical research scientist to be contacted by study staff for advice on medical questions or problems in the event that the established communication pathways between the study site and Sponsor's representatives are not available. The contact details of this individual (Medical Monitor) will be documented in the Study Contact List located in the Investigator Trial Master File held at the study site.

Contact details for the Medical Monitor are not intended for direct use by study participants. To facilitate access to appropriately qualified medical personnel for study-related medical questions and/or problems, participants will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the participant's study identification number, contact information for the study site/PI. The site should contact the Medical Monitor in the event that the PI cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the PI.

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16.0 CLINICAL STUDY PRODUCT

Prior to use in the clinical study, the test material will be securely stored at ambient conditions. Unused test material will be returned to the Sponsor.

The Sponsor assumes responsibility for the purity, stability, characterization and adequate preservation of the test material. The Sponsor assumes responsibility for determining the test material is safe for use in humans as described in this protocol.

17.0 RECORD RETENTION

All original documentation and records pertaining to the conduct of this study will be retained by PPD for 15 years from the time the final CSR is issued.

At any time prior to the completion of the 15th archival year, the Sponsor may submit a written request to obtain custody of these documents and records once the PPD archive period has been completed. This transfer shall be performed at the expense of the Sponsor. In the absence of such written requests, related records and documents shall be destroyed at the end of the PPD archive period, with no further notice, in a manner that renders them useless.

18.0 PARTICIPANT CONFIDENTIALITY

PPD will ensure the names/identities of all study participants are kept confidential; participants' names/identities will not appear in any source documents or study-related records provided to the Monitor/Sponsor. Should study records be required for inspection, participants' names/identities should be redacted and replaced by their study ID number.

19.0 INDEMNIFICATION

The Sponsor agrees to indemnify, defend, and hold harmless PPD from any demands, costs, or judgements arising out of or connected with the non-negligent use of the test material or performance of activities to be carried out pursuant to this Protocol. PPD shall notify the Sponsor within 10 working days after receipt of notice of injury, claim or lawsuit. In cases where a service agreement exists, the terms of the service agreement prevail.

20.0 COMMUNICATION AND PUBLICATION OF RESULTS

The Sponsor shall retain ownership of all study data, data analysis and reports which result from this study. All information generated by the study should be regarded as confidential. The CSR is for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report, nor the name of PPD, nor any member of its staff, may be used in connection with the advertising or sale of any product or process without prior written authorization by a legally binding officer of PPD

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21.0 PROTOCOL APPROVAL

For PPD (e-Signatures):

PPD

PI (Signature) Date

PPD

PI Name (Print)

PPD M.D. PPD

SI (Signature) Date

PPD M.D.

SI Name (Print)

For the Sponsor (e-Signatures):

Name	GSK CH Position
PPD	Head of Clinical Development
	Regional Clinical Operations Director
	Head of Biostatistics and Data Management

Signature Page for 218006 TMF-215847 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: PPD
Reason for signing: Approved	Name: PPD Role: Approver Date of signature: PPD
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