Clinical Protocol

207640

CONFIDENTIAL

SUMMARY INFORMATION

Title:	Determination of the Sun Protection Factor of a Cosmetic Daily Defence Skin Cream
Protocol Number:	207640
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) St George's Avenue, Weybridge, Surrey, KT13 0DE, UK. Tel: PPD
Product Name:	Physiogel Daily Defence Protective Day Cream Light
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD

Key Protocol Authors:	
PRIMARY CONTACT **Clinical Study Manager:**	PPD GSKCH, St George's Avenue, Weybridge, Surrey, KT13 0DE, UK. Tel: PPD
PRIMARY CONTACT **Clinical Research Scientist:**	PPD, Ph.D. GSKCH, St George's Avenue, Weybridge, Surrey, KT13 0DE, UK. Tel: PPD
Biostatistician:	PPD
Medical Affairs Lead:	PPD
Clinical Supplies:	PPD
Data Manager:	PPD

Principal Investigator:	PPD **MARIANNE BRANDT (DIPL.-PHYS.)** **EMAIL:** PPD **TEL:** PPD
Study Site Name & Address:	proDERM Institute for Applied Dermatological Research Kiebitzweg 2

	22869 Schenefeld/Hamburg Germany
Study Site Telephone Number:	Tel: PPD
Study Examiner(s):	To be assigned per site staff designation log at study start.

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

1) I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current ICH GCP guidelines.

2) I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

3) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.

4) I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	PPD
Investigator Qualifications:	
Investigator Signature:	
Date of Signature/ Agreement:	DD/MMM/YYYY

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PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate Independent Ethics Committee (IEC) in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IEC as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1	Non-Substantial/Minor ☒	The Principal Investigator and Data Manager for this study were changed.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	Summary Information, Page 2	Signature: PPD
Protocol Version No.: 2	Substantial/ Major ☐				Date: PPD
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:

SCHEDULE OF EVENTS

Procedure/Assessment	Visit 1	Visit 2[1] 0-7 Days after Visit 1	Visit 3 1 Day after Visit 2	Visit 4[1] 0-7 Days after Visit 3	Visit 5 1 Day after Visit 4
	Subject Screening	Provisional MED Irradiation (UV exposure)	Provisional MED Determination	Test Irradiation (UV exposure)	MEDp and MEDu Determination and SPF Calculation for Test and Reference Sunscreen
Informed Consent	X				
Demographics	X				
Medical History	X				
Current / Concomitant Medication	X	X[2]	X	X[2]	X
Individual Typology Angle (ITA°)	X				
Fitzpatrick Skin Type Assessment	X				
In/Exclusion Criteria	X	X[2,3]			
Subject Eligibility	X	X[2]			
Continued Eligibility		X[2]	X	X[2]	X
Randomisation		X			
Provisional Minimum Erythemal Dose (MEDu) Irradiation		X			
Visual Grading of Exposure Sub-Sites (Test Sites)[4]			X		X
Study Product Application to Randomly Assigned Test Sites on the Back				X	
Study Irradiation				X	
Adverse Events		X	X	X[2]	X
Subject Discharge from Study					X

1. Visit 2 may be combined with Visit 1; Visit 4 may be combined with Visit 3. If these visits are not combined, they must happen within 7 calendar days of one another. Therefore, the total duration of the study for each subject could range from 3 to 16 calendar days.
2. Not required if this visit is combined with the previous visit.
3. To include a review of exclusion criteria in Appendix 2.
4. Visual Grading of skin must happen 16-24 hours after irradiation.

PROTOCOL SYNOPSIS FOR STUDY 207640

Brief Summary

An important parameter of efficacy for sunscreen products is the Sun Protection Factor (SPF). SPF is a measure of how much solar energy (UV radiation) is required to produce sunburn on protected skin (i.e. in the presence of sunscreen) relative to the amount of solar energy required to produce sunburn on unprotected skin. In this study, the SPF of the test product is to be determined according to the International Standards Organization (ISO) 24444:2010 methodology (*In vivo determination of the sun protection factor*).

This study will be conducted in accordance with the Declaration of Helsinki and according to the current International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
To determine the Sun Protection Factor of the test product	Arithmetical mean of all valid individual sun protection factor (SPFi) values; where SPFi = Minimal Erythemal Dose of product treated (MEDp) test sites in relation to unprotected (MEDu) test sites 16-24 hours after exposure to ultraviolet (UV) radiation.
To evaluate the general safety of the test product	Frequency and severity of Adverse Events

Study Design

Overall Design
A single-center, randomized, evaluator blind, intra-individual comparison, no treatment and positive controlled clinical study to determine the SPF of Physiogel Daily Defence Protective Day Cream Light as per ISO 24444:2010. The provisional minimal erythemal dose of unprotected skin (MEDu) for each subject will be determined before starting the main test in order to center the UV dose ranges for the exposures of MEDu and MEDp. As the first step, a virgin area of skin on the back will be exposed to a preliminary series of UV exposures. The location of the irradiated test site for the provisional MEDu measurement will be randomised for all

subjects. In this study, there will be a total of four irradiated test sites. Two test sites will be located below the scapula line, either side of the spine. The remaining two areas will be located below these sites and above the waist.

Six exposure sub-sites positioned within the randomised test area and centered on the estimated MEDu will be exposed to incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered will be chosen so that the estimated MEDu will be irradiated at the 4th of the 6 sub-sites. The estimated MEDu will be predicted based on the subject's mean Individual Typology Angle (ITA°) value. As the second step, a trained evaluator will assess the irradiated sub-sites for signs of unambiguous erythema 16-24 hours after UV exposure to determine the provisional MEDu. The provisional MEDu will be the lowest dose of UV radiation that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure.

Once the provisional MEDu for a subject has been determined, the three remaining test sites will be demarcated. The test product (Physiogel Daily Defence Protective Day Cream Light) and positive control (P3 reference sunscreen formulation) will be applied to two of the three virgin test sites. The other test site will remain unprotected. The order of product application (test product, reference product and unprotected test site) will be randomised over the entire test group. Once the test product and positive control have been applied to the assigned test sites, the subject will undergo a second series of incremental UV exposures. For the unprotected site, the range of UV doses administered shall be selected using the subject's provisional MEDu. Six exposure sub-sites centered on the provisional MEDu shall be exposed with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered to subjects will be chosen such that the provisional MEDu will be irradiated at the 4th of the 6 sub-sites. For the product protected sites, the UV doses administered shall be selected using the subject's expected MEDp, which is the multiple of the provisional MEDu for the subject and the expected SPF of either the test product (21) or reference sunscreen formulation (16). A minimum of 6 sub-sites centered on the expected MEDp shall be exposed with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered to subjects will be chosen such that the expected MEDp will be irradiated at the 4th of the 6 sub-sites.

The minimum number of valid individual SPF (SPFi) results shall be 10 and the maximum number of valid SPFi results shall be 20. In order to achieve between 10 and 20 valid results, a maximum of five individual invalid results may be excluded

from the calculation of the mean SPF. Consequently the actual number of test subjects used will fall between a minimum of 10 and a maximum of 25 subjects (i.e. a maximum of 20 valid results plus 5 rejected invalid results). The study will include subjects of more than one Fitzpatrick phototype (I, II or III). It will not be permitted to adjust the expected SPF of the test product from subject to subject.
Visit 1 – Subject Screening
The following assessments will be conducted: 1. Informed Consent 2. Demographics 3. Medical History 4. Current / Concomitant Medication 5. ITA° Measurement 6. Fitzpatrick Skin Type Assessment 7. In/Exclusion Criteria 8. Subject Eligibility
Visit 2 – Provisional MED Irradiation (UV Exposure)
The following assessments will be conducted: 1. Current / Concomitant Medication* 2. Continued Eligibility* 3. Exclusion Criteria* 4. Subject Eligibility* 5. Randomisation 6. Provisional Minimal Erythemal Dose (MED) Irradiation 7. Adverse Events *Not required if Visit 2 is combined with Visit 1
Visit 3 – Provisional MED Determination
The following assessments will be conducted: 1. Current / Concomitant Medication 2. Continued Eligibility 3. Visual Grading of Exposure Sub-Sites (Test Sites)* 4. Adverse Events *Visual grading of skin must occur 16-24 hours after completion of the Provisional MED Irradiation procedure
Visit 4 – Test Irradiation (UV Exposure)
The following assessments will be conducted:

1. Current / Concomitant Medication* 2. Continued Eligibility* 3. Test Product and Reference Sunscreen Application to Randomly Assigned Test Sites on the Back 4. UV Exposure of Test Product Treated, Reference Sunscreen Formulation Treated and Unprotected Test Sites. 5. Adverse Events *Not required if Visit 4 is combined with Visit 3
Visit 5 – MEDp and MEDu determination and SPF calculation for test and reference sunscreen
The following assessments will be conducted: 1. Current / Concomitant Medication 2. Continued Eligibility 3. Visual Grading of Exposure Sub-Sites to Determine MEDp and MEDu and calculate SPF* 4. Adverse Events 5. Subject Discharge from Study * Visual grading of skin must occur 16-24 hours after completion of the test irradiation procedure

Type and Planned Number of Subjects

Healthy volunteers aged between 18-70 years (inclusive) with Fitzpatrick phototype I, II or III, an ITA° value greater than 28° and who are untanned on the test area will be recruited for this study. The study will contain a population of subjects of more than one Fitzpatrick phototype.

To complete the study successfully, the minimum number of valid individual sun protection factor (SPFi) results will be 10 and the maximum number of valid SPFi results will be 20 for both the test product and positive control. In order to achieve between 10 and 20 valid SPFi results, a maximum of 5 individual invalid results may be excluded from the calculation of the mean SPF. Consequently, the actual number of subjects used for the study will fall between a minimum of 10 and a maximum of 25 (i.e. a maximum of 20 valid SPFi results plus 5 rejected invalid results).

In order to determine the number of test subjects, the 95% confidence interval (95% CI) of the mean SPF shall be taken into account. A minimum of 10 subjects shall be tested. The test shall be considered valid for the first 10 subjects if the resulting range of the 95% CI of the mean SPF is within ±17% of the mean SPF. If it is not within ±17% of the mean SPF, the number of subjects shall be increased stepwise from the minimum number of 10 until the 95% CI statistical criterion is met (up to a maximum

of 20 valid results from a maximum of 25 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.

Product Information

	Test Product	Reference Product
Product Name	Physiogel Daily Defence Protective Day Cream Light	P3 Standard
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available
Expected SPF	21	16
Application Quantity	2.00 ± 0.05 milligrams per square centimeter (mg / cm^2)	2.00 ± 0.05 mg / cm^2
Route of Administration	Topical	Topical

Statistical Methods

The SPF result for the test product and for the reference sunscreen formulation is calculated as the arithmetical mean of all valid SPFi values. The minimum number of valid SPFi values shall be 10 and the maximum number of valid SPFi values 20. A maximum of 5 results may be excluded from the calculation of the mean SPF, but each exclusion shall be justified. A sixth invalid result automatically invalidates the whole test for that test product and no SPF can be calculated for it. In addition, if the mean SPF obtained for the reference sunscreen formulation (P3) does not fall within the acceptance limits of the reference values (i.e. between SPF 13.7-17.7, inclusive) then the entire test shall be rejected.

The statistical criterion for all SPF measurements is that the 95% confidence interval (CI) of the mean SPF measured shall fall within a range of ±17 % of the mean measured SPF. This applies to test and reference sunscreen products.

Consequently, the actual number of subjects tested is defined as the number (minimum 10) required to produce a mean test product SPF with a 95% CI which falls within a range of ±17 % of the measured mean SPF for the test product and a mean reference product SPF between 13.7-17.7, inclusive, and which has a 95 % CI which falls within the range of ±17 % of the measured mean SPF for the reference product.

A minimum of 10 valid results is only sufficient if the statistical criterion is fulfilled for the test product and positive control. If not, the number of subjects is increased

from 10, for both the test product and positive control, until the statistical criterion is met, with up to a maximum of 20 valid results.

1. INTRODUCTION

The International Standard specifies a method for the *in vivo* determination of the SPF of sunscreen products. It is applicable to products that contain any component able to absorb, reflect or scatter ultraviolet (UV) rays and which are intended to be placed in contact with human skin. It provides a basis for the evaluation of sunscreen products for the protection of human skin against erythema induced by solar UV rays.

The test is restricted to an area of the back of selected human subjects. A section of each subject's skin is exposed to UV light without any protection and another (different) section is exposed after application of the sunscreen product under test. One further section is exposed after application of an SPF reference sunscreen formulation which is used for validation of the procedure.

To determine the SPF, incremental series of delayed erythemal responses are induced on a number of small sub-sites within the test area. These responses are visually assessed for presence of erythema 16 hours (h) to 24 h after UV exposure, by the judgment of a competent evaluator. Individual subject SPF values are determined by dividing the lowest dose of irradiation that results in erythema on skin protected with the sunscreen by the lowest dose of irradiation that results in erythema on unprotected skin. The SPF for a sunscreen is the arithmetic mean of all valid individual subject SPF results.

2. OBJECTIVE(S) AND ENDPOINT(S)

Objective(s)	Endpoint(s)
Primary	
To determine the Sun Protection Factor of the test product	Arithmetical mean of all valid individual sun protection factor (SPFi) values; where SPFi = Minimal Erythemal Dose of product treated (MEDp) test sites in relation to unprotected (MEDu) test sites 16-24 hours after exposure to ultraviolet (UV) radiation.
To evaluate the general safety of the test product	Frequency and severity of Adverse Events

3. STUDY PLAN

3.1. Study Design

Overall Design

A single-center, randomized, evaluator blind, intra-individual comparison, no treatment and positive controlled clinical study to determine the SPF of Physiogel Daily Defence Protective Day Cream Light as per ISO 24444:2010.

The provisional minimal erythemal dose of unprotected skin (MEDu) for each subject will be determined before starting the main test in order to center the UV dose ranges for the exposures of MEDu and MEDp. As the first step, a virgin area of skin on the back will be exposed to a preliminary series of UV exposures. The location of the irradiated test site for the provisional MEDu measurement will be randomised for all subjects. In this study, there will be a total of four irradiated test sites. Two test sites will be located below the scapula line, either side of the spine. The remaining two areas will be located below these sites and above the waist.

Six exposure sub-sites positioned within the randomised test area and centered on the estimated MEDu will be exposed to incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered will be chosen so that the estimated MEDu will be irradiated at the 4th of the 6 sub-sites. The estimated MEDu will be predicted based on the subject's mean Individual Typology Angle (ITA°) value. As the second step, a trained evaluator will assess the irradiated sub-sites for signs of unambiguous erythema 16-24 hours after UV exposure to determine the provisional MEDu. The provisional MEDu will be the lowest dose of UV radiation that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure.

Once the provisional MEDu for a subject has been determined, the three remaining test sites will be demarcated. The test product (Physiogel Daily Defence Protective Day Cream Light) and positive control (P3 reference sunscreen formulation) will be applied to two of the three virgin test sites. The other test site will remain unprotected. The order of product application (test product, reference product and unprotected test site) will be randomised over the entire test group. Once the test product and positive control have been applied to the assigned test sites, the subject will undergo a second series of incremental UV exposures. For the unprotected site, the range of UV doses administered shall be selected using the subject's provisional

MEDu. Six exposure sub-sites centered on the provisional MEDu shall be exposed with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered to subjects will be chosen such that the provisional MEDu will be irradiated at the 4th of the 6 sub-sites. For the product protected sites, the UV doses administered shall be selected using the subject's expected MEDp, which is the multiple of the provisional MEDu for the subject and the expected SPF of either the test product (21) or reference sunscreen formulation (16). A minimum of 6 sub-sites centered on the expected MEDp shall be exposed with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered to subjects will be chosen such that the expected MEDp will be irradiated at the 4th of the 6 sub-sites.

The minimum number of valid individual SPF (SPFi) results shall be 10 and the maximum number of valid SPFi results shall be 20. In order to achieve between 10 and 20 valid results, a maximum of five individual invalid results may be excluded from the calculation of the mean SPF. Consequently the actual number of test subjects used will fall between a minimum of 10 and a maximum of 25 subjects (i.e. a maximum of 20 valid results plus 5 rejected invalid results).

The study will include subjects of more than one Fitzpatrick phototype (I, II or III).

It will not be permitted to adjust the expected SPF of the test product from subject to subject.

Visit 1 – Subject Screening

The following assessments will be conducted:

1. Informed Consent
2. Demographics
3. Medical History
4. Current / Concomitant Medication
5. ITA° Measurement
6. Fitzpatrick Skin Type Assessment
7. In/Exclusion Criteria
8. Subject Eligibility

Visit 2 – Provisional MED Irradiation (UV Exposure)

The following assessments will be conducted:

1. Current / Concomitant Medication*
2. Continued Eligibility*
3. Exclusion Criteria*
4. Subject Eligibility*

5. Randomisation 6. Provisional Minimal Erythemal Dose (MED) Irradiation 7. Adverse Events *Not required if Visit 2 is combined with Visit 1
Visit 3 – Provisional MED Determination
The following assessments will be conducted: 1. Current / Concomitant Medication 2. Continued Eligibility 3. Visual Grading of Exposure Sub-Sites (Test Sites)* 4. Adverse Events *Visual grading of skin must occur 16-24 hours after completion of the Provisional MED Irradiation procedure
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The following assessments will be conducted: 1. Current / Concomitant Medication* 2. Continued Eligibility* 3. Test Product and Reference Sunscreen Application to Randomly Assigned Test Sites on the Back 4. UV Exposure of Test Product Treated, Reference Sunscreen Formulation Treated and Unprotected Test Sites. 5. Adverse Events *Not required if Visit 4 is combined with Visit 3
Visit 5 – MEDp and MEDu determination and SPF calculation for test and reference sunscreen
The following assessments will be conducted: 1. Current / Concomitant Medication 2. Continued Eligibility 3. Visual Grading of Exposure Sub-Sites to Determine MEDp and MEDu and calculate SPF* 4. Adverse Events 5. Subject Discharge from Study * Visual grading of skin must occur 16-24 hours after completion of the test irradiation procedure

3.2. Subject Restrictions

Lifestyle, Medications and Treatments
During the entire study (screening – Last Subject Last Visit (LSLV)): 1. Subjects must not apply any leave-on cosmetics (e.g. creams, lotions, oily

cleansing products) to the test area.
2. Subjects must not apply any detergents (e.g. soaps, shampoos, and bath and shower products) to the test area throughout the entire course of the study.
3. Subjects must avoid any sun exposure, UV-therapy and/or artificial tanning.

3.3. Type and Planned Number of Subjects

Healthy males and females aged between 18-70 years (inclusive) with Fitzpatrick phototype I, II or III, an ITA° value greater than 28° and who are untanned on the test area will be recruited for this study. The study will contain a population of subjects of more than one Fitzpatrick phototype.

The SPF result for the test product and for the reference sunscreen formulation is calculated as the arithmetical mean of all valid SPFi values. The minimum number of valid SPFi values shall be 10 and the maximum number of valid SPFi values 20. A maximum of 5 results may be excluded from the calculation of the mean SPF, but each exclusion shall be justified. A sixth invalid result automatically invalidates the whole test for that test product and no SPF can be calculated for it. In addition, if the mean SPF obtained for the reference sunscreen formulation (P3) does not fall within the acceptance limits of the reference values (i.e. between SPF 13.7-17.7, inclusive) then the entire test shall be rejected.

The statistical criterion for all SPF measurements is that the 95% confidence interval (CI) of the mean SPF measured shall fall within a range of ±17 % of the mean measured SPF. This applies to test and reference sunscreen products.

Consequently, the actual number of subjects tested is defined as the number (minimum 10) required to produce a mean test product SPF with a 95% CI which falls within a range of ±17 % of the measured mean SPF for the test product and a mean reference product SPF between 13.7-17.7, inclusive, and which has a 95 % CI which falls within the range of ±17 % of the measured mean SPF for the reference product.

A minimum of 10 valid results is only sufficient if the statistical criterion is fulfilled for the test product and positive control. If not, the number of subjects is increased from 10, for both the test product and positive control, until the statistical criterion is met, with up to a maximum of 20 valid results.

Subjects will be recruited from the site database and via advertisement in local papers.

3.4. Study Design

As UV rays are responsible for most of the Sun's damaging effects on the skin, the erythemal protective efficiency of sunscreen products is tested within this range of wavelengths. Therefore, the definition of the spectrum of the UV solar simulator is limited to the terrestrial UV wavelengths, i.e. from 290 nanometers (nm) to 400 nm. Wavelengths below this range (<290 nm) do not occur in terrestrial sunlight and should be excluded, whilst those above this range (>400 nm) may cause undesirable side effects (particularly thermal effects) and should be removed using appropriate devices.

This study is designed to be compliant with international standard ISO 24444:2010 which mandates a controlled product dose of 2.00 ± 0.05 milligrams (mg) per square centimeter (cm^2) of test site area.

The dorsum (back) is chosen as the anatomical region for the test. The individual product test sites and the unprotected test site will be delineated within the region between the scapula line and the waist. Skeletal protrusions and extreme areas of curvature will be avoided and test sites will be free from blemishes and have an even colour tone.

The total area of the individual test sites for provisional MEDu determination, product application and the untreated site will be 40 cm^2 and there will be a minimum distance of 1 centimeter (cm) between the borders of adjacent test sites to ensure no overlap of product and UV exposure. In addition, the minimum distance between borders of each exposure sub-site will be at least 0.8 cm and the distance between any exposure sub-site and any edge of the test site will be at least 1 cm. Test sites will be delineated using a marker and template made from non-absorbent materials in a manner which will not interfere with the test or harm the subject. Prior to product application, test sites may be cleaned by using a dry cotton pad or equivalent.

The positions of the test product and reference sunscreen test sites will be distributed randomly on the backs of subjects over the whole test group in order to reduce error arising from anatomical differences in the skin. The test site used to determine the unprotected minimal erythemal dose (MEDu) will be randomised as one of the test sites across the back and across subjects. Test site demarcation, product application and irradiation procedures will be conducted with the subject lying horizontally on their front.

A reference sunscreen formulation (P3) will be included as a comparator to verify the test procedure.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Safety Statement.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. CONSENT
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form

2. AGE
Aged between 18 and 70 years inclusive

3. GENDER
Subject is male or female

4. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee no clinically significant and relevant abnormalities in medical history or upon physical examination

5. SKIN TYPE/CONDITION
A. Subjects with a Fitzpatrick Skin Type of I, II or III B. Subjects with an ITA° greater than 28°

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. PREGNANCY
Women who are known to be pregnant or who are intending to become pregnant over the duration of the study

2. BREAST-FEEDING
Women who are breast-feeding or lactating

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
A. Subjects having used medication with known photo-toxic and/or photo-sensitizing potential (e.g. hypericum perforatum, antibiotics, blood pressure regulating agents) up to 14 days prior to screening B. Subjects with a history of systemic therapy with anti-inflammatory agents or analgesics (e.g. diclophenac) up to 3 days prior to screening C. Subjects with dermatological conditions D. Subjects with a history of abnormal response to the sun E. Subjects who are tanned or have had sun exposure on the back area in the previous 4 weeks prior to screening F. Subjects having marks, blemishes or nevi or presenting existing sun damage in the test area G. Subjects having excessive hair, moles, tattoos, scars or other imperfections in the test area that could influence the investigation H. Subjects with a history of systemic therapy with immuno-suppressive drugs (e.g. corticosteroids) and/or antihistamines (e.g. anti-allergics) up to 7 days prior to screening I. Subjects with a non-uniform skin colour or hyperpigmentation in the test area J. Subjects with a medical history of dysplastic nevi or melanoma K. Subjects with one of the following illnesses that might require regular systemic medication: Insulin-dependent diabetes, cancer L. Subjects with asthma, unless medicated M. Subjects with an electronic implant (e.g. pace maker, insulin pump, hearing aid) that cannot be removed during irradiation N. AIDS and infectious hepatitis, if known to the subjects

4. ALLERGY/ INTOLERANCE
A. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients B. Known allergy to latex

5. CLINICAL STUDY/ EXPERMENTAL PRODUCT
A. Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days prior to screening B. Participation in another clinical study involving UV exposure to the same test site up to 2 months prior to screening C. Previous participation in this study

6. SUBSTANCE ABUSE
Recent history (within the last 5 years) of alcohol or other substance abuse

7. LIFESTYLE
A. Subjects who have used a tanning bed or other tanning treatment on the back area up to 1 month prior to screening B. Subjects accustomed to using tanning beds C. Subjects who have used self-tanning products on the back area in the previous 1 month prior to screening

8. PERSONNEL
An employee of the sponsor or the study site or members of their immediate family

9. AGE
Subjects who will turn 71 years old before completing all assessment visits

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening of subjects will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

1. The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
2. The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
3. In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject's record.
4. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.5. Subject Replacement

Subjects who withdraw from the study post-randomization will be replaced if necessary to meet the ISO statistical criteria. No more than 25 subjects will be randomised for this study.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study.

The end of the study is defined as the date of the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

The following study products will be supplied by the Clinical Supplies Department, GSKCH:

	Test Product	Reference Product
Product Name	Physiogel Daily Defence Protective Day Cream Light	P3 Standard
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available
Expected SPF	21	16
Application Quantity	2.00 ± 0.05 mg / cm^2	2.00 ± 0.05 mg / cm^2
Route of Administration	Topical	Topical

Other items to be supplied by the Clinical Supplies Department, GSKCH:

Name of Item	Purpose
N/A	N/A

5.2. Application Schedule

Test sites intended for UV exposure shall be free from blemishes and have an even colour tone. The total area for test site study product application will be 40 cm^2. Test site demarcation, product application, UV exposures and MED assessments will be conducted with the subject lying horizontally on their front in stable conditions and in a room with controlled temperature (22 ± 4 °C).

The positions of the unprotected test site for provisional MEDu, test product, reference sunscreen and unprotected test sites will be randomised on each subject and over the whole group in order to reduce error arising from anatomical differences in skin. There will be a minimum distance of 1 cm between the borders of adjacent test sites to ensure no overlap of product and UV exposure. Prior to product application, the test site may be cleaned using a dry cotton pad or equivalent. The test sites will be delineated by a method which does not interfere with the procedures or assessments or harm the subject, using a skin marker and template made from non-absorbent material. Test sites will not overlap with the site previously used for the provisional MEDu assessment.

The amount of test product and reference sunscreen formulation applied to the skin before spreading will be 2.00 ± 0.05 mg / cm^2 (i.e. 78.0 – 82.0 mg, inclusive). The balance used to weigh the products must be calibrated and capable of weighing to the nearest 0.0001 grams (g) (i.e. to the nearest 0.1 mg). All products will be homogeneous and will be shaken, if necessary, before weighing to ensure uniform dispersion.

When handling the product during weighing or before application to the skin, appropriate measures will be taken to prevent evaporative loss of the volatile components as it is important that the total quantity of weighed product is transferred to the product application site. In particular, study staff will apply the test product to subjects immediately after weighing and the containers filled with product will remain sealed when not in use.

The amount of product to be applied will be weighed in a syringe. The syringe will be loaded with sufficient product to deliver 2.00 ± 0.05 mg / cm^2 to the test site and weighed alongside a new, unsaturated finger cot. The syringe will then be evacuated directly on to the test site. To aid uniform coverage, droplets (approximately 20) of the product will be deposited within the test site, then spread over the whole test site using the weighed finger cot, applying a light pressure. The spreading time will be in the range of 35 ± 15 seconds. Once spreading is complete, the used finger cot and evacuated syringe will be weighed again and the total mass of applied product calculated and recorded. If the mass of total applied product is less than 78.0 mg or greater than 82.0 mg the test site will not undergo UV exposure. If there is sufficient space on the subject's back, between the scapula line and waist, a new 40 cm^2 site will be demarcated and will be positioned at least 1 cm from the borders of the other four test sites. The new test site will only undergo UV exposure if the total mass of applied product is 78.0 to 82.0 mg, inclusive. If there is insufficient space on the subject's back to accommodate the test product, positive control and unprotected sites then the subject will not undergo any UV exposure and they will be discontinued from further participation in the study.

5.3. Application Modification

No modification of product application is permitted.

5.4. Product Compliance

Controlled application of study product to test sites will be conducted by a trained technician. A second technician will oversee product application to ensure compliance with the protocol.

5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol.

5.6. Overdose

An overdose is a deliberate or inadvertent administration of a product at a dose higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied and the applications will be performed and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

5.7. Rescue Therapy

No rescue therapy is required in this study.

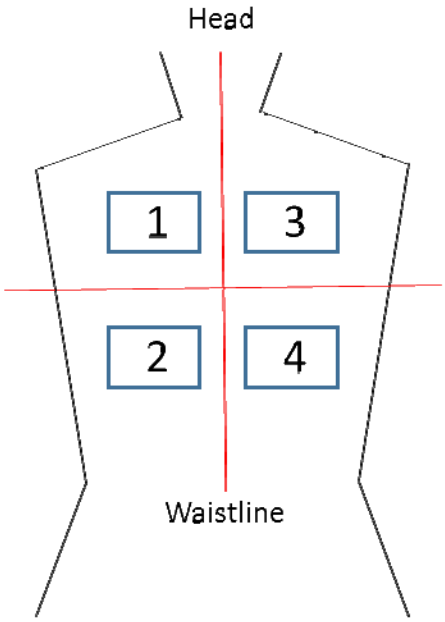
5.8. Product Assignment

The positions of the unprotected test site for provisional MEDu, test product, reference product and unprotected test site will be distributed randomly on the backs of subjects over the whole test group in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH or assigned CRO, prior to the start of the study, using validated software.

5.8.1 Randomization

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomized according to the randomization schedule to achieve balance between left upper (Site 1), left lower (Site 2), right upper (Site 3) and right lower (Site 4) of back as per Figure 1.

Figure 1: Test site locations and numbering



5.8.2 Blinding

This is a single-blind (outcome evaluator) study. Therefore, the trained grader responsible for assessing MEDu and MEDp at Visit 5 will be blinded to the product allocation of subjects. The trained grader responsible for assessing the provisional MEDu at Visit 3 will, necessarily, not be blinded since only one test site will be exposed to UV radiation.

5.8.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Wherever possible the Investigator (or designee) must contact the Sponsor prior to breaking the blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

The study blind must be returned to GSKCH at the end of the study.

5.9. Packaging and Labelling

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

The test product Physiogel Daily Defence Day Cream Light ([redacted]) will be supplied in white pumps with a study label affixed. Each study label will contain, but not be limited to, protocol number, treatment group code and directions for storage.

The reference product (P3 Standard) will be supplied in 2 ounce bottles. The original bottle label will be over-wrapped with white vinyl wrap. A study label will be affixed to each bottle supplied and the label text will contain, but not be limited to, protocol number, treatment group code and directions for storage.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study.

5.9.1. Accountability of Product

All products supplied are for use only in this clinical study and should not be used for any other purpose.

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current and will contain the following information:

1. The identification of the subject to whom the study product was dispensed.
2. The date(s) and quantity of the study product applied to the subject.

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.9.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place, protected from sunlight, with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Events section.

Adherence to the study design requirements, including all assessments and procedures are essential and required for study conduct.

6.1. Visit 1 – Subject Screening

6.1.1. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject, will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Subjects should be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

6.1.2. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender, race, Fitzpatrick skin type (see 6.1.5 for details) and Individual Typology Angle (see 6.1.4 for details).

6.1.3. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.4. Individual Typology Angle (ITA°)

A tri-stimulus chromameter (Minolta CR 400, Langenhagen, Germany) which utilizes the L*, a*, b* colour space and complies with International Commission on Illumination (CIE) recommendations will be used to measure the colour of each subject's skin (dorsum). Subjects will rest for 10 minutes in the prone position, with the skin area uncovered, to eliminate contact or stress-related redness and marks. During measurements, care will be taken to apply the cone aperture of the reflectance colorimeter sensing head so that it just makes contact with the skin, without any pressure, to avoid any skin "blanching" effect. Four measurements will be taken on the back of each subject, between the waist and shoulder line, and the individual L*, and b* values will be recorded as source data. The ITA° will be calculated as per Equation 1 and recorded on the CRF.

$$\text{ITA}^\circ = \left\{ \text{arc tangent} \left[\frac{(L^* - 50)}{b^*} \right] \right\} \frac{180}{3.14159} \qquad \text{(Equation 1)}$$

*arc tangent is expressed in radians.

The mean ITA° and historical data will be used to estimate the MEDu for each subject. The estimated MEDu will be recorded on the CRF.

6.1.5. Fitzpatrick Skin Type Assessment

Fitzpatrick skin type assessment will be conducted by a trained, qualified technician or physician using the scale below.

CCI

The Fitzpatrick skin type will be recorded on the CRF.

6.1.6. Inclusion/Exclusion Criteria

Inclusion/exclusion criteria will be assessed by the Investigator or designee and subject compliance with each criterion recorded on the CRF.

6.1.7. Subject Eligibility

Subject eligibility to participate in the study will be assessed by the Investigator or medically qualified designee and recorded on the CRF.

6.2. Visit 2 – Provisional MED Irradiation (UV Exposure)

Before starting the main test, a provisional MEDu will be determined for each subject in order to centre to UV dose ranged for the exposures of MEDu and MEDp.

6.2.1. Concomitant Medication

Any concomitant therapy taken since the last visit and throughout the study will be recorded on the CRF by the Investigator or medically qualified designee.

6.2.2. Exclusion Criteria

Subject compliance with exclusion criteria in Appendix 2 will be re-assessed by the Investigator or designee and subject compliance with each criterion recorded on the CRF.

6.2.3. Subject Eligibility

Following the review of the exclusion criteria specified in 6.2.2, subject eligibility to continue in the study will be assessed by the Investigator or medically qualified designee and recorded on the CRF.

6.2.4. Continued Eligibility

The Investigator or designee will ascertain whether there have been any deviations from the protocol since the last visit, whether the subject has adhered to the lifestyle restrictions since the last visit and whether, in their opinion, the subject is eligible to continue in the study and their decision will be recorded on the CRF.

6.2.5. Randomisation

Subject randomisation will be conducted as per the process detailed in Section 5.8.1.

6.2.6. Provisional Minimal Erythemal Dose Irradiation

The specification of the solar simulator output is included in Appendix 3. A UV dose is the result of multiplying the UV source irradiance by the episode duration. In this study, a solar simulator with 6 light guides exposing all sub-sites for the same duration but with varied irradiance values will be used. Before UV exposure of each test site, irradiance values will be measured and recorded with a radiometer which has been calibrated with a spectroradiometric measurement of the solar simulator output.

A suitable warm-up time of at least 10 minutes will be allowed for the UV solar simulator to stabilize before starting exposures. This is to ensure a consistent irradiance over the whole exposure period. UV exposures and MED assessments will be conducted in stable conditions, with the subject lying horizontally on their front (prone) and in a room with controlled temperature (22 ± 4 °C).

Test sites intended for UV exposure shall be free from blemishes and have an even colour tone. In this study, there will be a total of four irradiated areas. Two areas will be located below the scapula line, either side of the spine. The remaining two areas will be located below these sites and above the waist. The location of the irradiated area for the provisional MEDu measurement will be randomised over the whole test group in order to reduce error arising from anatomical differences in skin.

Six exposure sub-sites centered on the estimated MEDu will be exposed with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered will be chosen so that the 4th of the 6 sub-sites will be irradiated with the estimated MEDu. The estimated MEDu will be predicted based on the subject's mean Individual Typology Angle (ITA°) value.

The minimum area of each exposure sub-site will be 0.5 cm^2. The minimum distance between borders of each exposure sub-site (spots) will be at least 0.8 cm. The distance between any exposure sub-site and any edge of the test site will be at least 1 cm.

Any extraneous exposure of the test sites to UV light (artificial or natural) will be avoided during this period and for a period of 24 hours after exposure. Any additional UV exposure to the test area will invalidate the whole test for the subject concerned.

6.2.7. Adverse Events

Adverse events will be assessed by the Investigator or designee and recorded on the CRF, as per the process detailed in Section 7. Localised erythema caused by exposure of the skin to UV radiation is expected and will not be reported as an adverse event.

6.3. Visit 3 – Provisional MEDu Determination

6.3.1. Concomitant Medication

Any concomitant therapy taken since the last visit and throughout the study will be recorded on the CRF by the Investigator or medically qualified designee.

6.3.2. Continued Eligibility

The Investigator or designee will ascertain whether there have been any deviations from the protocol since the last visit, whether the subject has adhered to the lifestyle restrictions since the last visit and whether, in their opinion, the subject is eligible to continue in the study and their decision will be documented on the CRF.

6.3.3. Visual Grading of Exposure Sub-Sites (Test Sites)

The MED is defined as the lowest dose of UV radiation that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 to 24 hours after UV exposure.

The MED assessment will be assessed visually by a trained grader with the subject lying horizontally on their front and in a room with controlled temperature (22 ± 4 °C). The same grader will assess all subjects in the study. The grader's eyesight must have been checked for normal colour vision and acuity within the previous year. Visual assessment will be performed in a room with matt, neutral wall colours with sufficient and uniform illumination. As only one site will be exposed to UV radiation for the detection of the provisional MEDu, the grader will, necessarily, not be blinded at this point in the study.

The provisional MEDu of each subject will be recorded on the CRF with units of mJ/cm^2.

6.3.4. Adverse Events

Adverse events will be assessed by the Investigator or designee and recorded on the CRF, as per the process detailed in Section 7. Localised erythema caused by exposure of the skin to UV radiation is expected and will not be reported as an adverse event.

6.4. Visit 4 – Test Irradiation (UV Exposure)

6.4.1. Concomitant Medication

Any concomitant therapy taken since the last visit and throughout the study will be recorded on the CRF by the Investigator or medically qualified designee.

6.4.2. Continued Eligibility

The Investigator or designee will ascertain whether there have been any deviations from the protocol since the last visit, whether the subject has adhered to the lifestyle restrictions since the last visit and whether, in their opinion, the subject is eligible to continue in the study and their decision will be documented on the CRF.

6.4.3. Study Product Application to Randomly Assigned Test Sites on the Back

Test sites intended for UV exposure shall be free from blemishes and have an even colour tone. The total area for test site study product application will be 40 cm^2. Test site demarcation, product application, UV exposures and MED assessments will be conducted in stable conditions with the subject lying horizontally on their front and in a room with controlled temperature (22 ± 4 °C).

The positions of the test product, reference sunscreen and unprotected test sites will be randomised over the whole group in order to reduce error arising from anatomical differences in skin. There will be a minimum distance of 1 cm between the borders of adjacent test sites to ensure no overlap of product and UV exposure. Prior to product application, the test site may be cleaned using a dry cotton pad or equivalent. The test sites will be delineated by a method which does not interfere with the procedures or assessments or harm the subject, using a skin marker and template made from non-absorbent material. Test sites will not overlap with the site previously used for the provisional MEDu assessment.

The amount of test product and reference sunscreen formulation applied to the skin before spreading will be 2.00 ± 0.05 mg / cm^2 (i.e. 78.0 – 82.0 mg, inclusive). The balance used to weigh the products must be calibrated and capable of weighing to the nearest 0.0001 grams (g) (i.e. to the nearest 0.1 mg). All products will be homogeneous and will be shaken before weighing to ensure uniform dispersion.

When handling the product during weighing or before application to the skin, appropriate measures will be taken to prevent evaporative loss of the volatile components. In particular, study staff will apply the test product to subjects immediately after weighing and the containers filled with product will remain sealed when not in use.

The amount of product to be applied will be weighed in a syringe. The syringe will be loaded with sufficient product to deliver 2.00 ± 0.05 mg / cm^2 to the test site and weighed alongside a new, unsaturated finger cot. The syringe will then be evacuated directly on to the test site. To aid uniform coverage, droplets (approximately 20) of the product will be deposited within the test site, then spread over the whole test site using the weighed finger cot, applying a light pressure. The spreading time will be in the range of 35 ± 15 seconds. Once spreading is complete, the used finger cot and evacuated syringe will be weighed again and the total mass of applied product calculated and recorded. If the mass of total applied product is less than 78.0 mg or greater than 82.0 mg the test site will not undergo UV exposure. If there is sufficient space on the subject's back, between the scapula line and waist, a new 40 cm^2 site will be demarcated and will be positioned at least 1 cm from the borders of the other four test sites. The new test site will only undergo UV exposure if the total mass of

applied product is 78.0 to 82.0 mg, inclusive. If there is insufficient space on the subject's back to accommodate the test product, positive control and unprotected sites then the subject will not undergo any UV exposure and they will be discontinued from further participation in the study.

6.4.4. UV Exposure of Test Product Treated, Reference Sunscreen Formulation Treated and Unprotected Test Sites

The specification of the solar simulator output is included in Appendix 3. A UV dose is the result of multiplying the UV source irradiance by the episode duration. In this study, a solar simulator with 6 light guides exposing all sub-sites for the same duration but with varied irradiance values will be used. Before UV exposure of each test site, irradiance values will be measured and recorded with a radiometer which has been calibrated with a spectroradiometric measurement of the solar simulator output.

A suitable warm-up time of at least 10 minutes will be allowed for the UV solar simulator to stabilize before starting exposures. This is to ensure a consistent irradiance over the whole exposure period. Irradiation procedures will be conducted with the subject lying horizontally on their front and in a room with controlled temperature (22 ± 4 °C).

The minimum area of each exposure sub-site will be 0.5 cm^2. The minimum distance between borders of each exposure sub-site (spots) will be at least 0.8 cm. The distance between any exposure sub-site and any edge of the test site will be at least 1 cm.

Exposure of the test site to UV radiation will start 15 to 30 minutes after the application of the test product. Exposure of the positive control site to UV radiation will start 15 to 30 minutes after application of the positive control. Exposure of the unprotected site to UV radiation may happen at any point after demarcation of the test sites and after the 10 minutes required for the solar simulator to warm up. Exposure of the unprotected site, positive control and test product sites will be conducted sequentially, in any order, on same subject on the same day.

For the unprotected site, the range of UV doses administered shall be selected using the subject's provisional MEDu. Six exposure sub-sites centered on the provisional MEDu shall be exposed with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered to subjects will be chosen such that the provisional MEDu will be irradiated on the 4^{th} of the 6 sub-sites.

For the test product and reference formulation protected sites, the UV doses administered shall be selected using the subject's expected MEDp, which is the multiple of the expected SPF of the study product and the provisional MEDu for the subject. A minimum of 6 sub-sites centered on the expected MEDp shall be exposed

with incremental UV doses using a geometric progression of 1.25. The dose of UV radiation administered to subjects will be chosen such that the expected MEDp will be irradiated on the 4th of the 6 sub-sites. After the UV exposure procedures are complete, reference and test product may be gently removed by wiping with a dry tissue.

Any extraneous exposure of the test sites to UV light (artificial or natural) will be avoided during this period and until visual evaluation is completed. Any additional UV exposure to the test area will invalidate the whole test for the subject concerned.

6.4.5. Adverse Events

Adverse events will be assessed by the Investigator or designee and recorded on the CRF, as per the process detailed in Section 7. Localised erythema caused by exposure of the skin to UV radiation is expected and will not be reported as an adverse event.

6.5. Visit 5 – MEDp and MEDu Determination and SPF Calculation for Test and Reference Sunscreen

6.5.1. Concomitant Medication

Any concomitant therapy taken since the last visit and throughout the study will be recorded on the CRF by the Investigator or medically qualified designee.

6.5.2. Continued Eligibility

The Investigator or designee will ascertain whether there have been any deviations from the protocol since the last visit, whether the subject has adhered to the lifestyle restrictions since the last visit and whether, in their opinion, the subject is eligible to continue in the study and their decision will be recorded on the CRF.

6.5.3. Visual Grading of Exposure Sub-Sites to Determine MEDp and MEDu

The MED is defined as the lowest dose of UV radiation that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 to 24 hours after UV exposure.

The MED determination will be assessed visually by a trained grader with the subject lying horizontally on their front in a room with controlled temperature (22 ± 4 °C). The same grader will assess all subjects in the study. The grader's eyesight must have been checked for normal colour vision and acuity within the previous year. Visual assessment will be performed in a room with matt, neutral wall colours with sufficient and uniform illumination. Erythemal responses will be observed in a blind manner. The grader must not be the same person as the one who performed product

application and exposure nor will the grader be aware of the test design (randomisation of test sites) for any subject.

The MEDu and MEDp values for each subject will be recorded on the CRF with units of mJ/cm^2.

6.5.4. Adverse Events

Adverse events will be assessed by the Investigator or designee and recorded on the CRF, as per the process detailed in Section 7. Localised erythema caused by exposure of the skin to UV radiation is expected and will not be reported as an adverse event.

6.5.5. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the CRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent
6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Adverse Event Definition:

1. An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout product.
2. 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 an investigational or washout product.

Events meeting AE definition include:

1. Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.
2. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
3. New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study.
4. Signs, symptoms, or the clinical sequelae of a suspected interaction.
5. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:

1. 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.
2. The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition..
3. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

4. Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
5. Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
6. Localised erythema caused by exposure of the skin to UV radiation.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

A. Results in death

B. Is life-threatening

NOTE: 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.

C. Requires hospitalization or prolongation of existing hospitalization

NOTE: 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 out-patient 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.

D. Results in disability/incapacity

NOTE: 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 or prevent everyday life functions but do not constitute a substantial disruption.

E. Is a congenital anomaly/birth defect

F. Other Situations

1. Medical or scientific judgment should be exercised in deciding whether 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 should also be considered serious.

2. Examples of such events are 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 or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

1. The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
2. The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.
3. There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
4. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).
5. AEs will be collected from the start of the provisional MEDu irradiation procedure and until 5 days following last administration of the study product.
6. SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
7. Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

1. Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2. Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
3. Severe: An event that prevents normal everyday activities. An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

1. The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
2. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
3. The investigator will use clinical judgment to determine the relationship.
4. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.
5. The investigator will also consult the Safety Statement, in the determination of his/her assessment.
6. For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
7. 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.**
8. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
9. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

1. AEs will be recorded in the AE section of the CRF.
2. Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in the subject's medical history.
3. AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee

must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***

4. The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
5. After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.
It is essential to enter the following information:

1. Protocol and subject identifiers
2. Subject's demography
3. Description of events, with diagnosis if available
4. Investigator opinion of relationship to study product (see section 8.3)
5. Criterion for seriousness.

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

1. Date of onset of AE
2. Date AE stopped, if relevant
3. Study product start date
4. Study product end date if relevant
5. Action taken on study product
6. Outcome if known

The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:
UK: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

1. After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.
2. All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.
3. 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 to elucidate as fully as possible the nature and/or causality of the AE or SAE.
4. Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.
5. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

1. The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH 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 GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
2. GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
3. Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
4. An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IEC, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

1. Pregnancy information will be collected on all pregnancies reported following the screening visit.

7.6.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:

1. The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after the screening visit. The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. 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 to GSKCH. 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.
2. While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.
3. A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK.
4. While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
5. If a subject becomes pregnant over the duration of the study, they must be withdrawn and their withdrawal should be recorded in the appropriate section of the CRF. If a subject later discovers they were pregnant after their participation in the study completed, their data will be considered valid for statistical analysis.

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in the Source Document Designation Form. In some cases the CRF can be used as a source document.

Each subject will be assigned and identified by a unique Screening Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

8.2. Case Report Form

A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded in the CRF or as part of the query text.

Adverse events and concomitant medications terms (if applicable) will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm™).

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CDs) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction

8.4. External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSKCH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSKCH via secured web portal or CD via mail carrier with tracking capabilities.

Proper reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Healthy volunteers aged between 18-70 years (inclusive) with Fitzpatrick phototype I, II or III, an ITA° value greater than 28° and who are untanned on the test area will be recruited for this study. The study will contain a population of subjects of more than one Fitzpatrick phototype.

To complete the study successfully, the minimum number of valid individual sun protection factor (SPFi) results will be 10 and the maximum number of valid SPFi results will be 20 for both the test product and positive control. In order to achieve between 10 and 20 valid SPFi results, a maximum of 5 individual invalid results may be excluded from the calculation of the mean SPF. Consequently, the actual number of subjects used for the study will fall between a minimum of 10 and a maximum of 25 (i.e. a maximum of 20 valid SPFi results plus 5 rejected invalid results).

In order to determine the number of test subjects, the 95% confidence interval (95% CI) of the mean SPF shall be taken into account. A minimum of 10 subjects shall be tested. The test shall be considered valid for the first 10 subjects if the resulting range of the 95% CI of the mean SPF is within ±17% of the mean SPF. If it is not within ±17% of the mean SPF, the number of subjects shall be increased stepwise from the minimum number of 10 until the 95% CI statistical criterion is met (up to a maximum of 20 valid results from a maximum of 25 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.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

All valid subject data with no major protocol deviations will be included in the SPF calculations. All subjects exposed to UV radiation will be included the safety population, irrelevant of whether they successfully complete the study.

9.2.2. Exclusion of Data from Analysis

Test data are deemed invalid and shall be rejected under the following circumstances:

- The series of UV exposures on a subject fails to elicit an erythemal response on any sub-site, 16-24 hours after exposure.
- Erythemal responses within an exposure series are randomly absent 16-24 hours after exposure.
- All sub-sites in the exposure series show an erythemal response 16-24 hours after exposure.

When one of the above criteria applies to the exposure of unprotected skin, test product or reference sunscreen formulation exposure sites, then all data for all products on that subject are invalid and shall be rejected. If data have to be rejected for the unprotected skin, test product or reference sunscreen formulation on more than five subjects, then the whole test is invalid and shall be rejected.

Any additional exposure of a test area to natural or artificial UV radiation will invalidate the whole test for that subject.

Major violations will be identified and any exclusion of subject data justified. Data deemed invalid due to protocol violations which are not related to the UV exposure procedures, such as illness, equipment failure, and subject drop out will not be included in analysis of efficacy and will not count towards the maximum of 5 invalid subject data. Data deemed invalid due to protocol violations related to the UV exposure procedures such as subject moving during irradiation will count towards the maximum of 5 invalid subject data.

9.2.3. Handling of Dropouts and Missing Data

No interpolation of missing data is permitted. Subjects with missing data will be declared invalid and excluded from analysis.

9.3. Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding / analysis (as appropriate).

9.3.1. Demographic and Baseline Characteristics

Subject information (age, identification code, Fitzpatrick skin phototype, ITA° value, age and gender) will be tabulated and reported.

9.3.2. Primary Analysis

The SPFi of each product on each subject is calculated from the individual MED on unprotected skin (MEDu) and the individual MED on product protected skin (MEDp) according to Equation 2:

$$SPFi = \frac{MED(\text{protected skin})}{MED(\text{unprotected skin})} = \frac{MEDp}{MEDu} \qquad \text{(Equation 2)}$$

SPFi values are expressed to 1 decimal place.

The SPF of the product is the arithmetical mean of the valid individual SPFi values obtained from the total number, n, of subjects used, expressed to one decimal place as per Equation 3.

$$SPF = \frac{(\Sigma SPFi)}{n} \qquad \text{(Equation 3)}$$

Its standard deviation, s, is given by Equation 4.

$$s = \sqrt{\left\{\frac{\left[\Sigma\left(SPFi^2\right)\right] - \left[\frac{(\Sigma SPFi)^2}{n}\right]}{(n-1)}\right\}} \qquad \text{(Equation 4)}$$

The 95 % confidence interval (95 %CI) of the mean SPF is expressed by Equation 5.

$$95\,\%\text{CI} = SPF - c \text{ to } SPF + c \qquad \text{(Equation 5)}$$

Where c is calculated as:

$$c = (t \text{ value}) \times \text{SEM} = \frac{(t \text{ value}) \times s}{\sqrt{n}} \qquad \text{(Equation 6)}$$

$$c = \frac{t \times s}{\sqrt{n}} \qquad \text{(Equation 7)}$$

$$\text{CI}[\%] = \frac{100 \times c}{SPF} \qquad \text{(Equation 8)}$$

And where

SEM is the standard error of the mean;

n is the total number of subjects used;

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

Table 1 – Student-t Distribution

N	10	11	12	13	14	15	16	17	18	19	20
t value	2.262	2.228	2.201	2.179	2.160	2.145	2.131	2.120	2.110	2.101	2.093

The mean SPF of the reference sunscreen formulation (P3) used in the test shall fall within the defined acceptance limits (lower limit, SPF 13.7; upper limit, 17.7) and shall comply with the ±17 % statistical criterion. If the acceptance SPF limits are not met, the entire test shall be rejected.

9.3.3. Safety Analysis

Adverse events details will be listed by subject.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

1. Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IEC for the trial protocol (including

amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.

2. Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
3. Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)
4. GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK or designee will monitor the study and site activity to verify that the:

1. Data are authentic, accurate, and complete.
2. Safety and rights of subjects are being protected.
3. Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSKCH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all

relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The sponsor will be available to help investigators prepare for an inspection.

10.5. Conditions for Terminating the Study

Upon completion or premature discontinuation of the study, the GSKCH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSKCH Standard Operating Procedures.

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/ follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).
In addition:

1. If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IEC, and should provide the sponsor and the IEC a detailed written explanation of the termination or suspension.
2. If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IEC and provide the IEC a detailed written explanation of the termination or suspension.
3. If the IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be

available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSKCH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH and the investigator. The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

ICH Topic 6 Guideline for Good Clinical Practice CPMP/ICH/135/95 17th July 1996.
World Medical Association Declaration of Helsinki, 59th General Assembly, Seoul 2008.
Cosmetics — Sun protection test methods — *In vivo* determination of the sun protection factor (SPF) (ISO 24444:2010).
Fitzpatrick, T.B., The validity and practicability of sun-reactive skin types I through VI. *Arch. Dermatol.* **124**, pp. 869-871, 1988.

12. REPORTING

The clinical study report will contain at least the following information:

a) Product identifier and expected SPF

b) Subject information (number, Fitzpatrick skin phototype, ITA° value, age and gender)

c) Characterization of the UV source (% RCEE compliance and intensity in units of radiant flux)

d) Reference sunscreen used

e) Individual MED for unprotected skin, test product protected skin and reference sunscreen protected skin

f) Individual SPFi values expressed to one decimal place, including all valid data and rejected data for the test product and for the reference sunscreen

g) Mean SPF values, standard deviation on the mean and 95% CI of the test product and reference formulation

h) Protocol deviations, if any

i) Identification, by subject, of the technician who conducted the test

j) Date of the test

k) PI signature page to confirm the study was conducted in compliance with this protocol and any amendments, the Principles of GCP and the Declaration of Helsinki.

The clinical study report will be authored by GSKCH and statistical analyses overseen by a member of the GSKCH Biostatistics and Data Management team. GSKCH may commission a professional medical writing service to support the reporting process. The PI will review the clinical study report to ensure the report accurately reflects the way the study was conducted. The PI will sign a page to confirm the study was conducted in compliance with the protocol, the Principles of GCP and the Declaration of Helsinki.

13. APPENDICES

13.1. Appendix 1 - Abbreviations

AE	Adverse Event
°C	Degrees Celsius
CD	Compact Disc
CI	Confidence Interval
CIE	International Commission on Illumination
CRF	Case Report Form
cm	Centimeter
cm^2	Square Centimeter
EDC	Electronic Data Capture
g	Gram
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
h	Hour
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ISO	International Standards Organisation
ITA°	Individual Typology Angle
ITT	Intention to Treat
J	Joule
LSLV	Last Subject, Last Visit
m	Meter
m^2	Square Meter
MED	Minimal Erythemal Dose
MEDu	Minimal Erythemal Dose of Unprotected Skin
MEDp	Minimal Erythemal Dose of Protected Skin
mg	Milligram
mJ	Millijoule
mm	Millimeter
nm	Nanometer
PI	Principal Investigator
PII	Personally Identifiable Information
PP	Per Protocol
RCEE	Relative Cumulative Erythemal Effectiveness
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SPFi	Individual Subject Sun Protection Factor

SPF	Sun Protection Factor
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
W	Watt

13.2. Appendix 2 – Exclusion Criteria to be reassessed at Visit 2

1. PREGNANCY
Women who are known to be pregnant or who are intending to become pregnant over the duration of the study

2. BREAST-FEEDING
Women who are breast-feeding or lactating

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
C. Subjects with dermatological conditions E. Subjects who are tanned or have had sun exposure on the back area in the previous 4 weeks prior to screening F. Subjects having marks, blemishes or nevi or presenting existing sun damage in the test area I. Subjects with a non-uniform skin colour or hyperpigmentation in the test area

13.3. Appendix 3 – Specification of the Solar Simulator Output

Table 1 - % RCEE acceptance limits for the UV solar simulator output

SIGNATURE PAGE

207640 Protocol.doc

Date	Signed By
10-May-2017 10:03:48	PPD
Justification	Clinical Operations Approval

Date	Signed By
11-May-2017 08:53:18	PPD
Justification	Biostatistics Approval

Date	Signed By
11-May-2017 13:45:23	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	