CONFIDENTIAL

STATISTICAL ANALYSIS PLAN FOR PROTOCOL 207583

STUDY Determination of the Sun Protection Factor (SPF) and in vitro UVA Protection Factor (UVAPF) of four developmental sunscreen formulations

BIOSTATISTICS DEPARTMENT

GLAXOSMITHKLINE CONSUMER HEALTHCARE

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The purpose of this Statistical Analysis Plan is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 207583. This SAP will be finalized prior to database freeze and treatment code un-blinding

1 Study details

An important parameter of efficacy for sunscreen products is the Sun Protection Factor (SPF). SPF is a measure of how much solar energy (ultraviolet (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 screening study, the SPF of the test products are to be determined according to the International Standards Organization (ISO) 24444:2010 methodology (*In vivo determination of the sun protection factor*).

A second important parameter of efficacy for sunscreen products is the ultraviolet-A protection factor (UVAPF). The UVAPF provides a measure of the ability of a sunscreen to protect against solar energy across the UVA spectral range (320 nanometers (nm) to 400 nm). In this study, the UVAPF of the test products are to be determined according to the ISO 24443:2012 methodology (*Determination of sunscreen UVA photoprotection in vitro*).
General safety and tolerability will be assessed based on the frequency and severity of Adverse Events (AEs).

1.1 Study design

1.1.1 SPF Determination

Overall Design
Determination of the SPF of the test products will be performed as a single-center, randomized, evaluator blind, intra-individual comparison, no treatment and positive controlled clinical study per ISO24444:2010. As this is a screening study, a limited number of subjects will be enrolled, to achieve 5 valid individual SPF results. 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 randomized for all subjects. In this study, there will be a total of seven irradiated test sites. Three test sites will be located below the scapula line and above the waist on the left side of the spine. The remaining four test sites will be located below the scapula line and above the waist on the right side of the spine. To determine the provisional MEDu, six exposure sub-sites positioned within one randomized test site 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. 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 six remaining test sites will be demarcated. The four test products and positive control (P3 reference sunscreen formulation) will be applied to five of the six virgin test sites. The other test site will remain unprotected. The order of product application (test products, reference product and unprotected test site) will be randomized over the entire test group. Once the test products 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 1.12. 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 products (30) 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 1.12. 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 target number of valid individual SPF (SPFi) results shall be 5. In order to achieve 5 valid results, a maximum of 3 individual invalid results may be excluded from the calculation of the mean SPF. Consequently, the actual number of test subjects randomized will fall between a minimum of 5 and a maximum of 8 subjects (i.e. a maximum of 5 valid results plus 3 rejected invalid results).

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

As this is a screening study, it will be permitted to adjust the expected SPF of each of the test products 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. Randomization 6. Provisional Minimum Erythemal Dose (MED) Irradiation 7. Adverse Events *Not required if Visit 2 is combined with Visit 1. If Visit 1 and 2 are not combined, Visit 2 shall happen within 7 calendar days of Visit 1.
Visit 3 – Provisional MED Evaluation
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. If Visit 3 and 4 are not combined, Visit 4 shall happen within 7 calendar days of 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

1.1.2 UVAPF Determination

Determination of the UVAPF of the test products will be performed as a single center, open-label, negative and positive controlled technical test per ISO24443:2012.

The test is based on the assessment of UV-transmittance through a thin film of sunscreen sample spread on a roughened substrate, before and after exposure to a controlled dose of radiation from a defined UV exposure source. Because of the several variables that cannot be controlled with typical thin film spectroscopic techniques, each set of sunscreen transmission data is mathematically adjusted so that the in vitro SPF data yield the same measured in vivo SPF value that was determined by in vivo testing. Samples are then exposed to a specific measured dose of UV radiation to account for the photostability characteristics of the test product.

The UV spectrophotometer used for transmission/absorbance measurements and the UVA radiometer (or spectroradiometer) used to measure the UV exposure source shall have been calibrated and validated prior to commencing the test. The Polymethylmethacrylate (PMMA) plates to be used as substrates shall have been certified by the supplier to fall within the acceptable plate profile parameters defined in Annex D of the ISO standard. A glycerin-treated PMMA plate will be used as a reference "blank".

The absorbance of glycerin and test product treated plates will be measured prior to any UV irradiation to acquire the initial UV absorbance spectrum data. The data collected from the glycerin treated plates will act as a baseline for test product measurements. The test product treated plates absorbance data will be mathematically adjusted using a coefficient "C" to achieve an in vitro SPF equal to the measured in vivo SPF to output the resulting initial UVA protection factor ($UVAPF_0$). Subsequently, the test product treated plates shall be exposed to a controlled dose of UV radiation, D, equal to $1.2 \times UVAPF_0$ and the in vitro absorbance post-UV exposure measured a second time. Finally, a mathematical adjustment of the second absorbance spectrum by multiplying with the same "C" coefficient provides the final adjusted absorbance values and the UVAPF of the test products.

The method is controlled by the use of a reference sunscreen formulation (S2) to verify the test procedure. The UVAPF test results of the reference S2 shall lie between the upper and lower limits (10.7, 14.7) as determined from in vivo testing results, otherwise the test procedure is considered invalid. SPF 16 is to be used as the in vivo SPF value for S2 for computation purposes (Appendix 5 of the protocol). The frequency of testing of the S2 standard is in accordance with the internal procedures of the study site (every 6 months). Provided the method has been verified by the study site within 6 months of the end of this test, there is no requirement to measure S2 specifically for this test. The final report shall include the necessary data to demonstrate successful verification of the UVAPF procedure with the S2 reference sunscreen formulation within the past 6 months prior to completion of this test.

1.2 Study objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To determine the Sun Protection Factor of the test products	Arithmetic 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.
Secondary Objectives	**Secondary Endpoints**
To determine the UVA Protection Factor of the test products	Arithmetic mean of all valid individual UVA protection factor (UVAPFi) values
To determine the critical wavelength of the test products	Wavelength for which the section under the integrated UV absorbance curve starting at 290 nm is equal to 90% of the integrated curve between 290 and 400 nm
To determine whether the test products provide broad spectrum sun protection	Ratio of the arithmetic mean SPF to the arithmetic mean UVAPF
To evaluate the general safety of the test product	Frequency and severity of Adverse Events.

1.3 Treatments

For the in vivo determination of the Sun Protection Factor of the test products, the following treatments will be used:

	Product Name	Product Formulation Code (MFC)	Expected SPF
Reference Product	P3 Standard	N/A (Sourced Commercially)	16
Test Product 1	CCI [redacted]	CCI [redacted]	30
Test Product 2	CCI [redacted]	CCI [redacted]	30
Test Product 3	CCI [redacted]	CCI [redacted]	30
Test Product 4	CCI [redacted]	CCI [redacted]	30

For the in vitro determination of the UVA Protection Factor of the test products, all test products (1-4) as described above along with following reference product will be used.

	Product Name	Product Formulation Code (MFC)
Reference Product	S2 Standard	N/A (Sourced Commercially)

1.4 Timepoints and visit windows

Deviations from the scheduled assessment times must be avoided. The following are the required assessment time windows for the determination of the SPF:

Visit	Time window
Visit 2	0-7 days after Visit 1 (allowed to be combined with Visit 1)
Visit 3	1 day after Visit 2
Visit 4	0-7 days after Visit 3 (allowed to be combined with Visit 3)
Visit 5	1 day after Visit 4

Visual grading of skin at Visit 3 must happen 16-24 hours after irradiation at Visit 2. Visual grading of skin at Visit 5 must happen 16-24 hours after irradiation at Visit 4.

No visit windows are applicable for in vitro determination of the UVAPF of the test products since this part of the study does not involve human subjects.

2 Data analysis

Data analysis will be performed by inVentiv Health Clinical. Prior to database hard lock a Blind Data Review Meeting (BDRM) will be conducted in which various aspects of the trial will be discussed and agreed. The statistical analysis software used will be SAS® version 9.4.

Except as described below, all listings will be produced for all randomized subjects.

2.1 Populations for analysis

Tables described in this section will be produced for all randomized subjects.

2.1.1 Subject disposition

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized. A summary will be provided of the number of subjects screened and the number of screen failures with reasons why subjects were not randomized.

Subject disposition will be summarized as the number and percentage of subjects (out of the number of randomized subjects) who complete the study, with the number who discontinue broken down by reason for discontinuation (Table 14.1.1). The table will also summarize the

number and percentage of subjects assigned to each analysis population (refer to section 2.1.3).

2.1.2 Protocol deviations

Protocol violations will be tracked by the study team throughout the conduct of the study. All violations will be reviewed prior to un-blinding and closure of the database to ensure all important violations are captured and categorised.

Major violations will be defined in the "Review Listing Requirement (RLR)" document.

A listing of protocol deviations will be provided (Listing 16.2.2).

2.1.3 Analysis populations

Four analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
All Screened Subjects	All subjects who are screened	Disposition
Randomized	All subjects who are randomized and may or may not receive the application of the study products.	Protocol deviations
Safety	All subjects exposed to UV radiation will be included the safety population, irrelevant of whether they successfully complete the study.	Safety analysis
Analysis Population	The analysis population includes those randomised subjects who undergo irradiation at Visit 4	SPF analysis

2.1.4 Subgroups/Stratifications

Not applicable

2.1.5 Centers pools

Not applicable

2.2 Patient demographics/other baseline characteristics

Demographic and Baseline characteristics summaries will be produced for the safety, Randomized and Analysis populations.

2.2.1 Demographic characteristics

Categorical demographic variables include sex, race, Ethnicity and Fitzpatrick skin type assessment. These variables will be summarized by the number and percentage of subjects with each relevant characteristic (Table 14.1.2.1 for safety, Table 14.1.2.2 for Randomized

and Table 14.1.2.3 for Analysis population). Age, Mean L* value, Mean b* value, and individual typology angle (ITAº) will be summarized by the mean, standard deviation, median, minimum and maximum values.

The Fitzpatrick scale is a numerical classification that is widely used by dermatologists to classify a person's skin type by their response to the sun exposure (Fitzpatrick, 1988).

Table 1: Fitzpatrick Scale for the Assessment of Skin Type

Skin Type	Sunburn and Tanning History
I	Always burns easily: never tans
II	Always burns easily: tans minimally
III	Burns moderately: tans gradually
IV	Burns minimally: always tans well
V	Rarely burns: tans profusely
VI	Never burns: deeply pigmented

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). 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 and recorded on the case report form (CRF) as

$$\text{ITA}^{o} = \text{aaaaaa ttaattttttttt} \left(\frac{(LL^{*}-50}{bb^{*}}\right) \frac{180}{3.14159}$$

*arc tangent is expressed in radians.

2.2.2 General medical history

Medical history data will not be presented in the study report. A data listing will be produced at the blinded data review stage, for evaluation of protocol violations only.

2.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

2.3.1 Study Product/drug Compliance and Exposure

Any protocol deviations associated with treatment applications will be listed at the blinded data review stage.

2.3.2 Concomitant medication

Concomitant medication/non-drug treatments data will not be presented in the study report. A data listing will be produced for evaluation of protocol violations only at the blinded data review stage.

2.4 Analysis of efficacy

2.4.1 Primary efficacy endpoint

Arithmetic mean of all valid individual sun protection factor (SPFi) values of each of the test products.

2.4.1.1 Primary efficacy endpoint definition

The primary analysis will be based on sun protection factor (SPF). The SPF of a product is the arithmetic mean of the valid individual SPFi values obtained from the total number, n, of subjects used. The target number of valid individual SPF (SPFi) results shall be 5. In order to achieve 5 valid results, a maximum of 3 individual invalid results may be excluded from the calculation of the mean SPF.

Individual SPFi for each product on each subject is defined as the ratio of his/her minimal erythemal dose of protected skin (MEDp) over unprotected skin (MEDu), i.e., SPFi = MEDp / MEDu. As each subject will have unprotected test site for provisional MEDu, four test product treated sites, a reference product treated site and unprotected test site, each subject will provide five individual SPFs, four for the test products and one for the reference product. The provisional MEDu, the MEDp at five product-treated sites and MEDu at the unprotected site of each subject determined by a trained grader.

2.4.1.2 Statistical hypothesis, model, and method of analysis

Summary statistics for SPF for test and reference product, including mean, standard deviation, median, min and max, will be presented by treatment. The 95% CIs for the mean SPFs of the treatments will be constructed via t-statistic and presented together with summary statistics (Table 14.2.1.1. for Analysis Population).

Except the 95% CI for mean SPF, there is no formal statistical inference to be performed.

2.4.1.3 Supportive analyses

Not applicable.

2.4.2 Secondary efficacy variables

Endpoints related to the in-vitro analysis constitute secondary efficacy endpoints. It includes following efficacy variables.

2.4.2.1 Secondary efficacy variable 1

To determine the UVA Protection Factor of the test products, valid individual UVA protection factor (UVAPFi) values will be used as the efficacy variable.

2.4.2.2 Secondary efficacy variable 2

Wavelength for which the section under the integrated UV absorbance curve starting at 290 nm is equal to 90% of the integrated curve between 290 and 400 nm will be used as an efficacy variable to determine the critical wavelengths.

2.4.2.3 Secondary efficacy variable 3

Ratio of the arithmetic mean SPF to the arithmetic mean UVAPF will be used to determine whether the test products provide broad spectrum sun protection.

2.4.3 Handling of missing values/censoring/discontinuations

Missing data will not be replaced or imputed. Subjects with missing data will be declared invalid and excluded from analysis.

2.5 Analysis of secondary objectives

2.5.1 To determine the UVA Protection Factor of the test products

The UVAPF of the product is the arithmetic mean of the individual plate UVAPFi values obtained from the total number, n, of plates used, expressed to one decimal point.

The individual UVAPF (UVAPFi) of each plate is calculated as

$$\mathrm{UVAPFi} = \frac{\int_{\lambda=320}^{\lambda=400} P(\lambda) \times I(\lambda) \times \mathrm{d}\lambda}{\int_{\lambda=320}^{\lambda=400} P(\lambda) \times I(\lambda) \times 10^{-A_e(\lambda)C} \mathrm{d}\lambda} \qquad \text{(Equation 1)}$$

Where

$P(\lambda)$ is the PPD action spectrum;

$I(\lambda)$ is the spectral irradiance received from the UVA source (UVA 320 nm to 400 nm for PPD testing);

$\mathrm{d}\lambda$ is the wavelength step (1 nm).

$A_e(\lambda)$ is the mean monochromatic absorbance of the test product layer after UV exposure;

C is the coefficient of adjustment;

Summary statistics for UVAPF, including mean, standard deviation, standard error, median, min and max, will be presented by treatment. The 95% CIs for the mean UVAPFs of the treatments will be constructed via t-statistic and presented together with summary statistics (Table 14.2.2.1. for Analysis Population).

If the calculated 95% CI is greater than 17 % of the mean UVAPF value, then testing of the product shall continue on additional plates until the 95% CI is $\leq$ 17 % of the mean provisional UVAPF. If this criterion is not fulfilled after 10 valid plates, then the entire test shall be rejected and repeated.

The UVAPF test results of the reference S2 should lie between the upper and lower limits (10.7, 14.7) as determined from *in vivo* testing results, otherwise the test procedure is considered invalid.

To find the values of individual plate UVAPFi, we have to compute the below values for each plate

1) *in vitro* SPF
2) C coefficient of adjustment
3) Initial UVA Protection Factor Before UV exposure (UVAPF0)
4) UV Exposure Dose
5) $A_e(\lambda)$ mean monochromatic absorbance of the test product layer after UV exposure;
6) $A_f(\lambda)$ - mean final monochromatic absorbance of the test product

1) Determination of in vitro SPF:

The UV solar simulator radiation (UV-SSR) source spectrum, ***I(λ)***, is multiplied with the corresponding erythema action spectrum sensitivity value, ***E(λ)***, at that wavelength to yield the sunburning effective energy at that wavelength. The resulting sunburning effective irradiance is integrated over the 290 nm to 400 nm range.

The sunscreen transmission values at each wavelength are multiplied with the erythemal effective energy at that wavelength and integrated over the same interval to yield the effective sunburning energy transmitted through the test product. The ratio of these two integrals is the *in vitro* calculated SPF value ($SPF_{in\ vitro}$).

Calculation of $SPF_{in\ vitro}$ is shown in Equation 9.

$$SPF_{in\ vitro} = \frac{\int_{\lambda=290}^{\lambda=400} E(\lambda) \times I(\lambda) \times d\lambda}{\int_{\lambda=290}^{\lambda=400} E(\lambda) \times I(\lambda) \times 10^{-A_0(\lambda)} d\lambda} \qquad \text{(Equation 9)}$$

Where,

$E(\lambda)$ is the erythema action spectrum (Appendix 9 of the protocol)

$I(\lambda)$ is the spectral irradiance received from the UV source (SSR for SPF testing, Appendix 9 of the protocol)

$A_0(\lambda)$ is the mean monochromatic absorbance of the test product layer before UV exposure;

$d\lambda$ is the wavelength step (1 nm).

2) C - Coefficient of adjustment

The initial absorbance curve values are multiplied by a scalar value "*C*" until the *in vitro* calculated SPF values are equal to the *in vivo* measured SPF. This is accomplished in an iterative calculation process.

$$\mathrm{SPF}_{in\ vitro,adj} = \mathrm{SPF}_{in\ vitro} = \frac{\int_{\lambda=290}^{\lambda=400} E(\lambda)\times I(\lambda)\times \mathrm{d}\lambda}{\int_{\lambda=290}^{\lambda=400} E(\lambda)\times I(\lambda)\times 10^{-A_0(\lambda)C}\mathrm{d}\lambda}$$

The "*C*" value typically lies between 0.8 and 1.6 for valid interpretation. If it is outside this range, new samples should be prepared to validate the original observations. **The "*C*" value for the reference S2 shall lie in this range 0.8 to 1.6 or the application procedure should be modified to achieve it.**

3) Initial UVA Protection Factor Before UV exposure ($UVAPF_0$)

The initial $UVAPF_0$ value is calculated for the purpose of determining the UV exposure dose. It is calculated in a manner similar to the calculation of the initial $SPF_{in\ vitro}$.

$$\mathrm{UVAPF}_0 = \frac{\int_{\lambda=320}^{\lambda=400} P(\lambda)\times I(\lambda)\times \mathrm{d}\lambda}{\int_{\lambda=320}^{\lambda=400} P(\lambda)\times I(\lambda)\times 10^{-A_0(\lambda)C}\mathrm{d}\lambda} \qquad \text{(Equation 11)}$$

Where

P (λ) is the PPD action spectrum (Appendix 9 of the protocol);

I (λ) is the spectral irradiance received from the UVA source (UVA 320 nm to 400 nm for PPD testing, Appendix 9 of the protocol);

$A_0(\lambda)$ is the mean monochromatic absorbance of the test product layer before UV exposure;

C is the coefficient of adjustment, previously determined;

$d\lambda$ is the wavelength step (1 nm).

4) UV Exposure Dose

The UV exposure dose, *D*, is the $UVAPF_0$ value multiplied by a factor of 1.2 in J/cm^2

$$D = \mathrm{UVAPF}_0 \times 1.2$$

The sample is exposed to full spectrum UV radiation but the dose is being defined by the UVA content. The UV exposure dose, *D*, for each test product will be recorded in the test report.

5) Ae(λ) - mean monochromatic absorbance of the test product layer after UV exposure;

After the UV exposure, the absorbance of the test samples will be re-measured on the same nine (9) spots as measured before the UV exposure using the same UV spectrophotometer and UV light source.

The mean UV absorbance values of nine (9) spots at each 1 nm wavelength increment for each test product after irradiation will be computed.

6) $A_f(\lambda)$ - mean final monochromatic absorbance of the test product;

After the UV exposure, the absorbance of the test samples shall be re-measured on the same spots as measured before the UV exposure using the same UV spectrophotometer and UV light source. The final absorbance values are equal to the observed absorbance values after the UV exposure, multiplied by the "*C*" value.

$$A_f(\lambda) = A_e(\lambda)C$$

2.5.2 To determine the critical wavelength of the test products

The critical wavelength for each test product is defined as the mean of the critical wavelength of all measured plates. These wavelengths will be displayed in (Table 14.2.2.1).
The critical wavelength of each plate is calculated from the mean UV absorption spectrum of each plate. This wavelength will be displayed in (Listing 16.2.2.2).

The UV absorption spectrum of each test product treated plate will be measured 9 times.

The critical wavelength (λ_c) of a sunscreen is defined as the wavelength at which the summed UV absorbance from 290 nm equals 90% of the total absorbance in the ultraviolet region (290-400 nm). It is expressed as.

$$\int_{290}^{\lambda_c} A(\lambda)d\lambda = 0.9\int_{290}^{400} A(\lambda)d\lambda$$

Where:
$A(\lambda)$ is the mean absorbance at each wavelength
$d\lambda$ is the wavelength interval between measurements

2.5.3 To determine whether the test products provide broad spectrum sun protection

Ratio of the arithmetic mean SPF to the arithmetic mean UVAPF will be computed to determine the broad spectrum sun protection (Table 14.2.2.2. for Analysis Population). For a sunscreen to be considered to offer broad spectrum sun protection, the SPF to UVAPF ratio should be less than 3.

2.5.4 Safety

2.5.4.1 Adverse events and Serious Adverse Events

All adverse events (AEs) will be summarized by primary system organ class and preferred term.

Treatment emergent adverse events (TEAEs), defined as the AEs reported after study product application, will be summarized by the number and percentage of subjects having any adverse event, any adverse event in each System Organ Class, and the number of occurrences of each individual adverse event (Table 14.3.1.1). All TEAEs will also be tabulated by severity (Table 14.3.1.2). Treatment emergent AEs suspected of a relationship to study medication will be presented in a similar manner (Table 14.3.1.3). For treatment related AEs, these will also be presented by severity (Table 14.3.1.4).

Deaths occurring during treatment (if any) will be listed (Listing 14.3.2.1) by treatment, including the date and study day of death, and the principal cause of death. Non-fatal serious adverse events causing study treatment discontinuation will be listed (Listing 14.3.2.2).

AEs will be collected from the start of provisional MEDu irradiation procedure until 5 days after the last administration of the study product. SAEs however, if assessed as related to study participation 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.

All AEs will be listed in Listing 16.2.7.1 for randomized subjects and Listing 16.2.7.2 for non-randomized subjects.

2.6 Analysis of other variables

2.6.1 MEDu and MEDp of SPF

MEDu and MEDp collected from study subjects are used to derive SPF. MEDu and MEDp themselves will not be summarised or analysed. However, a listing for all MED determinations will be provided including the provisional determination (at Visit 3) of the unprotected skin and the final determination (at Visit 5) of both protected and unprotected skin (Please keep one decimal place for all MEDx) (Listing 16.2.6.1).

2.6.2 Prerequisite variable to compute UVAPF

All required variable to compute the UVAPF as per section 2.5.1 will be listed in the (Listing 16.2.6.2 and 16.2.6.3)

2.7 Interim analysis

No interim analysis is planned.

2.8 Sample size calculation

In-Vivo:

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 results for each test product and for the reference sunscreen formulation are calculated as the arithmetic mean of all valid SPFi values. The target number of valid SPFi values shall be 5. A maximum of 3 results may be excluded from the calculation of the mean SPF, but each exclusion shall be justified. If a fourth invalid result occurs for a particular test product, that test product shall not be tested further but an SPF may still be calculated. If a fourth invalid result occurs for the reference sunscreen formulation, the study shall be stopped. Consequently, the total number of subjects randomized may fall between 5 and 8, requiring approximately 11 subjects to be screened.

In-vitro:

In order to determine the number of test plates, the 95% confidence interval (95% CI) of the mean UVAPF shall be taken into account.

At least four plates prepared with each test sunscreen should be used to establish the protection aspects of each test sample. Additional plates shall be added incrementally to the sampling if the 95 % CI is greater than 17 % of the mean value of the UVAPF value, until the 95 % CI is less than 17 % of the mean UVAPF value.

If this criterion is not fulfilled after 10 valid plates, then the entire test shall be rejected and repeated.

3 Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol version 3.0 [(Dated: 16/May /2017)].

4 Appendix 1:

4.1 List of Tables, Listings and Figures

4.2 Tables

Table Number	Table Title (Population)	Template
14.1.1	Subject Disposition (All Screened Subjects)	Appendix 2
14.1.2.1	Subject Demographics and Baseline Characteristics (Safety Population)	Appendix 2
14.1.2.2	Subject Demographics and Baseline Characteristics (Randomized Population)	14.1.2.1
14.1.2.3	Subject Demographics and Baseline Characteristics (Analysis Population)	14.1.2.1
14.2.1.1	Summary of Sun Protection Factor by Treatment	Appendix 2

Table Number	Table Title (Population)	Template
	(Analysis Population)	
14.2.2.1	Summary of UVA Protection Factor by Treatment	Appendix 2
14.2.2.2	Ratio of SPF and UVA Protection Factor by Treatment (Analysis Population)	Appendix 2
14.3.1.1	Treatment Emergent Adverse Events (Safety Population)	Appendix 2
14.3.1.2	Treatment Emergent Adverse Events by Severity (Safety Population)	Appendix 2
14.3.1.3	Treatment Emergent Treatment Related Adverse Events (Safety Population)	14.3.1.1
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4.3 Listings

Listing Number	Listing Title (Population)	Template
14.3.2.1	Listing of Deaths (Randomized population)	16.2.7.1
14.3.2.2	Listing of Serious Adverse Events leading to Discontinuation (Randomized population)	16.2.7.1
16.1.7	Randomization Information (Randomized Population)	Appendix 2
16.2.2	Individual Subject Protocol Deviations (Randomized Population)	Appendix 2
16.2.6.1	Individual Subject Efficacy Data (Randomized Population)	Appendix 2
16.2.6.2	Individual Plate Data by Treatment	Appendix 2
16.2.6.3	Individual and Mean Monochromatic Absorbance Values by Treatment	Appendix 2
16.2.6.4	Listing of the identification for Technician (Randomized Population)	Appendix 2
16.2.7.1	All Adverse Events (Randomized Population)	Appendix 2
16.2.7.2	All Adverse Events (Non-Randomized Subjects)	16.2.7.1

Note: If there are no data to display generate a null listing.

4.4 Top line Outputs:

Table/Listing Figure Number	Table/Listing/Figure Title (Population)
14.1.1	Subject Disposition (All Screened Subjects)
14.1.2.2	Subject Demographics and Baseline Characteristics (Analysis Population)
14.2.1.1	Summary of Sun Protection Factor by Treatment (Analysis Population)
14.3.1.1	Treatment Emergent Adverse Events (Safety Population)
16.2.7.1	All Adverse Events (Randomized Population)

5 Appendix 2:

5.1 Templates for the Tables, Listings and Figures

This is a guideline which will give the guidance of treatment labels that will be used for the table header and in the figures, listings and in the footnotes.

The treatment labels for the column headings will be as follows:

- P3 Standard
- CCI
- CCI
- CCI
- CCI

Protocol: 207583

Table 14.1.1
Subject Disposition
All Screened Subjects

All Screened Subjects (N=XX)

	Overall(N=XX) n (%)
TOTAL NUMBER OF SUBJECTS SCREENED	xx
SUBJECTS NOT RANDOMIZED	Xx (xx.x)
DID NOT MEET STUDY CRITERIA	xx (xx.x)
ADVERSE EVENTS	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)
PROTOCOL DEVIATION	xx (xx.x)
WITHDRAWAL OF CONSENT	xx (xx.x)
OTHER	xx (xx.x)
SUBJECTS RANDOMIZED	xx (xx.x)
COMPLETED	xx (xx.x)
DID NOT COMPLETE	xx (xx.x)
DID NOT MEET STUDY CRITERIA	
ADVERSE EVENT	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)
PROTOCOL DEVIATION	xx (xx.x)
WITHDRAWAL OF CONSENT	xx (xx.x)
OTHER	xx (xx.x)
RANDOMIZED POPULATION	xx (xx.x)
SAFETY POPULATION	xx (xx.x)
ANALYSIS POPULATION	xx (xx.x)

PPD

Note to programmer: For subjects not randomized and subjects not completing the study, the reasons should be consistent with the reasons in eCRF.

Protocol: 207583

Table 14.1.2.1
Subject Demographics and Baseline Characteristics
Safety Population

Safety Population (N=XX)

	Overall (N=XX)
SEX n (%)	
MALE	xx (xx.x)
FEMALE	xx (xx.x)
RACE n (%)	
ASIAN – CENTRAL/SOUTH ASIAN HERITAGE	xx (xx.x)
AFRICAN AMERICAN/AFRICAN HERITAGE	xx (xx.x)
AMERICAN INDIAN OR ALASKAN NATIVE	xx (xx.x)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	xx (xx.x)
WHITE – WHITE/CAUCASIAN/EUROPEAN HERITAGE	xx (xx.x)
...(include all captured as in eCRF)	xx (xx.x)
AGE (YEARS)	
n	XX
MEAN	XX.X
SD	XX.XX
MEDIAN	XX.X
MINIMUM	XX
MAXIMUM	XX
ITA[o]	
n	XX

	Overall (N=XX)
MEAN	XX.X
SD	XX.XX
MEDIAN	XX.X
MINIMUM	XX
MAXIMUM	XX
FITZPATRICK SCALE FOR SKIN TYPE	
I = ALWAYS BURNS EASILY: NEVER TANS	xx (xx.x)
II = ALWAYS BURNS EASILY: TANS MINIMALLY	xx (xx.x)
III = BURNS MODERATELY: TANS GRADUALLY	xx (xx.x)
IV = BURNS MINIMALLY: ALWAYS TANS WELL	xx (xx.x)
V = RARELY BURNS: TANS PROFUSELY	xx (xx.x)
VI = NEVER BURNS: DEEPLY PIGMENTED	xx (xx.x)

PPD

Note to programmer: please include summary for Ethnicity, Mean L* value, Mean b* value and Mean ITA.

Protocol: 207583

Table 14.2.1.1
Summary of Sun Protection Factor by Treatment
Analysis Population

Analysis Population (N=XX)

	CCI (N=XX)	CCI (N=XX)	CCI (N=XX)	CCI (N=XX)	P3 Standard (N=XX)
VISIT 5		xx	xx	xx	xx
n (number of invalid cases)	xx	xx	xx	xx	xx
n (number of valid cases)	xx	xx	xx	xx	xx
MEAN	x.xx	x.xx	x.xx	x.xx	x.xx
SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
MEDIAN	x.x	x.x	x.x	x.x	x.x
MIN	X.x	X.x	X.x	X.x	x.x
MAX	X.x	X.x	X.x	X.x	X.x
95% CI	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)

Note to programmer: 1) Keep 1 decimal place for median, min, max. 2) Keep two decimal places for mean, 95% CI.
3) Keep three decimal places for SD.

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Table 14.2.2.1
Summary of UVA Protection Factor by Treatment
Analysis Population

Analysis Population (N=XX)

Variable	CCI [redacted] (N=XX)	CCI [redacted] (N=XX)	CCI [redacted] (N=XX)	CCI [redacted] (N=XX)	S2 Standard (N=XX)
MEAN	x.xx	x.xx	x.xx	x.xx	x.xx
SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
MEDIAN	x.x	x.x	x.x	x.x	x.x
MIN	X.x	X.x	X.x	X.x	x.x
MAX	X.x	X.x	X.x	X.x	X.x
95% CI	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
95% CI is $\leq$ 17% of the mean UVAPF	Y/N	Y/N	Y/N	Y/N	Y/N[3]
critical wavelength	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x

PPD [redacted]

Note to programmer: 1) Keep 1 decimal place for median, min, max.
2) Keep two decimal places for mean, 95% CI. & 3) Keep three decimal places for SD.
3) For 'S2 Standard' Y&N depends upon the lower & upper limit [10.7, 14.7]. If UVAPF is lie within these limits then it will be 'Y' otherwise 'N'.

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Table 14.2.2.2
Ratio of SPF and UVA Protection Factor by Treatment
Analysis Population

Analysis Population (N=XX)

	CCI (N=XX)	CCI (N=XX)	CCI (N=XX)	CCI (N=XX)
Ratio of SPF and UVA Protection Factor	x.xx	x.xx	x.xx	x.xx

PPD

Note to programmer: 1) Keep 1 decimal place for median, min, max.
2) Keep two decimal places for mean, 95% CI. & 3) Keep three decimal places for SD.

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Table 14.3.1.1
Summary of Treatment Emergent Adverse Events
Safety Population

Safety Population (N=xx)

System Organ Class Preferred Term	CCI [redacted] (N=XX)		...	P3 Standard (N=XX)	Overall (N=XX)	
	n (%)	nAE			n (%)	nAE
NUMBER OF SUBJECTS WITH AT LEAST ONE AE	xx (xx.x)	xx	...	... ...	xx (xx.x)	xx
NUMBER OF SUBJECTS WITH NO AE	xx (xx.x)	xx	...	... ...	xx (xx.x)	xx
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	xx (xx.x)	xx	...	... ...	xx (xx.x)	xx
ERYTHEMA	xx (xx.x)	xx	...	... ...	xx (xx.x)	xx
DERMATITIS	xx (xx.x)	xx		... ...	xx (xx.x)	xx
GASTROINTESTINAL SYSTEM	xx (xx.x)	xx		... ...	xx (xx.x)	xx
ABDOMINAL PAIN	xx (xx.x)	xx		... ...	xx (xx.x)	xx
DRY MOUTH	xx (xx.x)	xx		... ...	xx (xx.x)	xx
VOMITING	xx (xx.x)	xx			xx (xx.x)	xx

n (%) = Number (percent) of subjects; nAE = Number of adverse events.

PPD [redacted]

Note to programmer: please include summary for CCI [redacted] CCI [redacted] and CCI [redacted] product.

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Table 14.3.1.2
Summary of Treatment Emergent Adverse Events by Severity
Safety Population

Safety Population (N=xx)

System Organ Class Preferred Term	CCI (N=XX)							P3 Standard (N=XX)							Overall (N=XX)					
	Mild		Moderate		Severe			Mild		Moderate		Severe			Mild		Moderate		Severe	
	n (%)	nAE	n (%)	nAE	n (%)	nAE		n (%)	nAE	n (%)	nAE	n (%)	nAE		n (%)	nAE	n (%)	nAE	n (%)	nAE
NUMBER OF SUBJECTS WITH AT LEAST ONE AE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx		xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx		xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ERYTHEMA	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DERMATITIS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
GASTROINTESTINAL SYSTEM	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ABDOMINAL PAIN	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DRY MOUTH	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
VOMITING	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

n (%) = Number (percent) of subjects; nAE = Number of adverse events.

PPD

Note to programmer: please include summary for CCI CCI and CCI product.

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Listing 16.1.7
Randomization Information
Randomized Population

Subject Number	Age/Sex/Race[1]	Randomization Number	Planned Test Site/Treatment Randomized	Actual Test Site/Treatment Randomized	Date of Randomization (dd/mmm/yyyy)
PPD					

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

PPD

Note to programmer: Check actual races captured in eCRF to adjust the race name and abbreviations.

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Listing 16.2.2
Individual Subjects Protocol Deviation
Randomized Population

Subject Number	Age/Sex/Race[1]	Visit	Deviation Sequence	Protocol Deviation
PPD				

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

PPD

Note to programmer: Check actual races captured in eCRF to adjust the race name and abbreviations.

Protocol: 207583

Listing 16.2.6.1
Individual Subjects Efficacy Data
Randomized Population

Subject Number	Age/Sex/Race[1]	Fitzpatrick skin type	Visit	Mean L	Mean B	Mean ITA	Site	Treatment	Variable	Variable Value	Excluded (Y/N)	Reason for Exclusion
PPD												

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

PPD

Note to programmer: Check actual races captured in eCRF to adjust the race name and abbreviations.

Protocol: 207583

Listing 16.2.6.2
Individual Plate Data by Treatment

Treatment	Plate	SPF in-Vivo	SPF-invitro	Coefficient of adjustment "C"	Initial UVAPF0	UV Exposure Dose	UVAPF	Critical Wavelength
...								

PPD

Protocol: 207583

Listing 16.2.6.3
Individual and Mean Monochromatic Absorbance Values by Treatment

Treatment	Plate	Time point	Wavelength	Spot 1	Spot 2	Spot 3	Spot 4	.....	Spot 9	$A_o(\lambda)$	$A_e(\lambda)$	$A_f(\lambda)$
		BEFORE UV EXPOSURE										
		AFTER UV EXPOSURE										

1) $A_o(\lambda)$: Mean monochromatic absorbance before UV exposure, $A_e(\lambda)$: Mean monochromatic absorbance before UV exposure and $A_f(\lambda)$- Final mean final monochromatic absorbance ($A_f(\lambda)$=C*$A_f(\lambda)$- where C- coefficient of determination for each plate)

PPD

Programming Note: 1) $A_f(\lambda)$ & $A_f(\lambda)$ will be displayed only for timepoint "AFTER UV EXPOSURE"

Protocol: 207583

Listing 16.2.6.4

Listing of the Identification for Technician
Randomised Population

Subject Number	Irradiation at Visit 2	Visual Grading at Visit 3	Product Application and Irradiation at Visit 4	Visual Grading at Visit 5
PPD				

PPD

Programming Note: The AP is just an example; please use the real data while creating the listing.

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Listing 16.2.7.1
All Adverse Events
Randomized Population

Treatment Group:

Subject Number	Age/Sex/Race [1]	Adverse Event (Preferred Term) (System Organ Class)	Start Date /Study Day[2]	Start Time	End Date	End Time	Frequency /Intensity [3]	Related to Study Product?	Action Taken re Study Product	Outcome	Serious ?	Withdrew?[4]
PPD												

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.
[2] Study day is the day relative to start of treatment, day 1 being the day of first treatment.
[3] INT = Intermittent and SGLE = Single.

[4] Did subject withdraw from study as a result of this adverse event?

PPD

Programming Note:

1. Repeat the same layout for the listing 16.2.7.2
2. Population should be used ‘Non randomized Subjects’
3. The fourth column should be only ‘Start Date’
4. Delete the footnote related to study day and adjust the numbers accordingly.