CLINICAL PROTOCOL

Protocol Title: Clinical Evaluation of Sunscreen Efficacy with the Sun Protection Factor Assay and Calculation of the Label SPF - ISO 24444 (2010) Test Method & Australia/New Zealand Test Method

Testing Facility: Consumer Product Testing Company, Inc.
70 New Dutch Lane
Fairfield, NJ 07004
PPD

Sponsor: GlaxoSmithKline Consumer Healthcare (GSK CH) Holdings (US) LLC
184 Liberty Corner Road
Warren, New Jersey 07059

GSK Trial Protocol Number: 215232

CPT Trial Number: S20-6811

Test Materials: .01 ChapStick Moisturizer, Classic Flavor
CCI CCI
.02 ChapStick Moisturizer, Strawberry Flavor
CCI CCI

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Protocol Acceptance:

For Consumer Product Testing Co., Inc.:

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ABBREVIATIONS

AE	–	Adverse Event
CFR	–	Code of Federal Regulations
CPT	–	Consumer Product Testing Company, Inc.
CRF	–	Case Report Forms
CTCAE	–	Common Terminology Criteria for Adverse Events
GCP	–	Good Clinical Practice
HIPAA	–	Health Insurance Portability and Accountability Act
ICF	–	Informed Consent Form
IRB	–	Institutional Review Board
ISO	–	International Organization for Standardization
ITA°	–	Individual Typology Angle
MED	–	Minimal Erythemal Dose
MEDu	–	Minimal Erythemal Dose on unprotected skin
MEDp	–	Minimal Erythemal Dose on protected skin
PI	–	Principal Investigator or designee
SAE	–	Serious Adverse Event
SOP	–	Standard Operating Procedure
SPF	–	Sun Protection Factor
SPFi	–	Individual Sun Protection Factor
UV	–	Ultraviolet
UVA	–	Ultraviolet A
UVB	–	Ultraviolet B
UVR	–	Ultraviolet Radiation

DEFINITIONS

Adverse Event (AE): Any untoward medical occurrence in a clinical trial subject, temporally associated with the use of a trial product, including any washout or lead-in product (or medical device), whether or not considered related to the trial product, including any washout or lead-in product (or medical device).

Approximately: A variance of 10% in the stated value is acceptable.

Belmont Report: A document entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" that was produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978. The Belmont Report identifies three fundamental ethical principles for all human subjects' research: respect for persons, beneficence, and justice.

Blinding: When research participants are unaware of the assigned "treatment." In a single-blinded trial, the subjects do not know what treatment they are receiving. In a double-blinded trial, the subjects AND the investigators are unaware of the treatment assigned, as are the monitors and statisticians in some cases. The objective of blinding is to limit the occurrence of conscious and unconscious bias in the conduct of and interpretation of a clinical trial. Such bias could arise from the influence that knowledge of treatment may have on the recruitment and allocation of subjects, subjects' subsequent care, the attitudes of subjects to the treatments, the assessment of endpoints, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim of blinding is to prevent identification of the treatments until all such opportunities for bias have been minimized.

Case Report Form (CRF): A record of information collected on each subject during the clinical trial. CRFs are also source documents.

Clinical Investigation: A systematic trial designed to evaluate a test material in humans.

Clinical Research: A trial in human subjects.

Clinical Trial: Any research study that prospectively assigns human participants or groups of humans to one or more interventions to evaluate the effects on outcomes. The terms "research", "clinical research". "clinical study", "study", "clinical trial", "trial", and "clinical investigation" are deemed synonymous.

Control Standard: For reference purposes, a control standard is run concurrently with the test material during the testing procedure (aka, "reference sunscreen formulation").

Declaration of Helsinki: A series of guidelines adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and amended subsequently. Recommendations include the procedures required to ensure subject safety in clinical trials, including informed consent and Ethics Committee reviews.

Erythema: Reddening of the skin caused by UVR.

Ethics Committee: An independent group of medical and nonmedical people who verify the integrity of a trial and ensure the safety, integrity, and human rights of the subjects (see Institutional Review Board).

Exclusion Criteria: Characteristics that would prevent a subject from qualifying for a research trial, as specified in the protocol.

Full Spectrum UV Radiation: UV radiation that includes both UVB (290 nm – 320 nm) and UVA (320 nm – 400 nm).

Good Clinical Practices (GCPs): International ethical and scientific quality standards for the design, conduct, monitoring, recording, auditing, analysis, and reporting of trials.

Health Insurance Portability and Accountability Act (HIPAA): Legislation passed in 1996 that includes a privacy rule creating national standards to protect personal health information.

Inclusion Criteria: A list of requirements that a subject must meet to qualify for a research trial, as specified in the protocol.

Individual Sun Protection Factor (SPFi): Ratio of the minimal erythemal dose on test material protected skin (MEDp) to the minimal erythemal dose on unprotected skin (MEDu) of the same subject:

$$SPFi = \frac{\text{MED (protected skin)}}{\text{MED (unprotected skin)}} = \frac{MEDp}{MEDu}$$

Individual Typology Angle (ITA°): A value characterizing the skin color of the subject.

Informed Consent: The verification of a person's willingness to volunteer in a research trial. The verification is requested only after the person has received complete, objective information about the research, including its objectives, potential benefits, risks and inconveniences, alternative therapies that may be available (if applicable), and the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (as amended). Consent is given by executing the Informed Consent Form (ICF).

Institutional Review Board (IRB): Any board, committee, or other group formally designated by an institution to review, approve the initiation of, and to conduct periodic review of research involving human subjects in compliance with 21 CFR 56. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

Investigator: A medical professional, usually a physician but also sometimes a nurse, pharmacist, or other professional, under whose direction a test material is given or dispensed. A principal investigator (PI) is responsible for the overall conduct of the clinical trial.

MedWatch Program: A national educational/promotional initiative to educate health professionals about the importance of reporting serious adverse events and important product problems, to facilitate reporting to the FDA if they choose to do so, and to provide feedback to the health professional community as new safety information becomes available.

Minimal Erythemal Dose (MED): The lowest dose of ultraviolet radiation (UVR) that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 h to 24 h after UV exposure.

Monitor: Sponsor or CRO representative who reviews trial records to determine that it is being conducted according to the protocol.

Monitoring: Reviewing a clinical trial, ensuring that conduct, proper records, and reports are in accordance with the approved protocol, standard operating procedures, GCPs, and regulatory requirements.

Panel: A group of subjects with a unique combination of test materials applied and a unique trial schedule.

Protocol: A detailed plan that sets forth the objectives, design, and methods for a clinical trial.

Protocol Amendment: Changes or clarifications made in writing to the original protocol.

Qualified Subject: A subject who has executed an Informed Consent Form and met all inclusion and exclusion criteria for the clinical trial.

Quality Assurance: Systems and procedures designed to ensure that a trial is being performed in compliance with the approved protocol, standard operating procedures, GCPs, and that the data being generated are accurate.

Randomization: A method of assigning trial test material such that each subject has an equal chance of being assigned to each treatment or control group. Randomization guards against selection bias.

Serious Adverse Event (SAE): Any adverse event (AE) that is fatal, life-threatening, or permanently disabling, or that results in new or prolonged hospitalization, in a congenital anomaly/birth defect, or is an important medical event.

Source Data: All information contained in original records and certified copies of results or observations.

Source Document: A document or form that is used to capture original, trial-related data or information. A source document may serve as the Case Report Form or the information may be transcribed onto a Case Report Form.

Sponsor: Individual, company, institution, or organization that takes responsibility for initiation, management, and financing of research.

Standard Operating Procedures (SOPs): Official, detailed, written instructions for the management of clinical trials. SOPs ensure that all the functions and activities of a clinical trial are carried out consistently and efficiently.

Subject: A patient or healthy person participating in a research trial.

Sun Protection Factor (SPF): The arithmetic mean of all valid individual SPFi values obtained from all subjects in the test.

Test Area: The area of the back between the scapula line and the waist.

Test Material: Any material or product that is the subject of testing or a clinical trial. This may also be referred to as a "test article" or "investigational material".

Test Site: The site where a test material or control standard is applied or the site used for the determination of the unprotected MED.

Test Subsite: An area within the test site that is exposed to UVR.

Ultraviolet Radiation (UVR): The radiation from 290 nm to 400 nm, with that from 290 nm to 320 nm being termed UVB, that from 320 nm to 340 nm being termed UVAII and that from 340 nm to 400 nm being termed UVAI.

1 Background Information

A sunscreen product in a form suitable for topical administration is generally recognized as safe and effective if it meets the requirements in the International Standard Test Method ISO24444 (2010) (reference 12.1). This protocol is designed to evaluate the Sun Protection Factor (SPF) of the test materials as sunscreen products, as per the requirements delineated in this methodology. In addition, this static methodology meets the requirements of the Australia/New Zealand standard (reference 12.2).

2 Trial Objective

The primary objective of this trial is to determine the SPF of two test materials using the methodology described in the International Standard Test Method (reference 12.1). This static methodology also meets the requirements of the Australia/New Zealand standard (reference 12.2).

3 Proposed Schedule

Proposed trial initiation, completion, and estimated reporting dates will be established prior to the start of testing.

4 Test Materials

4.1 Identification

ChapStick Moisturizer, Classic Flavor (CCI [redacted] and ChapStick Moisturizer, Strawberry Flavor (CCI [redacted] will be uniquely identified by a CPT trial number. CPT will record the test material name, physical description, lot number (if available), Sponsor, and date received into the log-in database. Each of the two test materials has an expected SPF of 15.

A control standard (Reference Sunscreen Formulation) will be run concurrently with the test materials. Three control standards are delineated within the methodology as follows:

Control Standard	Mean SPF	Acceptance Limits (Mean ± 2SE)	
		Lower limit	Upper Limit
P2	16.1	13.7	18.5
P3	15.7	13.7	17.7
P7	4.4	4.0	4.8

For the two test materials in this trial, control standard P2 will be used.

4.2 Storage

ChapStick Moisturizer, Classic Flavor, and ChapStick Moisturizer, Strawberry Flavor, unless otherwise specified, will be stored at ambient temperature and humidity in the container(s) in which they are received by CPT.

The control standard will be stored in a refrigerator at 4ºC to 8ºC and ambient humidity. The control standard will be allowed to warm to room temperature prior to use (approximately 60 minutes).

4.3 Disposition

All remaining test materials (unused and used, including empty containers) will be returned to the Sponsor at the following address within 2 months of trial completion:

GSK Consumer Healthcare R&D
Consumer Study Supplies
1211 Sherwood Ave
Richmond, VA 23220
Attention: Returned Study Supplies
Protocol #215232
PPD

The control standard will be returned to the refrigerator and used in additional trials until the entire control standard has been used or the expiration date has been reached.

5 Selection and Withdrawal of Subjects

5.1 Number of Subjects

Potential subjects will be recruited for the clinical trial from the CPT database per the CPT standard operating procedure.

An initial assessment of up to 5 valid subjects may be conducted to evaluate a preliminary SPF value. An additional 5 valid subjects may be added to the initial 5 subjects to form a complete panel. Per the ISO24444 (2010) test method, testing of up to 25 subjects may be needed to achieve a minimum of 10 valid results (see below for more detail). For this trial, the maximum number of qualified subjects has been set by the Sponsor to 15 subjects. Addition of subjects beyond 15 must be approved in writing by the Sponsor. Results shall be recorded for each panel.

A maximum of 5 individual results from qualified subjects may be excluded from the calculation of the mean SPF but each exclusion must be justified (Section 7.1). A minimum of 10 valid subjects is only sufficient if the 95% confidence interval of the mean SPF is within ±17.0% of the mean SPF. Otherwise, the number of subjects shall be increased stepwise from 10 until the statistical criterion is met, up to a maximum of 20 valid results from a maximum of 25 qualified subjects tested. If the statistical criterion has not been met after 20

valid results from a maximum of 25 subjects, then the test shall be rejected. For details on the sequential procedure and calculations, see reference 12.1.

Subjects who meet all of the inclusion criteria (Section 5.2) and none of the exclusion criteria (Section 5.3) will qualify for trial participation. Subjects cannot all be of the same skin phototype.

5.2 Inclusion Criteria

1. Subject must read and execute an informed consent document (that includes a HIPAA statement) indicating that the subject has been informed of all pertinent aspects of the trial before any assessment is performed;

2. Subject must be 18 to 70 years of age inclusive, at the signing of the informed consent;

3. Subject must complete a Medical History Form (MHF) prior to their trial initiation;

4. Subject must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures;

5. Subject must agree not to expose their back to additional sunlight or tanning beds, as either can alter the test results;

6. Subject must agree not to apply any topical skin-care product to the test sites during this trial;

7. Male or female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the trial and for 14 days after the last application of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active;

8. Female subjects of childbearing potential must be willing to comply with urine pregnancy testing requirements prior to initiation of trial testing procedures and as may be required for the duration of the trial;

9. Subject must be considered dependable and capable of understanding and following directions;

10. Subject must have self-perceived Fitzpatrick skin phototype I, II, or III:

Skin Phototype	Sunburn and Tanning History
I	Always burn easily; never tans
II	Always burns easily; tans minimally
III	Burns moderately; tans gradually; and

11. Subject must have an ITA° value >28°, determined by the Testing Facility by colorimetric methods, within 1 week of trial participation.

5.3 Exclusion Criteria

1. Subject is in ill health as determined by the Principal Investigator;
2. Subject is an employee of the Clinical Division of the investigational site or a member of their immediate family;
3. Subject is a GSK CH employee directly involved in the conduct of the trial or a member of their immediate family;
4. Female subject is pregnant or intending to become pregnant over the duration of the trial or any female subject of childbearing potential who fails to produce a negative urine pregnancy test;
5. Female subject who is lactating (self-reported);
6. Subject using medication with photo-sensitizing potential;
7. Subject has a history of adverse reactions or hypersensitivity to azo dyes, cosmetics, OTC drugs, or other topical personal care products;
8. Subject taking medications other than birth control that could influence the purpose, integrity or outcome of the trial;
9. Subject has used topical or systemic steroids, antihistamines, or antibiotics within 7 days of trial initiation or during the trial;
10. Subject has used anti-inflammatory medications within 7 days of trial initiation or during the trial, that in the opinion of the PI, could interfere with the trial;
11. Subject has used medication suspected of causing photobiological reactions (e.g., tetracyclines, thiazides, etc.), that has not been taken by the subject through a summer season;
12. Subject has a dermatological condition;
13. Subject has a history of abnormal response to the sun, or a condition such as lupus erythematosus or skin cancer;
14. Subject uses tanning beds frequently;
15. Subject whose test site was exposed to sunlight within the previous 4 weeks;
16. Subject has a sunburn, suntan, uneven skin color, visible skin disease, scarring, or tattoo that would interfere with evaluation of test results;

    Note: The presence of non-dysplastic nevi, blemishes, or moles will be acceptable if, in the PI's judgment, they will neither compromise the clinical trial, nor jeopardize a subject's safety. A subject with dysplastic nevi should be disqualified.

17. Subject has existing sun damage in the test site;

18. Subject has excessive hair in the test area and are unwilling to have it clipped; or

19. Subject whose test sites have been used for clinical testing in which they were exposed to ultraviolet radiation within the past 2 months.

5.4 Lifestyle Considerations

5.4.1 Medications and Treatments

During the active trial period (screening through end of evaluation visit):

1. Subjects must not expose their backs to additional sunlight or a tanning bed, since exposure to either will alter response to the test.

2. Subjects must not apply any topical skin-care product to the test sites during this trial.

5.4.2 Contraception

All male subjects able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active trial period and for 14 days after the last dose of investigational product.

The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy that meets the GSK definition (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).

The list does not apply to females of reproductive potential with same sex partners or for subjects 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception (reference 12.3).

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system

3. Combined estrogen and progestogen oral contraceptive
4. Injectable progestogen
5. Contraceptive vaginal ring
6. Percutaneous contraceptive patches
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the trial, and this male is the sole partner for that subject. The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Male subjects with female partners of child-bearing potential must comply with the following contraception requirements from the time of first dose of trial medication until 14 days after the last dose of trial medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from site personnel: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

    - Contraceptive subdermal implant
    - Intrauterine device 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 investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5.5 Withdrawal of Subjects

The subject is free to withdraw their consent to participate in the trial at any time and for any reason, in accordance with the Principles of the World Medical Association Declaration of Helsinki (as amended). The PI also has the right to withdraw a subject from the trial for safety, lack of efficacy, or administrative reasons.

Possible reasons why a subject may be withdrawn from the trial include the following:

1. Experiences an AE or SAE;
2. Develops, during the trial, symptoms or conditions listed in the exclusion criteria, including hypersensitivity to the test material or pregnancy;
3. Takes medications that are contraindicated, as described in the exclusion criteria;
4. Incurs a protocol violation such as failure to comply with the specified treatment regimen or failure to comply with the visit schedule; or

5. Requests an early discontinuation due to:
   - A clinical event for which the PI did not consider removal from the trial to be necessary;
   - Other (non-specific) subject-initiated reason.

5.6 Disposition of Withdrawn Subjects

The date the subject is withdrawn from the trial and the reason for discontinuation will be recorded on the Case Report Form (CRF). Attempts will be made to conduct all evaluations scheduled for the final trial visit as soon as possible after the subject is withdrawn from the trial.

When a subject fails to return for scheduled trial visits, the PI will make a reasonable effort to contact the subject and determine why the subject failed to return. This information will be recorded on the CRF. When a subject is withdrawn from the trial (regardless of the reason), the PI will encourage the subject to complete all evaluations which may be necessary to assure that the subject is free of untoward effects, and to seek appropriate follow-up for any continuing problem.

6 Methodology

Each potential subject must provide informed consent before participating in the trial. The informed consent process fully apprises the potential subject of the risks and benefits to them and to society for participating in the trial. The Informed Consent Form (ICF) will clearly state that designated Testing Facility personnel will be able to view each potential subject's medical records. If the potential subject agrees to participate in the trial, the potential subject will execute the ICF with their signature and date. The CPT staff who conducted the informed consent process will also execute the document by signing and dating the ICF. Each subject will be given a signed copy of the Informed Consent Form. If the subject has questions about their rights, they may contact a Subject Rights Advocate at any time during or after trial participation. The length of the trial is expected to be 3-10 days.

Each task outlined in this methodology will be carried out by CPT staff members that have been trained, per CPTs SOPs and policies, to perform those tasks.

CPT staff member(s) will complete the following screening procedures with subjects to confirm eligibility after informed consent is obtained:

- Check previously determined colorimetric ITA° value to ascertain if collection of a new value is needed. Sponsor requires an ITA° value >28°, determined by the Testing Facility by colorimetric methods (reference 12.1), be obtained within 1 week of trial participation.
- Inquire about any changes to medical and medication history on file via an MHF;
- Conduct a contraception check;
- Skin examination;
- Confirm that the subject meets the inclusion/exclusion criteria;

- For female subjects of childbearing potential, a urine pregnancy test will be administered, per the manufacturer's instructions (subject urinates into paper cup, then inserts dipstick into urine per instructions, urine is dumped into toilet by subject) and test will be collected by laboratory staff. CPT staff will verify subject has disposed of urine. No urine is collected. Pregnancy test results will be noted on the Urine Pregnancy Test Results Log and the test dip stick will be disposed of in a waste receptacle. The urine pregnancy test will have a sensitivity of at least 25 mIU/mL. A negative pregnancy result is required before any test material is applied to the subject. Pregnancy tests may be repeated when potential pregnancy is suspected during participation in the trial (e.g., one menstrual cycle is missed during the testing period), as per request of the IRB, or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from the trial.

6.1 Instrumentation

Xenon arc solar simulators (150 W or 300 W) equipped with WG320 and UG11 filters shall be used as the source of full spectrum UV radiation (Solar Light Company, Philadelphia, PA). This instrument, described in detail (reference 12.4), provides a stable, continuous spectral output in both the UVB range (290 nm – 320 nm) and the UVA range (320 nm – 400 nm) that is similar to sunlight. Qualified technician(s) trained in the use of this instrument will be responsible for its operation.

The performance of the solar simulators depends on the spectral output. Therefore, the solar simulator spectral output specification is described in terms of cumulative erythema effectiveness by successive wavelength bands from 290 nm to 400 nm. The erythemal effectiveness of each wavelength band is expressed as a percentage of the total erythemal effectiveness from less than 290 nm to 400 nm, or as the Relative Cumulative Erythemal Effectiveness (% RCEE). The maximal irradiance is confirmed to avoid the feeling of excessive heat during the irradiations. The following table indicates the % RCEE acceptable output limits for the solar simulators.

Spectral Range (nm)	Measured % RCEE	
	Lower Limit	Upper Limit
<290		<0.1
290-300	1.0	8.0
290-310	49.0	65.0
290-320	85.0	90.0
290-330	91.5	95.5
290-340	94.0	97.0
290-400	99.9	100.0

Additionally, the total radiometric proportion of the solar simulator UVAI irradiance and UVAII irradiance shall be ≥60% and ≥20%, respectively, of the total UV irradiance.

Solar simulators shall be provided an appropriate warm-up period, after which, they are expected to have no significant time-related fluctuations in radiation emissions. Each solar simulator shall have good beam uniformity in the exposure plane and shall meet the % RCEE

acceptance limits for UV solar simulator output. Total irradiance shall not exceed 1,600 W/m^2. The minimal beam irradiance at any subsite shall not be lower than 10% below the maximum beam irradiance at any subsite.

The lamp output shall be measured after warm-up with a UV intensity meter (Model PMA2100, Solar Light Company, Philadelphia, PA) equipped with the appropriate detector before and after the test period. To ensure that solar simulators deliver the appropriate spectrum of UV radiation, their spectral output shall be measured semi-annually with an accurately calibrated spectroradiometer.

All instruments shall be calibrated and maintained per CPT's SOPs.

6.2 Determination of Minimal Erythemal Dose (MEDu)

6.2.1 Methodology

Within 1 week prior to the test material phase, a provisional MEDu of each subject shall be determined by a progressive sequence of timed UV radiation exposures, each of which shall be graduated incrementally by 25% over that of the previous exposure. The test sites shall be evaluated for erythema according to the MED Scoring Scale (Section 6.2.2). The MED is the lowest dose of UVR that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 h to 24 h after UV exposure (Score of 1 or greater on the MED Scoring Scale).

On the same day as the test material is irradiated, an MEDu shall be determined by a progressive sequence of timed UV radiation exposures. The exposures shall be graduated incrementally by 25% over that of the previous exposure, and the graduation must be consistent with that of the MEDp test sites. Further, the MEDu test site must be in close proximity to the MEDp test sites. The Test sites shall be evaluated for erythema according to the MED Scoring Scale (Section 6.2.2). The MED is the lowest dose of UVR that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 h to 24 h after UV exposure (Score of 1 or greater on the MED Scoring Scale).

6.2.2 MED Scoring Scale

Score	Description
0	No reaction
0.5	Equivocal reaction, barely perceptible erythema with no clearly defined border
1	Mild but definite erythema with clearly defined borders
2	Moderate clearly defined erythema
3	Strong erythema, edema
4	Bulla or vesiculation

6.3 Determination of Minimal Erythemal Dose on Protected Skin (MEDp)

6.3.1 Test Material Application

The test sites expected to be used in this trial will be 40 cm^2. A sufficient number of 40 cm^2 test sites shall be outlined with a surgical marking pen on the subject's back between the scapulae and the beltline, lateral to the midline, while avoiding any anatomical areas containing extreme curvature. The lines shall be drawn on the subject while in the testing position (upright or prone). These test sites shall be designated for the test material(s) and control standard, with an adjacent test site designated for a concurrent MEDu determination (Section 6.2.1).

Assignment of the test sites for test material(s), control standard, and MEDu shall follow a randomization schedule generated using a validated version of the statistical software R 3.6.1. For each subject, 4 test sites will have a random assignment number for up to two test materials, control standard, and MEDu, with at least 3 of the test sites being utilized for application. If a subject is tested at only 3 test sites, the subsequent randomization assignment will also involve only 3 test sites, with the corresponding test material used as the primary assignment to maintain balancing of treatment allocation.

Test material preparation, test material application, UV exposures, and MED assessments shall each be performed by trained technicians in ambient conditions (18-26°C) according to CPT's SOPs and the International Standard Test Method (reference 12.1).

A portion of test material(s) or control standard shall be applied to the appropriate 40 cm^2 test site and spread evenly over the test site using a finger cot that has not been pre-saturated with the test material or control standard. This application shall provide a test material film of approximately 2.00 ± 0.05 mg/cm^2, using 80 ± 2 mg of material. The actual weight applied shall be recorded on the CRF. To aid spreading, droplets of test material or control shall be deposited within the test site, and then spread over the whole test site using light pressure. Spreading time should be in the range of 35 ± 15 seconds.

There must be a minimum distance of 1 cm between the borders of adjacent test material application test sites, and the test sites must be randomly distributed on the subject's back and throughout the panel. The area of each subsite shall be at least 0.5 cm^2 and the distance between borders of each subsite shall be at least 0.8 cm. The minimum distance between any subsite and the edge of its test site shall be 1 cm.

6.3.2 UV Exposures

Between 15 and 30 minutes after test material or control standard application, all test sites shall be divided into 6 subsites which shall receive a progressive sequence of timed UV radiation exposures. UV exposures shall be selected for each subsite based upon the previously determined MEDu, as described in

Section 6.2.1, and the expected SPF of the test material(s) or of the control standard.

The exposure shall be increased in geometric progression, using the following dose increments in relation to the expected SPF values:

Test Site	Expected SPF	Dose Increment
MEDu	N/A	1.25 (25%)
P2 Standard	16.1	1.25 (25%)
Test Material(s)	15	1.25 (25%)

Subjects will be in the same position (either prone or seated upright) used during test material application, irradiation, and MED assessments. After irradiation is completed, the control standard and test material(s) may be gently removed using a cotton pad with a mild lotion such as makeup remover or other similar product.

6.3.3 Evaluation

After irradiation is completed, all immediate responses will be recorded on a CRF. These include several types of typical responses such as immediate reddening, immediate darkening or tanning, and an immediate generalized heat response. After immediate responses are noted, each subject will be required to shield the exposed test areas from further UV radiation until evaluation of the test sites the following day.

The MEDu, MEDp, and the MED for the control standard will be evaluated by a trained CPT staff member 16 to 24 hours after UV exposure to determine an MED. The MED is the lowest dose of ultraviolet radiation (UVR) that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 h to 24 h after UV exposure (a score of 1 or greater on the MED Scoring Scale). Evaluations will be conducted in a room with matte, neutral wall colors and under uniform illumination of at least 450 lux with the subject in the same position (either seated upright or prone) as when the subject was irradiated.

In order to maintain the blinding and to avoid introducing any bias, the person who evaluates the MED responses shall not be the same person who applies the test material or control standard or administers the UV radiation (i.e., blinded evaluator).

7 Statistical Methods

7.1 Rejection of Data

Test data from a qualified subject shall be invalid and rejected for any of the following reasons:

- If the exposure series fails to elicit an MED response on either the treated or unprotected test sites;
- If the responses on the treated test sites are randomly absent (which indicated the test material (or control standard) was not spread evenly);
- If all subsites on the exposure series show an erythemal response upon evaluation; or
- If the subject was noncompliant (e.g., subject withdraws from the test due to illness or work conflicts; subject does not shield the exposed test sites from further UV radiation until the MED is read, etc.).

If data are rejected for any one test material on more than 5 qualified subjects, then the entire test for that material is invalid and shall be rejected. If data are rejected for the control standard (Reference Sunscreen Formulation) on more than 5 qualified subjects, then the entire test is invalid and shall be rejected.

7.2 SPF Calculation for a Test Material on a Subject

The SPF is defined as the ratio of the energy of exposure to full spectrum UVR, 290 nm – 400 nm, to produce erythema in human skin in the presence of a test material (or control standard), applied at 2 mg/cm^2, to that in its absence and is calculated as follows:

$$SPFi = \frac{\text{MED (protected skin)}}{\text{MED (unprotected skin)}} = \frac{MEDp}{MEDu}$$

SPFi is expressed to one decimal place.

7.3 SPF Calculation for a Test Material for the Panel

The SPF of the test material (or control standard) is defined as the arithmetical mean of all of the valid individual (SPFi) values obtained from the total number (n) of subjects used, expressed to one decimal point:

$$SPF = (\Sigma SPFi) / n$$

Its standard deviation(s) is:

$$s = \sqrt{[(\Sigma SPFi^2) - ((\Sigma SPFi)^2 / n)) / (n-1)]}$$

The 95% Confidence Interval (95% CI) for the mean SPF is expressed as:

$$95\%\ CI = SPF - c \text{ to } SPF + c$$

where c is calculated as:

c = (t value) x SEM = (t value) x s / √ n

c = t x s / √ n

CI[%] = 100 x c / SPF

SEM = standard error of the mean

n = total number of subjects used

t = t value from the "two-sided" Student-t distribution table at a probability level $p = 0.05$ and with degrees of freedom $v = (n-1)$

The statistical criterion for all SPF measurements is that the 95% CI on the mean SPF measured shall fall within a range of ±17.0% of the measured mean SPF. This applies to test material SPF measurement and control standard SPF measurement.

Consequently, the actual number of subjects tested is defined as the number (minimum ten) required to produce a mean test material (or control standard) SPF with a 95% CI, which

falls within a range of ±17.0% of the measured mean SPF for the test material and a mean reference SPF which has a 95% CI that falls within the range of ±17.0% of the measured mean SPF for the control standard.

A minimum of 10 valid results is only sufficient if the statistical criterion is fulfilled. If not, the number of subjects may be increased from ten until the statistical criterion is met up to a maximum of 20 valid results (i.e., a maximum of 20 valid results plus 5 rejected invalid results). **Note that for this trial the Sponsor has set a maximum of 15 subjects. Written approval is needed from Sponsor if more than 15 subjects are required.** For details on the sequential procedure and calculations, see reference 12.1.

7.4 Statistical Analysis Plan

All computations and statistical analyses of the data will be performed by CPT using Microsoft Excel 365 (2021) and will be reviewed by the Quality Assurance Department internally at CPT. Since all statistical methods are specified in this protocol and they are all in accordance with ISO 24444: 2010 (E), a separate Reporting Analysis Plan (RAP) will not be created for this trial.

A listing with all the individual subject results will be tabulated along with summary statistics, including the average SPF, the number of valid pieces of data used to calculate the average, the standard deviation, the standard error of the mean, the critical t-value from a 2-sided Student's t-distribution, the c value (or t value X SEM), the upper and lower 95% Confidence Interval bounds, and the Confidence Interval percentage (or CI[%]) on the mean SPF (see Section 7.3 for details on calculation). A passed or failed grade will also be provided in the listing. Excluded subjects will be flagged accordingly, and reasons for exclusion will be provided in the listing.

8 Adverse Event and Serious Adverse Events

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the trial product or the trial, or that caused the subject to discontinue the trial product or trial.

8.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical trial subject, temporally associated with the use of a trial product including any washout or lead-in product (or medical device), whether or not considered related to the trial product, including any washout or lead-in product (or medical device).

NOTE: 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 trial product including any washout or lead-in product (or medical device).

Events Meeting the AE Definition:

- Unexpected or unusual reactions which occur within the test area that cannot be completely described by the scale in 6.2.2.(e.g., hives) 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 from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after trial product administration even though it may have been present before the start of the trial.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial product 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" or "failure of expected pharmacological action" 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 fulfill 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 the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g., appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.
- Localized erythema caused by exposure of the skin to UV radiation is expected and will not be reported as an adverse event.

8.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event 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 the disease under trial, 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 subject 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 subject 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 baseline 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 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 subject 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 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the trial by the completion (signature) of the ICF and until 14 days following last administration of the trial product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

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

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the trial, and he/she considers the event to be reasonably related to the trial product or trial participation, the investigator must promptly notify the sponsor.

8.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the trial product(s), participation in the trial, or a trial procedure, or that caused the subject to discontinue the trial product or trial.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as "How do you feel" will be assessed and any AE's recorded in the CRF and reported appropriately.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the trial subject. In addition, each trial subject will be questioned about AEs.

Each AE is to 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 investigator (or medically qualified designee) to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is not acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

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

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the trial visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

8.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

8.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator trial master file. Original SAE forms will be retained in the investigator trial master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available

- Investigator opinion of relationship to trial product (or trial procedure, if appropriate)
- Criterion for seriousness.

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

- Date of onset of AE
- Date AE stopped, if relevant
- Trial product start date
- Trial product end date if relevant
- Action taken in relation to the trial product
- 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 trial number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after trial site personnel learn of the event. The investigator 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 Trial Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:

PPD

The GSK CH Study Manager or designee 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.

8.5 Evaluating Adverse Events

8.5.1 Assessment of Intensity

The investigator or medically qualified designee will make an assessment of intensity for each AE reported during the trial and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, 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 that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

8.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements.
For each AE (serious and non-serious), the investigator (or medically qualified designee) must provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship (Section 8.5.3) and will also consult the Safety Statement, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the trial product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.5.3 Relationship to Test Material

The relationship or association of the AE to a test material will be characterized as unlikely, possible or probable (reference 12.5). Assessments shall be recorded on the CRF.

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

For safety analyses, AEs that are classified as a possible or probable association to a test material shall be considered test material-related AEs.
Follow-up of the AE, after the date of 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.

8.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each subject and provide further information on the subject'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 subject is lost to follow-up.

The investigator 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 the 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 on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the trial, and considers the event reasonably related to the trial product or trial participation, the investigator will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email bo PPD

The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSKPPD

The investigator will submit any updated SAE data to GSK CH within the designated reporting time frames.

8.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

8.8 Regulatory Reporting Requirements 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 product under clinical investigation. Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

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

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 necessary.

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 and then file it along with the Investigator's Brochure in the investigator trial master file, and will notify the IRB/IEC, if appropriate according to local requirements.

8.9 Pregnancy

8.9.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the trial from the signing of informed consent until 14 days after last administration of trial product.

8.9.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box PPD within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD Original pregnancy information forms will be retained in the investigator trial master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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 subject who becomes pregnant while participating will be withdrawn from trial. If a subject later discovers they were pregnant after their participation in the trial completed, their data will be considered valid for statistical analysis.

9 Data Documents

All data reflecting subject experiences with the trial regimen will be reported by the PI to the Sponsor. One document serves as both the source and CRF document. Data and observations shall be recorded on CRFs. The CRFs are peer reviewed by the clinic staff, as well as reviewed by CPT's Quality Assurance Unit.

CRFs include all original records of observations, results, and activities necessary to reconstruct and evaluate the trial. CRFs include, for example, ICFs, subject notes, and any other records of procedures performed during the trial. All CRFs are to be executed by the PI in a timely manner. Data is reviewed by looking at the CRFs. Correction of CRFs will be according to the SOPs at CPT.

10 Quality Control and Quality Assurance

10.1 Trial Monitoring by the Sponsor

In accordance with current FDA regulations and GCP guidelines, the Sponsor's Monitor or designee may periodically inspect all trial related data at research facilities, and clinical laboratory facilities associated with this trial at mutually convenient times during or after completion of the trial (reference 12.6). The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the trial, verify the accuracy and completeness of CRFs, assure that all protocol requirements, applicable FDA laws and regulations, and PI's obligations are being fulfilled, and to resolve any inconsistencies in the CRFs.

10.2 Trial Reviewing by CPT Quality Assurance Unit

CPT's Quality Assurance Unit shall periodically audit the trial for compliance with the approved protocol (or written instructions provided by the Sponsor), CPT's SOPs, and all applicable laws and regulations. The Quality Assurance Unit shall review trial records,

documents, and reports for accuracy, completeness, consistency, and compliance with the approved protocol (or written instructions received from the Sponsor), CPT's SOPs, and all applicable laws and regulations.

10.3 Data Maintenance

Trial data shall be maintained in accordance with the intent and purpose of GCP guidelines, CPT's SOPs, and all applicable laws and regulations. Where trial data is entered into electronic databases, audits shall be conducted to verify accuracy of data entries against CRFs. Quality Assurance Unit reviewing will be conducted in accordance with CPT's SOPs to assure the quality and integrity of the clinical data.

11 Obligations of the Sponsor, the Monitor, and the PI

11.1 Sponsor Obligations

The Sponsor's medical oversight responsibilities are detailed below. Subjects will be provided with a Subject Contact Card to carry with them in case of a medical emergency.

11.1.1 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the Study Contact List located in the investigator trial master file held at the trial site.

The contact number is only to be used by investigational staff seeking advice on medical questions or problems in the event that the established communication pathways between the investigational site and the trial team are not available.

The contact number is not intended for direct use by trial subjects. To facilitate access to appropriately qualified medical personnel on trial-related medical questions or problems, subjects will be provided with a contact card.

The contact card will provide, as a minimum, protocol identifiers, the subject's trial identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

11.2 Ethics

The Sponsor, the Monitor, and the PI will assure that all aspects of this trial are conducted in accordance with all applicable regulations and laws guiding the protection of human subjects (including the regulations requiring informed consent (reference 12.7) and the approval and ongoing review of the research by an IRB (reference 12.8)). The trial will be conducted in accordance with the Principles of the Declaration of Helsinki (as amended) and the Belmont Report, with GCP, and CPT's SOPs.

11.3 Institutional Review Board (IRB)

Where applicable, prior to enrollment of subjects into the trial, as required by federal regulations (reference 12.8), the standard protocol, ICF, MHF, and Investigator's Brochure will be reviewed and approved by an appropriate IRB. The PI will assure that all aspects of the institutional review will be conducted in accordance with current federal regulations. A letter documenting the IRB approval with the names and titles of the IRB members may be received by the Sponsor upon request. Amendments to the protocol or the ICF will be subject to the same requirements as the originals.

The PI shall submit a progress report, at least annually to the IRB, of those test material-specific trials approved by the IRB. This report shall include: the total number of test materials evaluated using this protocol; a description of any changes in trial procedures or

amendments to the protocol; deviations from the protocol; the number and type of subjects evaluated; the number of subjects who discontinued (and the reasons for discontinuation); the number of subjects who completed the trial; and a description of any AEs.

11.4 Informed Consent

Written informed consent must be obtained from each potential subject prior to entering the trial (reference 12.7). Potential subjects will be informed of the nature of the trial and shall receive complete answers to any questions raised during the consenting process. An executed ICF shall be provided to each subject. The PI must assure that executed ICFs will be obtained from each subject prior to trial entry, and that the informed consent process will be conducted in accordance with applicable local, state, and federal laws and regulations. Executed ICFs will be retained by the PI with the CRFs.

11.5 Research Subject Confidentiality

The names and identities of all research subjects shall be maintained in strict confidence by CPT and will not appear on CRFs or other records provided to the Monitor or the Sponsor. While the names and identities of the subjects need not be divulged, the records must be available for inspection. This can be accomplished by redacting the subject's names and replacing the name with the subject's trial ID number. The ICF must include appropriate statements explaining these requirements. If this policy conflicts with local regulatory restrictions or institutional requirements, the Sponsor or Monitor shall notify CPT prior to trial initiation.

11.6 Deviation from the Protocol

The PI 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 the subjects. In that event, the PI must notify the IRB and the Sponsor in writing within 5 working days after the change is implemented.

Any other changes to this protocol must be made in the form of a formal amendment to the protocol and must be approved in writing by the PI, the Sponsor, and the IRB prior to implementation.

11.7 Clinical Trial Records

During the trial, the PI will maintain adequate records for the trial. This may include medical records, records detailing the progress of the trial for each subject, laboratory reports, CRFs, executed ICFs, test material disposition records, correspondence with the IRB, AE reports and information regarding subject discontinuation or completion of the trial.

Trial documentation may include all CRFs, monitoring logs, correspondence between the Sponsor and the PI, protocols, amendments, and deviations, test material supplies receipt, dispensing and final disposition records, IRB correspondence and approvals and executed ICFs.

All records pertaining to the conduct of the clinical trial including signed CRFs, ICFs, test material accountability records, and other trial documentation shall be retained in the CPT archives for a minimum of **15 years.** At any time prior to the completion of the tenth archival year, the Sponsor may submit a written request to obtain custody of these records and documents once the CPT archive period has been completed. This transfer shall be performed at the expense of the Sponsor. In the absence of such written requests, trial-related records and documents shall be destroyed at the end of the CPT archive period, with no further notice, in a manner that renders them useless.

11.8 Final Report

A Final Report, describing the following will be prepared and sent to the Sponsor upon completion of the trial:

- Date of the clinical trial
- Test material identification and expected SPF
- Subject information, excluding identifiers per HIPAA
- Characterization of the UV source
- Control standard used
- Individual MEDu, MEDp for test material and MED for control standard
- SPFi to one decimal place, including all valid data and all rejected data for test material and for control standard
- Mean SPF values, standard deviation on the mean and 95% confidence interval
- Protocol deviations, if any
- Adverse events, if any
- Amendments, if any
- Identification, by subject, of the technician who conducted the procedure
- Other reporting requirements specified by the Australia/New Zealand standard, Appendix A (reference 12.2)

11.9 Communication and Publication of Results

The Sponsor shall retain ownership of all CRFs, data analysis and reports, which result from this trial. All information obtained as a result of the trial will be regarded as confidential.

The Final Report or Report summary is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the Report nor the name of CPT 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 CPT.

12 References

12.1 International Standard ISO 24444:2010(E).

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