Clinical Protocol

207468

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Proof of Concept (POC) Clinical Study to Evaluate the Appearance of Fine Lines and Wrinkles on a Developmental Cosmetic Moisturising Cream in Healthy Subjects Presenting Visible Signs of Ageing.
Protocol Number:	207468
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) Trading Limited. St George's Avenue, Weybridge, Surrey, KT13 0DE, UK. Tel: PPD
Product Name:	Fine Lines and Wrinkles Moisturising Cream
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD

Key Protocol Authors:	
PRIMARY CONTACT **Clinical Research:**	PPD, BSc (Hons), Dip. GSKCH St George's Avenue, Weybridge, Surrey KT13 0DE Tel: PPD
PRIMARY CONTACT **Clinical Study Manager:**	PPD, MSc Tel: PPD
Biostatistician:	PPD, MA
Clinical Supplies:	PPD
Medical Expert:	PPD MD, Ph.D.

Principal Investigator:	Stephan Bielfeldt (Dipl. Bio-Ing)

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.

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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines.

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

- 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.

- 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:	

Table of Content

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.

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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 ☒	Correction to the details of the Corneometry data storage system Clarified that Mascara and Lipstick is not to be worn on assessment days	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	Section 6.2.4 Corneometry Assessment Section 3.2 Subject restrictions Lifestyle/Dietary on the day of the site visit.	Signature: PPD
Protocol Version No.: 2.0	Substantial/ Major ☐				Date: PPD

Amendment No.:2	Non-Substantial/Minor ☒	To delete the word 'equal rating' in the Inclusion Criteria to remove Interpretation.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☒ Yes ☐ No	Synopsis- study design Synopsis- Diagnosis and main criteria for Inclusion 3.1 Study design 3.3 Type and Planned number of subjects 3.4 Study design and dose justification 4.1 Inclusion Criteria	Signature: PPD
Protocol Version No.:3.0	Substantial/ Major ☐				Date: PPD

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 Day -3	Visit 2[1] Day 1	Visit 3[1] Day 15 (+/- 24 hrs)	Visit 4[1] Day 29 (+/- 24 hrs)
	Screening / Washout	Baseline Treatment	Week 2 Treatment	Week 4 Treatment
Informed consent	X			
Demographics	X			
Medical History	X			
Current / Concomitant medication	X	X	X	X
Adverse Events		X	X	X
Fitzpatrick Skin Type Assessment (Appendix 2)	X			
Diary Review (Compliance)[4]		X	X	X
Continued Eligibility		X	X	X
Clinical Fitzpatrick Wrinkle Score in Periocular / Crow's Feet Area (Appendix 3)[3]	X	X	X	X
Inclusion / Exclusion Criteria	X	X		
Subject Eligibility[6]	X	X		
Study Cleanser and Diary Dispensing	X			
Randomisation[2]		X		
USR- CliP High Resolution Images Left and Right Side of Face [3,5,7]		X		X
DermaTOP Measurement[3] Periocular / Crow's Feet Area		X	X	X
TEWL Measurement[3] in Sub-ocular/ Cheek Area		X	X	X
Corneometer Measurement[3] in Sub-ocular/ Cheek Area		X	X	X
Cutometer Measurement[3] in Sub-ocular/ Cheek Area		X	X	X
Test Product(s) Dispensing		X		
Supervised Test Product Application		X	X	
Test Product, Study Cleanser and Diary Return				X
Subject Discharge from Study				X

1. On the day of site visit, subjects will be instructed to cleanse their face in the morning with tap water only and not to apply the test product or control. Measurements and assessments will be performed at least 12 hours after the last application of test products.
2. Subjects to be randomised to one of three treatment groups: test product/positive control, test product/no treatment or positive control/no treatment at the baseline visit.
3. Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity between 40-60%) for a period of at least 30 minutes before the clinical and instrumental assessments are performed (EEMCO, 1997).
4. Diary to be reviewed by investigator or designee to confirm and encourage subject compliance.
5. At the end of the study, a blinded lay panel will assess all of the high resolution images for Texture by texture ranking (Appendix 4).
6. Inclusion criteria 7b to be reviewed at Screening and Baseline.
7. A 30 minute waiting time will occur in an acclimatised room after the USR-CliP High Resolution Images.

PROTOCOL SYNOPSIS FOR STUDY 207468

Brief Summary

This is a single-site, 3-arm, randomised, evaluator-blind, positive controlled (Olay ProX Wrinkle Smoothing Cream) and no-treatment controlled split-face POC study to evaluate the cosmetic appearance of fine lines and wrinkles delivered following 4 weeks of twice-daily application of the test product in healthy subjects presenting visible signs of ageing.

It is hypothesised that the test product, which contains humectants to moisturise the stratum corneum (SC), will help to reduce the appearance of fine lines and wrinkles caused by skin dryness. It is also hypothesised that by moisturising the skin and depositing lipids on the skin surface, that skin elasticity and barrier function will also be improved.

The chosen application site for the treatment period is the face, to include the Periocular / Crow's Feet Area for fine lines and wrinkles, the whole face for texture, and the Sub-ocular/ Cheek Area for barrier function, hydration and elasticity. There are three treatment groups included in this study; Test Product/ No Treatment, Test Product/Positive Control and Positive Control/No Treatment. Treatment groups will be further randomised to which side of the face treatment is to be applied.

The objective of this POC clinical study is to evaluate the cosmetic appearance of fine lines and wrinkles delivered following 4 weeks of twice-daily application of the test product compared to no treatment in healthy subjects presenting visible signs of ageing.

To measure the appearance, clinical and instrumental assessments will be performed throughout the study: clinical assessments of fine lines and wrinkles by clinical Fitzpatrick wrinkle score in Periocular / Crow's Feet Area, clinical assessments of texture by ranking high resolution images by a lay panel, instrumental assessments of fine lines and wrinkles by DermaTOP, skin barrier function measured by Transepidermal Water Loss (TEWL) (using a Tewameter), skin moisturisation using a Corneometer, and elasticity using a Cutometer.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluation of wrinkle dimensions (change from baseline) of test product compared to no treatment on the Periocular / Crow's Feet Area.	DermaTOP parameter R_a at 4 weeks.
Secondary	
Evaluation of wrinkle dimensions (change from baseline) of test product and positive control compared to no treatment in the Periocular / Crow's Feet Area.	DermaTOP parameter R_a at 2 weeks and 4 weeks (positive control only)
	DermaTOP parameters $R_{z,}$ S_a and S_{tm} at 2 and 4 weeks
	Clinical Fitzpatrick Wrinkle Score at 2 and 4 weeks
Evaluation of skin moisturisation (change from baseline) of test product and positive control compared to no treatment on the Sub-ocular/ Cheek Area.	Instrumental Corneometer values at 2 and 4 weeks
Evaluation of texture (change from baseline) of test product and positive control compared to no treatment on the full face.	Texture ranking at 4 weeks
Evaluation of skin elasticity (change from baseline) of test product and positive control compared to no treatment on the Sub-ocular/ Cheek Area.	Instrumental Cutometer parameters R5 and R7 at 2 and 4 weeks
Evaluation of skin barrier (change from baseline) of test product and positive control compared to no treatment on the Sub-ocular/ Cheek Area.	Instrumental Trans-Epidermal Water Loss (TEWL) values at 2 and 4 weeks
To evaluate the general safety of the study products	Assessment of frequency and severity of Adverse Events (AEs)

Study Design

Overall Design
This is a single-site, 3-arm, randomised, evaluator-blind, positive controlled (Olay ProX Wrinkle Smoothing Cream) and no-treatment controlled split-face POC study to evaluate the cosmetic appearance of fine lines and wrinkles provided by 4 weeks of twice-daily application of the test product in healthy subjects presenting visible signs of ageing. Subjects will give their written consent prior to any study procedures taking place. At the Screening Visit, only healthy female subjects aged 30 to 65 (inclusive), with a Fitzpatrick phototype I-IV, a visual Clinical Fitzpatrick Wrinkle Score of 3-6 in the Periocular / Crow's Feet Area ~~with an equal~~ ~~rating~~ on both sides of the face (Appendix 3), with self-reported sensitive skin will be considered eligible to continue in the study. Eligible subjects will undergo a 3 day washout period, where they will be asked to avoid using any other skin care products (moisturisers, lotions, creams, soaps, cleansing products, foundations etc.) on their face from the screening visit until Visit 2 (Day 1) other than the study cleanser provided (Simple™ Kind to Skin Moisturising Facial Wash™). Subjects will be asked to use the cleanser mornings and evenings in the washout period and during the study. On clinic days, subjects will use the cleanser in the evenings only and wash their face in the morning with tap water. Subjects successfully completing the washout phase and who continue to be eligible, will have their wrinkles assessed using the Clinical Fitzpatrick Wrinkle Score. Subjects who meet all the inclusion/exclusion criteria will be randomised to one of three treatment groups: test product/positive control, test product/no treatment or positive control/no treatment at the baseline visit. Product application within treatment group will be further randomised to either the right or left side of the face. Diary Cards will be provided and reviewed at each site visit by the Investigator or designee to confirm and encourage subject compliance. Subjects will be required to

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complete the diary card every day to record application of test and study cleanser products.

Subjects will be instructed to apply each test product to the assigned side of the face, as applicable, (approximately 2 mg / cm^2) twice-daily (morning and evening, approximately 8-12 hours apart), for 4 weeks (28 days). Subjects will return to the site on Day 15 (Visit 3) and 29 (Visit 4) without applying the test product at home that morning.

After randomisation, subjects who consent will have high resolution images taken on the left and right side of their face. Instrumental measures will follow in the following order: DermaTOP (Periocular / Crow's Feet Area), TEWL (Sub-ocular/ Cheek Area); Corneometer (Sub-ocular/ Cheek Area); Cutometer (Sub-ocular/ Cheek Area). The same schedule of events (except randomisation and high resolution photos) will be repeated for Day 15 (Visit 3). Day 29 (Visit 4) will be a repeat of Visit 2 (Day 1) (except randomisation).

Prior to all instrumental measurements and clinical assessments, subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity between 40-60%) for a period of at least 30 minutes [EEMCO, 1997].

On Day 1 (Visit 2) and Day 15 (Visit 3) on-site application of product will be supervised by the study site staff and will be performed only after the clinical and instrumental measurements are completed.

After the study has completed, all of the high resolution images will be evaluated by blinded lay persons to rank the appearance of texture.

Visit 1 - Screening / Washout Visit

1. Informed consent
2. Demographics
3. Medical History
4. Current / Concomitant medication
5. Fitzpatrick Skin Type assessment (Appendix 2)
6. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
7. Inclusion / Exclusion Criteria
8. Subject Eligibility
9. Study Cleanser and Diary Dispensing

Visit 2 - Baseline Visit

The following assessments will be conducted in the order written:

1. Current / Concomitant medication
2. Adverse Events
3. Diary Review (Compliance)
4. Continued Eligibility
5. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
6. Inclusion / Exclusion Criteria
7. Subject Eligibility
8. Randomisation
9. High Resolution Photos for Texture Assessment (Appendix 4)
10. DermaTOP Assessment
11. TEWL Assessment
12. Corneometer Assessment
13. Cutometer Assessment
14. Test Product(s) Dispensing
15. Supervised Test Product Application

Visit 3- Day 15 (Week 2)

The following assessments will be conducted in the order written:

1. Current / Concomitant medication
2. Adverse Events
3. Diary Review (Compliance)
4. Continued Eligibility
5. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
6. DermaTOP Assessment
7. TEWL Assessment
8. Corneometer Assessment
9. Cutometer Assessment
10. Supervised Test Product Application

Visit 4 – Day 29 (Week 4)

The following assessments will be conducted in the order written:

1. Current / Concomitant medication
2. Adverse Events
3. Diary Review (Compliance)
4. Continued Eligibility
5. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
6. High Resolution Photos for Texture Assessment (Appendix 4)
7. DermaTOP Assessment
8. TEWL Assessment
9. Corneometer Assessment
10. Cutometer Assessment

11. Test Product, Subject Cleanser and Diary Return
12. Subject Discharge from Study

Type and Planned Number of Subjects

Approximately 90 healthy subjects will be screened to randomise at least 72 subjects to ensure 66 subjects complete the entire study. This will ensure approximately 44 subjects per treatment arm (test product, positive control, no treatment) or 22 per treatment group (test product/no treatment, test product/positive control, positive control/no treatment).

The sample size is based on clinical considerations. With 40 subjects, a difference between test product and no treatment in the change from baseline in R_a of at least 46% of the magnitude of the within-subject standard deviation of the difference would be detectable at two-sided alpha=0.05 with approximately 80% power.

Diagnosis and Main Criteria for Inclusion

Healthy female volunteers, aged 30 to 65 (inclusive) with a Fitzpatrick phototype score of I-IV, presenting visible signs of ageing with a visual Clinical Fitzpatrick Wrinkle Score of Score 3-6 in the Periocular / Crow's Feet Area ~~with an equal rating~~ on both sides of the face (Appendix 3), with self-reported sensitive skin will be considered eligible to continue in the study.

Product Information

	Test Product	Reference Product
Product Name	Developmental Cosmetic Moisturising Cream	Olay ProX Wrinkle Smoothing Cream
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available (UK)
Application Quantity	approx. 2 mg /cm^2	approx. 2 mg /cm^2
Route of Application	Dermal Topical	Dermal Topical
Application Instructions	Dispense two pumps of product (equating to approximately 0.6 mL) onto your fingertips and apply evenly to the randomly assigned side of the face, to include, the crow's feet area, cheek,	Subjects will be instructed to apply a pea-sized amount of the positive control product (equating to approximately 0.5g) onto your fingertips and apply evenly to the randomly assigned side of the face, to

	forehead and chin twice daily, (morning and evening), after cleansing. Daily applications should be approximately 8-12 hours apart. Subjects will be reminded that as with all facial skin care products, care should be taken to avoid getting into the eyes. If contact does occur, then rinse thoroughly with water.	include the crow's feet area, cheek, forehead and chin , twice daily (in the morning and evening), after cleansing. Daily applications should be approximately 8-12 hours apart. Subjects will be reminded that as with all facial skin care products, care should be taken to avoid getting into the eyes. If contact does occur, then rinse thoroughly with water.

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

Name of Item	Purpose
Simple™ Kind to Skin Moisturising Facial Wash	Study Cleanser (Subjects will be asked to use the study cleanser mornings and evenings in the washout period and during the study. On the clinic days, subjects will use the cleanser in the evenings only and to wash their face in the morning with tap water).

Statistical Methods

A formal statistical analysis plan (SAP) will be prepared by GSKCH prior to database finalisation.

All efficacy analyses will be performed on the intent to treat (ITT) population defined as all subjects randomised with at least one post-baseline study assessment. Additional analyses will be performed using the per-protocol (PP) population defined as all subjects in the ITT population without a major protocol violation. All major protocol violations, including treatment use compliance, will be identified prior to

database finalisation. Safety analyses will be based on the safety population defined as all subjects with at least one product application on either side of the face.

Baseline and change from baseline in DermaTOP parameters R_a, R_z, S_a and S_{tm} will be summarised (N, mean, standard deviation, median, minimum and maximum) by treatment arm (test product, Olay ProX Wrinkle Smoothing Cream, no treatment) for each study visit (weeks 2 and 4). For each parameter, test product versus no treatment and positive control versus no treatment will be compared for the change from baseline at 2 weeks, and 4 weeks (primary endpoint), using analysis of covariance (ANCOVA) with subject (random effect), treatment, and side of face as main effects and baseline value as covariate. This approach allows for the inclusion of data from all subjects treated with a given treatment arm (test product, positive control or no treatment) regardless of the treatment group (test product/no treatment, test product/positive control, positive control/no treatment) to which they were randomised to derive estimates of treatment effect. If the assumption of normality is rejected, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and pairwise treatment comparison, together with the 95% confidence intervals.

The same presentation and analysis methods, as outlined above, will be performed using change from baseline for other parameters; clinical Fitzpatrick wrinkle score assessment, TEWL values, Corneometer values and Cutometer parameters R5 and R7, separately for the Sub-ocular/ Cheek Area. The texture assessment resulting from the ranking of photos will inherently be an assessment of change from baseline. As such, the data resulting from these rankings will be tabulated by treatment arm as proportions with baseline image better and Day 29 image better and analysed using a logistic regression.

As this is a POC study, there will be no adjustment to the critical alpha level of 0.05 to account for inflation due to multiplicity. P-values resulting from inferential testing will be considered primarily as summary statistics.

Adverse events will be summarised by treatment arm.

1. INTRODUCTION

Wrinkle development, as a direct consequence of skin ageing, has important social and psychological impacts which have become exaggerated with longer life expectancy and changing social values. The skin ageing process can be separated into two simultaneous processes – chronological (or intrinsic) ageing and extrinsic ageing (induced by cumulative exposures to environmental factors, especially UV light) [Abella ML, 2006].

There are many factors at play in skin ageing, one of which involves free radicals, which are both generated internally through normal metabolic processes and produced as a consequence of external factors, including UV exposure.

As the protective anti-oxidant mechanisms decline in age, free radicals accumulate in the body and alter both the proteins and the DNA in the skin. The chronic inflammatory state compromises skin health and accelerates the aging process; for example, proteolytic enzymes are produced, resulting in collagen degradation [Bennett MF, 2007].

Other changes resulting from the intrinsic and extrinsic factors that impact the appearance of fine lines, wrinkles and texture include the following, thickness of the epidermis, cellular turnover rate of both the epidermis and the SC declines, and epidermal differentiation is altered [Gilchrest BA, 1983, Wulf HC, 2004]. The dermis becomes thinner as major structural molecules including collagen, elastin and glycosaminoglycan decrease in amount [West MD 1989, Millis AJ 1992, and Wick M 1994]. Metalloproteinase activity also decreases in photodamaged skin and the structure of these molecules becomes disorganised and crosslinked [Varani J 2000, Francis C 1984, Lavker RM 1987, Uitto J 1989, Kligman LH 1986].

Convolution of dermal-epidermal junction (Rete ridges) flattens with age, resulting in a loss of mechanical strength. This also leads to decreased microcirculation to the upper dermis and, thus, decreased nourishment to the epidermis [Quan T 2004, Lohwasser C 2006].

Age-related changes in inter- and intra-cellular signalling lead to decreases in collagen synthesis. Changes in hyaluronic acid content within the skin varies with age. Hyaluronic acid is a natural moisturiser within the skin binding up to 1000 times its weight in water. Age-related declines result in compromised moisturisation and firmness [Ghersetich I, 1994, Schachtschabel DO 1978]. Decrease in intracellular energy sources including Adenosine Tri-Phosphate (ATP) and Nicotinamide adenine

dinucleotide phosphate (NADH) lead to an inability of skin cells to sustain youthful skin biochemistry, thereby reducing the skin's ability to maintain and restore youthful skin structure [Bisset DL, 2005].

Collectively, the changes, work together to compromise skin's elasticity, firmness and structure, which contributes to areas of collapse and irregularity and ultimately manifests as fine lines, wrinkles and texture problems.

A key wrinkle-prone region of concern is the periorbital area; this is where the first signs of ageing usually appear [Kaczvinsky JR, 2009]. The periorbital area includes not only the crow's feet region but also the intraorbital/ infraorbital region [Bissett DL, 2005].

Skin Texture can be found on many areas of the face, which include bumpy texture and enlarged pores. Areas of concern are usually found on nose and cheek area.

It is hypothesised that the test product, which contains humectants to moisturise the SC, will help to reduce the appearance of fine lines and wrinkles caused by skin dryness. It is also hypothesised that by moisturising the skin and depositing lipids on the skin surface, that skin elasticity, barrier function and texture will also be improved.

Stratum Corneum (SC) hydration state has profound influence on its biomechanical properties, bulk rheology, turgor and, thus, resulting micro- and macro-topography where, in simple terms, increased hydration promotes a smoother, less wrinkled SC surface. Moreover, when SC hydration is elevated for days or weeks, enhanced specific activity of SC desquamatory enzymes contributes to further incremental smoothing of SC surface topography [Berardesca E, 2015].

A clinical study, which explored the suggested link between excessive sebum secretion and an increased appearance of pores, as well as the effects of a 2% niacinamide containing facial moisturiser, showed that twice-daily use of the moisturiser reduced both sebum production and pore parameter compared to baseline measures. Overall, self-assessed facial skin appearance improved after using the niacinamide-containing moisturiser. Women reported a noticeable decrease in oiliness, large/open pores and balanced oily and dry areas of the face [Osborne R, 2003].

A method for evaluating changes in skin surface profiles is fringe projection by DermaTOP, in which phase-shifted fringe patterns are projected onto the skin by a computer-controlled digital projection system. These images are used to retrieve the 3-Dimensional (3D) surface contour of the skin [Callaghan T.M, 2008].

Quality standardised high resolution digital photography can also visibly demonstrate facial lines and wrinkles with accuracy. Coupled with image ranking it is particularly useful in providing before and after images [Callaghan T.M, 2008].

Of the many undesirable changes in the skin with age, the loss of skin resilience and skin sagging as a consequence of both intrinsic and extrinsic ageing is very apparent. The cutometer, a method based on skin deformation can measure elasticity by distortion of the skin via suction [Wilhelm K.-P, 2008].

The objective of this POC clinical study is to evaluate the cosmetic appearance of fine lines and wrinkles benefit delivered by 4 weeks of twice-daily application of the test product on fine lines and wrinkles, texture, barrier function, hydration and elasticity to subjects presenting visible signs of ageing.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Evaluation of wrinkle dimensions (change from baseline) of test product compared to no treatment on the Periocular / Crow's Feet Area.	DermaTOP parameter R_a at 4 weeks.
Secondary	
Evaluation of wrinkle dimensions (change from baseline) of test product and positive control compared to no treatment in the Periocular / Crow's Feet Area.	DermaTOP parameter R_a at 2 weeks and 4 weeks (positive control only)
	DermaTOP parameters R_z, S_a and S_{tm} at 2 and 4 weeks
	Clinical Fitzpatrick Wrinkle Score at 2 and 4 weeks
Evaluation of skin moisturisation (change from baseline) of test product and positive control compared to no treatment	Instrumental Corneometer values at 2 and 4 weeks

on the Sub-ocular/ Cheek Area.	
Evaluation of texture (change from baseline) of test product and positive control compared to no treatment on the full face.	Texture ranking at 4 weeks
Evaluation of skin elasticity (change from baseline) of test product and positive control compared to no treatment on the Sub-ocular/ Cheek Area.	Instrumental Cutometer parameters R5 and R7 at 2 and 4 weeks
Evaluation of skin barrier (change from baseline) of test product and positive control compared to no treatment on the Sub-ocular/ Cheek Area.	Instrumental Trans-Epidermal Water Loss (TEWL) values at 2 and 4 weeks
To evaluate the general safety of the study products	Assessment of frequency and severity of Adverse Events (AEs)

3. STUDY PLAN

3.1. Study Design

Overall Design
This is a single-site, 3-arm, randomised, evaluator-blind, positive controlled (Olay ProX Wrinkle Smoothing Cream) and no-treatment controlled split-face POC study to evaluate the cosmetic appearance of fine lines and wrinkles provided by 4 weeks of twice-daily application of the test product in healthy subjects presenting visible signs of ageing. Subjects will give their written consent prior to any study procedures taking place. At the Screening Visit, only healthy female subjects aged 30 to 65 (inclusive), with a Fitzpatrick phototype I-IV, a visual Clinical Fitzpatrick Wrinkle Score of 3-6 in the Periocular / Crow's Feet Area ~~with an equal rating~~ on both sides of the face (Appendix 3), with self-reported sensitive skin will be considered eligible to continue in the study. Eligible subjects will undergo a 3 day washout period, where they will be asked to avoid using any other skin care products (moisturisers, lotions, creams, soaps, cleansing products, foundations etc.) on their face from the screening visit until Visit

2 (Day 1) other than the cleanser provided (Simple™ Kind to Skin Moisturising Facial Wash™). Subjects will be asked to use the study cleanser mornings and evenings in the washout period and during the study. On clinic days, subjects will use the cleanser in the evenings only and wash their face in the morning with tap water.

Subjects successfully completing the washout phase and who continue to be eligible, will have their wrinkles assessed using the Clinical Fitzpatrick Wrinkle Score.

Subjects who meet all the inclusion/exclusion criteria will be randomised to one of three treatment groups: test product/positive control, test product/no treatment or positive control/no treatment at the baseline visit. Product application within treatment group will be further randomised to either the right or left side of the face.

Diary Cards will be provided and reviewed at each site visit by the Investigator or designee to confirm and encourage subject compliance. Subjects will be required to complete the diary card every day to record application of test and study cleanser products.

Subjects will be instructed to apply each test product to the assigned side of the face, as applicable, (approximately 2 mg / cm^2) twice-daily (morning and evening, approximately 8-12 hours apart), for 4 weeks (28 days). Subjects will return to the site on Day 15 (Visit 3) and 29 (Visit 4) without applying the test product at home that morning.

After randomisation, subjects who consent will have high resolution images taken on the left and right side of their face. Instrumental measures will follow in the following order: DermaTOP (Periocular / Crow's Feet Area), TEWL (Sub-ocular/ Cheek Area); Corneometer (Sub-ocular/ Cheek Area); Cutometer (Sub-ocular/ Cheek Area). The same schedule of events (except randomisation and high resolution photos) will be repeated for Day 15 (Visit 3). Day 29 (Visit 4) will be a repeat of Visit 2 (Day 1) (except randomisation).

Prior to all instrumental measurements and clinical assessments, subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity between 40-60%) for a period of at least 30 minutes [EEMCO, 1997].

On Day 1 (Visit 2) and Day 15 (Visit 3) on-site application of product will be supervised by the study site staff and will be performed only after the clinical and

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instrumental measurements are completed.

After the study has completed, all of the high resolution images will be evaluated by blinded lay persons to rank the appearance of texture.

Visit 1 – Screening / Washout Visit

The following assessments will be conducted in the order written:

1. Informed consent
2. Demographics
3. Medical History
4. Current / Concomitant medication
5. Fitzpatrick Skin Type assessment (Appendix 2)
6. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
7. Inclusion / Exclusion Criteria
8. Subject Eligibility
9. Study Cleanser and Diary Dispensing

Visit 2 – Baseline Visit

The following assessments will be conducted in the order written:

1. Current / Concomitant medication
2. Adverse Events
3. Diary Review (Compliance)
4. Continued Eligibility
5. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
6. Inclusion / Exclusion Criteria
7. Subject Eligibility
8. Randomisation
9. High Resolution Photos for Texture Assessment (Appendix 4)
10. DermaTOP Assessment
11. TEWL Assessment
12. Corneometer Assessment
13. Cutometer Assessment
14. Test Product(s) Dispensing
15. Supervised Test Product Application

Visit 3- Day 15 (Week 2)

The following assessments will be conducted in the order written:

1. Current / Concomitant medication
2. Adverse Events
3. Diary Review (Compliance)
4. Continued Eligibility

5. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
6. DermaTOP Assessment
7. TEWL Assessment
8. Corneometer Assessment
9. Cutometer Assessment
10. Supervised Test Product Application

Visit 4 – Day 29 (Week 4)

The following assessments will be conducted in the order written:

1. Current / Concomitant medication
2. Adverse Events
3. Diary Review (Compliance)
4. Continued Eligibility
5. Clinical Fitzpatrick Wrinkle Score (Appendix 3)
6. High Resolution Photos for Texture Assessment (Appendix 4)
7. DermaTOP Assessment
8. TEWL Assessment
9. Corneometer Assessment
10. Cutometer Assessment
11. Test Product, Study Cleanser and Diary Return
12. Subject Discharge from Study

3.2. Subject Restrictions

Lifestyle/ Dietary

During the entire study (screening – LSLV):

Subjects are not permitted to join any other cosmetic or therapeutic study.

Subjects must not be planning on taking holiday outside of their home country.

Subjects must avoid water sports including sailing, diving, swimming and winter sports including skiing and snowboarding.

Subjects must not smoke or start smoking during the study (including use of e-cigarettes).

Subjects will not be permitted to use any other skin care products (moisturisers, moisturising foundations, lotions, creams, sunscreens, soaps, cleansing, exfoliation

products, etc.) or begin the use of any new facial products on their face following the screening visit and for the duration of the study, other than the study cleanser Simple™ Kind to Skin Moisturising Facial Wash and the assigned test products provided. Subjects will be asked to use the study cleanser mornings and evenings in the washout period and during the study.
On the day of site visit: Subjects will be required to attend the screening and baseline visit wearing no make-up. ~~Mascara and lipstick are permitted to be worn.~~ Subjects must cleanse their face with only tap water on the morning of the visit at least 2 hours prior to the visit. Subjects will use the cleanser in the evenings only and wash their face in the morning with tap water. Subjects must not apply any other cosmetic or medicated treatment on the face, including the test products provided (Subjects will be instructed to apply the test product at least 12 hours before the study appointment). Subjects must bring their test products with them to the study site. Subjects must not consume coffee or any product containing caffeine or alcohol 2 hours priors to the scheduled visit until the end of their visit. No hard physical exercises (with heavy sweating), sauna, swimming within 24 hrs of the site visit.
Medications and Treatments
During the entire study (screening – LSLV): Subjects must not use any study prohibited medication as specified in the exclusion criteria. Subjects must not use any other cosmetic or medicated treatment on the face, other than the test products provided.

Female subjects of child-bearing potential must use effective contraception

Subjects must not change any hormonal treatment or contraception that they may be receiving and must have used the same contraception for 3 months prior to screening.

Subjects must not undergo any aesthetic, cosmetic or dermatological treatment in the treatment area (face or eyes) including facial hair removal, except for plucked eye brows.

Subjects must avoid photodynamic therapy, laser therapy, microdermabrasion for acne.

Subjects must avoid exposure to artificial ultraviolet (UV) light or cosmetic procedures (includes tanning beds, Intense Pulsed Light (IPL), etc.) for the duration of the study.

3.3. Type and Planned Number of Subjects

Healthy female volunteers, aged 30 to 65 (inclusive) with a Fitzpatrick phototype score of I-IV, presenting visible signs of ageing with a visual Clinical Fitzpatrick Wrinkle Score of Score 3-6 in the Periocular / Crow's Feet Area ~~with an equal rating~~ on both sides of the face (Appendix 3), with self-reported sensitive skin will be considered eligible to continue in the study.

Approximately 90 healthy subjects will be screened to randomise at least 72 subjects to ensure 66 subjects complete the entire study. This will ensure approximately 44 subjects per treatment arm (test product, positive control, no treatment) or 22 per treatment group (test product/no treatment, test product/positive control, positive control/no treatment).

The sample size is based on clinical considerations. With 40 subjects, a difference between test product and no treatment in the change from baseline in R_a of at least 46% of the magnitude of the within-subject standard deviation of the difference would be detectable at two-sided alpha=0.05 with approximately 80% power.

3.4. Study Design and Dose Justification

This is a single-site, 3-arm, randomised, evaluator-blind, positive controlled (Olay ProX Wrinkle Smoothing Cream) and no-treatment controlled split-face POC study to evaluate the cosmetic appearance of fine lines and wrinkles provided by 4 weeks of

-

twice-daily application of the test product in healthy subjects presenting visible signs of ageing.

A split-face design has been selected to enable each subject to act as their own control. Subjects will be recruited to ensure they present the same wrinkle grades on both sides of their face at screening and baseline and a left-right treatment randomisation will be employed to ensure a consistent baseline between groups.

A positive control has been included in the design to help validate the trial results. Olay ProX Wrinkle Smoothing Cream has been selected as the positive control in light of favourable literature data concerning the wrinkle benefits of formulations containing similar cosmetic ingredients [Kaczvinsky 2009] and clinically proven claims made under the manufacturer.

It is hypothesised that the test product, which contains humectants to moisturise the SC, will help to reduce the appearance of fine lines and wrinkles caused by skin dryness. It is also hypothesised that by moisturising the skin and depositing lipids on the skin surface, that skin elasticity and barrier function will also be improved.

The application quantity of the study product(s) has been selected to reflect typical consumer usage of these types of products approximately 2 mg/cm^2 [Simion, 2006].

The inclusion criteria number 7, “Skin Type, of Visual Clinical Fitzpatrick Wrinkle Score Wrinkle Score 3-6 in the Periocular / Crow’s Feet Area ~~with an equal rating~~ on both sides of the face”, (a mild to moderate population for fine lines and wrinkles) has been selected based on clinical considerations to ensure a homogeneous population.

A common technique to measure periorbital wrinkles is the DermaTOP system. The technique is a non-invasive, fringe projection technique that allows 3-D information to be gathered from the skin’s surface and has been evaluated in several studies as a sensitive approach with which to precisely demonstrate the effects of topical preparations on the topography of human skin [Kaczvinsky 2009].

The Sub-ocular/ Cheek Area will also be evaluated using a variety of other well established instrumental measures (TEWL, Corneometer, Cutometer) in order to inform future study design.

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 30 and 65 years inclusive.

3. GENDER
Subject is 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. CONTRACEPTION
Females of childbearing potential who are, in the opinion of the investigator, practising a reliable method of contraception. Adequate contraception is defined as abstinence, oral contraceptive, either combined or progestogen alone OR injectable

progestogen OR implants of levonorgestrel OR estrogenic vaginal ring OR percutaneous contraceptive patches OR intrauterine device or intrauterine system OR double barrier method (condom or occlusive cap [diaphragm or cervical vault caps] plus spermicidal agent [foam, gel, film, cream, suppository]) OR male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject.

6. COMPLIANCE
Willingness to actively participate in the study and to attend all scheduled visits.

7. SKIN TYPE
a) Fitzpatrick phototype I-IV (Appendix 2) b) Visual Clinical Fitzpatrick Wrinkle Score 3- 6 in the eye (crow's feet) area ~~with an equal rating~~ on both sides of the face (Table 1/Appendix 3) at screening and baseline. c) Subjects with self-reported sensitive skin

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.

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
a) Any history of significant dermatological diseases or conditions or medical conditions known to alter skin appearance or physiologic response (e.g. diabetes,) which could, in the opinion of the Investigator, preclude topical application of the investigational products and/or interfere with the evaluations. b) Change in contraception within the last 3 months. c) Presence of open sores, pimples, cysts, irritated skin, hairs or tattoos at the application site. d) Active dermatosis (local or disseminated) that might interfere with the results of

the study.

e) Considered immune compromised.
f) Currently using any medication which in the opinion of the investigator, may affect the evaluation of the study product, or place the subject at undue risk.
g) Use of the following topical or systemic medications: immunosuppressants, antihistamines, non-hormonal anti-inflammatory drugs, and corticosteroids up to 2 weeks before screening visit.
h) Intention of using any oral or topical steroids
i) Regular use of inhaled steroids (occasional use is permitted)
j) Regular use of topical anti-itch medications (occasional use permitted; the product should be applied with an applicator but not to the proposed application areas.
k) Use of any topical drug or medication in the proposed application areas.
l) Intention of being vaccinated during the study period or has been vaccinated within 3 weeks of the screening visit.
m) Currently receiving allergy injections, or received an allergy injection within 7 days prior to Visit 1, or expects to begin injections during study participation.
n) Blepharitis, conjunctivitis, uveitis.
o) Topical ocular treatment within the last month.
p) Aesthetic, cosmetic or dermatological treatment on the face within the last 3 months.
q) Intense sun exposure, UV-treatments or tanning salon visit within the last 2 weeks.

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

5. CLINICAL STUDY/ EXPERIMENTAL PRODUCT
a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 14 days of the screening visit. b) Previous participation in this study.

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

7. PERSONNEL

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

8. LIFESTYLE
A smoker

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomised, 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 electronic 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:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible where possible.
- 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.
- 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.

- 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-randomisation will not be replaced.

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 completion of the texture image ranking exercise.

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	Skin Care fine lines and wrinkles Chassis	Olay ProX Wrinkle Smoothing Cream
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available (UK)
Application Quantity	approx. 2 mg /cm^2	approx. 2 mg /cm^2
Route of Application	Dermal Topical	Dermal Topical
Application Instructions	Dispense two pumps of product (equating to approximately 0.6 mL) onto your fingertips and apply evenly to the randomly assigned side of the face, to include, the crow's feet area, cheek, forehead and chin twice daily, (morning and evening), after cleansing. Daily applications should be approximately 8-12	Subjects will be instructed to apply a pea-sized amount of the positive control product (equating to approximately 0.5g) onto your fingertips and apply evenly to the randomly assigned side of the face, to include the crow's feet area, cheek, forehead and chin , twice daily (in the morning and evening), after cleansing. Daily applications should be approximately 8-12 hours

	hours apart. Subjects will be reminded that as with all facial skin care products, care should be taken to avoid getting into the eyes. If contact does occur, then rinse thoroughly with water.	apart. Subjects will be reminded that as with all facial skin care products, care should be taken to avoid getting into the eyes. If contact does occur, then rinse thoroughly with water.

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

Name of Item	Purpose
Simple™ Kind to Skin Moisturising Facial Wash	Study cleanser (Subjects will be asked to use the study cleanser mornings and evenings in the washout period and during the study. On the clinic days, subjects will use the cleanser in the evenings only and to wash their face in the morning with tap water).

5.2. Application Schedule

The usage instructions for the study has been selected to reflect typical consumer usage; approximately 2 mg/cm^2 (Simion FA, 2006).

A washout period is included to standardise each subject's skin care regimen prior to entering the test phase. During the washout period, subjects will be requested to replace their current facial cleanser with the (Simple™ Kind to Skin Moisturising Facial Wash) cleanser. Subjects will be asked to use the cleanser mornings and evenings in the washout period and during the study. On the day of the site visit, subjects will use the cleanser in the evenings only and to wash their face in the morning with tap water.

Subjects will be instructed to apply the study product(s) to clean and dry skin.

During the test phase, subjects will be instructed to apply two pumps of test product (equating to approximately 0.6 mL) and/or a pea-sized amount (equating to

approximately 0.5g) of the positive control product to the randomly assigned side of the face, to include, cheeks, forehead and chin (approximately 2 mg/cm^2) twice daily, (morning and evening), after cleansing.

The first use of the products will be under supervision at the study site at Baseline (Day 1). Subsequent use of study products will be applied by the subject at home, as instructed by site staff. Subjects will bring their allocated study products with them to each post-baseline visit, having applied test and/or reference product at least 12 hrs prior to their appointment time.

Subjects will need to be reminded to bring all their study products (test/reference product and cleanser) with them to the study site for the subsequent visits. Study Product will be returned at Day 29 (Visit 4).

5.3. Application Modification

No modification of product application is permitted in this study.

5.4. Product Compliance

Subjects will be supervised when using the study product at the Baseline (Day 1) visit for the first time and at Visit 3 (Day 15) at the site to ensure compliance. A record of the dispensing and administration of the study products will be kept using the dispensing and administration log and the eCRF.

Diary Cards will be used to promote compliance and familiarisation during the study days. Subjects will not be excluded due to over or under use in applications but will be reminded to use the study products as per the instructions provided and to complete the diary card on a daily basis to encourage compliance.

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 study product at a dose higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the study products will be supplied, 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

Subjects will be randomised to one of 3 treatment groups in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software:

Test product/no treatment

Test product/positive control

Positive control /no treatment

Randomisation will further include specification of which side of the face to which each of the treatments is to be applied. This will ensure that each treatment will be applied to each side of the face across all subjects.

5.8.1 Randomisation

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 randomised according to the randomisation schedule. Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

The randomisation number will be associated with the treatment group and which side of face (either right and/or left) to which study product is to be applied.

The high resolution images will be randomised offline (in advance) using a standard block-wise randomisation algorithm on a standard PC (Dell Optiplex 9010). The randomisation algorithm is saved in order to reproduce the randomisation, if

necessary. The PC is not linked to the rater screens. The randomisations are stored as text file which are directly used by the presentation software (proDERM Onlinescore, used by the grader). There will be a single randomisation file per grader, so that the images will be presented to every grader in a different sequence.

5.8.2 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes will be blinded to the random assignments of product.

Investigators or designee dispensing the product will be aware of the treatment group randomisation including side of face to which treatment will be applied and must not divulge information to the other study staff or assessors.

The assessor performing the measurements will be blinded to the treatment group randomisation.

5.8.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which side of the face product(s) have been applied 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 study cleanser (Simple Kind to Skin Moisturising Facial Wash) to be used throughout the study will be supplied in commercial packs that will be over-wrapped in opaque vinyl to obscure any commercial branding as much as possible. The tubes will be supplied with a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number and directions for storage.

The Test product CCI [redacted] will be supplied in pump tubes with a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number, treatment group code, application side (Right or Left) and directions for storage.

The Reference product (Olay ProX Wrinkle Smoothing Cream) will be supplied in commercial packs that will be over-wrapped with opaque vinyl to obscure any commercial branding as much as possible. The jars will be supplied with a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number, treatment group code, application side (Right or Left) 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:

- The identification of the subject to whom the study product was dispensed.
- The date(s) and quantity of the study product dispensed to the subject.
- The date(s) and quantity of the study product returned by the subject (if applicable).

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 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 - Screening Visit

6.1.1 Telephone Screening

Prior to the screening visit, telephone screening of interested subjects may be conducted. This will be conducted by the site recruitment staff or designee.

Prior to the screening visit potential subjects may be provided with the Subject Information Sheet and given the opportunity to ask any questions with the Dermatologist prior to signing the Informed Consent form at the screening visit.

6.1.2. 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, to refuse the high resolution images even if they choose to enter the trial, or to withdraw from the trial 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.

Subjects may be contacted ahead of the screening visit and provided with the Informed Consent to read and consider in advance to give sufficient opportunity to discuss with the Investigator prior to consenting.

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender, race and Fitzpatrick skin type.

6.1.4. 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.

6.1.5. Clinical Fitzpatrick Wrinkle Assessment in Periocular / Crow's Feet Area

Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity between 40-60%) for a period of at least 30 minutes before the clinical assessments are performed [EEMCO, 1997].

A blinded, trained and qualified examiner will perform Clinical Fitzpatrick Wrinkle Score assessments by visually grading the crow's feet area under standard conditions of illumination. Non-polarised lighting (LED panels with a colour temperature of 6000 Kelvin and a colour rendering index of 96, Eva Lux Bench, by Orion Techno Lab), which causes a shine (by turning on only the upper light source) that enhances topographic features (fine lines and wrinkles). Subjects will have their hair and clothing covered with black drapes. Conditions (lighting, distance and head position) will be fixed by using a chin rest fixed on the Eva Lux Bench at all time points for the same subject. These assessments will be performed at Visit 1 (day -3), Visit 2 (day 1), Visit 3 (Day 15) and Visit 4 (Day 29).

Refer to Table 1 below for the 9-point visual rating scale (VRS) used in this assessment [Elsner P, 2011]. Refer to Wrinkle Score according to Fitzpatrick at the end of Appendix 3 for a visual differentiation of each score/class.

Table 1: Fitzpatrick Wrinkle Score Periocular / Crow's Feet Area

Fitzpatrick Wrinkle Score			
CCI [redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

6.2. Visit 2 - Baseline Visit Day 1

Subjects will be randomised to a treatment group and side of face (Left or Right) to which each product should be applied after all the assessments below are performed (baseline). First use of the product(s) will be supervised by site staff as per directions provided, however this will be after all clinical and instrumental measures have been taken on the day.

Subjects will be acclimatised in a controlled environment (temperature 20-22ºC, relative humidity between 40-60%) for a period of at least 30 minutes before the instrumental and clinical assessments are performed (at each time point) [EEMCO, 1997].

6.2.1 USR- CliP High Resolution Images

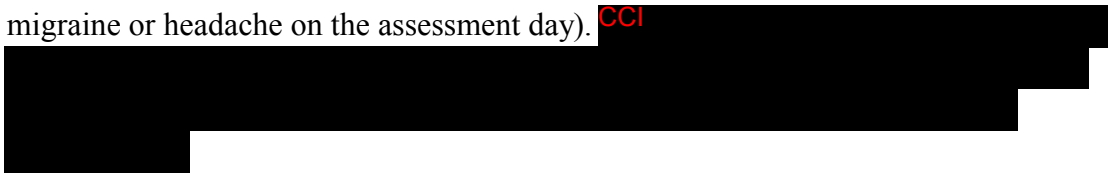
CCI [redacted]

CCI

Informed consent will be sought from the subjects for the use of photographs taken of their face during this study and for the purpose of Ad-hoc analysis by the sponsor company.

After the study has completed, all of the high resolution images will be assessed by 24 lay raters at one time to evaluate texture (pores, smoothness and unevenness).

The lay raters will come to the study site on image assessment days and will be informed about the assessment and will give their written informed consent to participate, which includes the following inclusion/exclusion criteria (Inclusion: 18 to 70 years; knowledge how to use a computer, Exclusion: problems with the eyes; change of lenses or glasses within the last 7 days before the start of the study; migraine or headache on the assessment day). CCI



The 24 lay raters will be recruited from ProDERMs database. Once the 'rater' Informed Consent is signed, proDERM are to explain the imaging assessment process (2 images on the same screen that have to ranked), and how the scale works and how the subjects are to use the software.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

6.2.2. DermaTOP Technique

CCI

CCI

CCI

CCI

CCI

CCI [redacted]

Please see below for definitions and formulas for the assessed DermaTOP parameters:

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.2.3 Transepidermal Water Loss (TEWL)

CCI

[redacted]

6.2.4. Corneometry Assessment

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

6.2.5.Cutometer Assessment

CCI

CCI

CCI

CCI

6.3. Visit 3 (Day 15)

Subjects will return to the study site without having applied product that morning.

® Cutometer is a registered trademark of Courage + Khazaka electronic GmbH

Subjects will repeat assessments as per Baseline, Visit 2 (Day 1), except for randomisation, product dispensing and USR CliP High Resolution Images.

Following clinical and instrumental assessments, subjects will apply product under site supervision.

6.4. Visit 4 (Day 29)

Subjects will return to the study site without having applied product that morning, no product will be applied on this day.

Subjects will repeat assessments as per Baseline, Visit 2 (Day 1) except for randomisation and product dispensing as this will occur on Baseline, Visit 2, and (Day 1) only.

Subjects will return the test product(s), cleanser and diary card. 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:

- 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.
- NOTE: An AE can therefore be any unfavourable 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:

- 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.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- 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:

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

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 fulfils 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, diarrhoea, 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 • 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. • 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:

- The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
- The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.
- 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.
- 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).
- AEs will be collected from the start of the washout product and until 5 days following last administration of the study product.
- 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.
- 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:

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

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- 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.
- 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.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- 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:

- AEs will be recorded in the AE section of the CRF.
- 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.
- 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)?"

- 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.
- 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:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see section 7.3)
- Criterion for seriousness.

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

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- 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:

- After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.
- 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.
- 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.
- 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.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

- 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.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- 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 fulfil specific regulatory and GCP requirements, regarding the product under investigation.
- 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:
• Pregnancy information will be collected on all pregnancies reported following administration of washout product. Information on pregnancy identified during the screening phase and prior to washout product administration does not need to be collected.

7.6.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
• The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the *washout product.* 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. • 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. • 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. • 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. • If the subject becomes pregnant during the study they should be withdrawn from the study and this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

Data Management will be performed by GSKCH. 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. Electronic 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^{TM}).

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 (CD(s)) 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/DVD 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

Approximately 90 healthy subjects will be screened to randomise at least 72 subjects to ensure 66 subjects complete the entire study. This will ensure approximately 44 subjects per treatment arm (test product, positive control, no treatment) or 22 per treatment group (test product/no treatment, test product/positive control, positive control/no treatment).The sample size is based on clinical considerations. With 40 subjects, a difference between test product and untreated in the change from baseline in R_a of at least 46% of the magnitude of the within-subject standard deviation of the difference would be detectable at two-sided alpha=0.05 with approximately 80% power.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

The 'Intent to treat' (ITT) population includes all subjects who are randomised into the study and have at least one post-baseline clinical assessment available. All efficacy analyses will be based on the ITT population.

The Per Protocol (PP) population will consist of the subset of ITT subjects which excludes those subjects with significant protocol deviations. Protocol deviations will be identified prior to database unblinding and will include, but not be limited to, non-compliance with the protocol or product application and use of prohibited

concomitant medications. Confirmatory analyses of at least the primary efficacy endpoint of DermaTOP R_a will be performed on the PP population.

The Safety population will include all subjects with at least one product application to either side of the face. All safety analyses will be performed using the Safety population.

9.2.2. Exclusion of Data from Analysis

No data will be excluded from any analysis.

9.2.3. Criteria for Evaluation

The primary objective will be to evaluate the change from baseline in wrinkle dimensions in the crow's feet area for the test product compared to no treatment after 4 weeks of twice daily product application. Given that this is a POC study, the study will be considered a success if at least a trend in favour of the test product is observed. There will be no adjustment to the critical alpha level of 0.05 to account for inflation due to multiplicity. P-values resulting from inferential testing will be considered primarily as summary statistics.

9.2.4. Handling of Dropouts and Missing Data

Missing data will not be replaced or imputed. Dropouts will be included in analyses up to the point of discontinuation.

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 finalisation of the protocol and prior to study unblinding / analysis (as appropriate) and performed by GSK.

9.3.1. Demographic and Baseline Characteristics

Age and baseline Fitzpatrick wrinkle assessment scores will be summarised descriptively using means, medians and standard deviations. Race and Fitzpatrick skin type scores will be summarised using frequency counts and percentages.

9.3.2. Primary Analysis(es)

All efficacy analyses will be performed on the intent to treat (ITT) population.

Baseline and change from baseline in DermaTOP parameters R_a, R_z, S_a and S_{tm} will be summarised (N, mean, standard deviation, median, minimum and maximum) by treatment arm (test product, Olay ProX Wrinkle Smoothing Cream, no treatment) for each study visit (weeks 2 and 4). For each parameter, test product versus no treatment and positive control versus no treatment will be compared for the change from baseline at 2 weeks, and 4 weeks (primary endpoint), using analysis of covariance (ANCOVA) with subject (random effect), treatment, and side of face as main effects and baseline value as covariate. This approach allows for the inclusion of data from all subjects treated with a given treatment arm (test product, positive control or no treatment) regardless of the treatment group (test product/no treatment, test product/positive control, positive control/no treatment) to which they were randomised to derive estimates of treatment effect.

If the assumption of normality is rejected, an appropriate transformation to the data will be performed to facilitate the above method of analysis. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and pairwise treatment comparison, together with the 95% confidence intervals. In the absence of an appropriate data transformation, non-parametric analysis will be performed.

9.3.3. Secondary Analysis(es)

The same presentation and analysis methods, as outlined above, will be performed using change from baseline for other parameters; clinical wrinkle assessment, TEWL values, Corneometer values and Cutometer parameters R5 and R7. The texture assessment resulting from the ranking of photos will inherently be an assessment of change from baseline. As such, the data resulting from these rankings will be tabulated by treatment arm as proportions with baseline image better and Day 29 image better and analysed using a logistic regression.

9.3.4. Safety Analysis(es)

Adverse Events (AE) will be tabulated according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Frequencies and percentages will be presented by treatment arm overall, for each system organ class,

and for each preferred term. Summaries of treatment-emergent AE's, treatment-related AEs, AEs leading to discontinuation, and serious AEs will be completed.

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 enrolment 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:

- Before initiating a trial, the investigator/institution should have written and dated approval/favourable 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.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)
- 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:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- 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:

- 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.
- 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.
- If the IEC terminates or suspends its approval/favourable 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.

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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

µl	Microlitres
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATP	Adenosine Tri-Phosphate
AUC	Area under Curve
CCD	charge coupled device
CD	Compact Disc
cm^2	Centimetre squared
CFR	Code of Federal Regulations
CRF	Case Report Form
DVD	Digital Versatile Disc
EDC	Electronic Data Capture
EEMCO	European Expert Group on Efficacy Measurement of Cosmetics and Other Topical Products
DIN EN ISO	Deutsches Institut für Normung (German institute for norms) EN= European Norm; ISO= International Organization for Standardisation
FOV	Field Of View
GCP	Good Clinical Practice
g	Gram
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ITT	Intention to Treat
LCD	Liquid Crystal Display
LSLV	Last Subject Last Visit

hr	Hour
mg	milligrams
mL	millilitre
mm	millimetre
MYSQL	Michael Widenius Structured Query Language
NADH	Nicotinamide adenine dinucleotide phosphate
OTC	Over The Counter
PC	Personal Computer
PII	Personally Identifiable Information
PP	Per Protocol
POC	Proof of Concept
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Stratum Corneum
TEWL	Transepidermal Water Loss
VRS	Visual Rating Scale
UV	Ultraviolet
3D	Three Dimensional

12.2. Appendix 2 - Fitzpatrick Skin Type

CCI

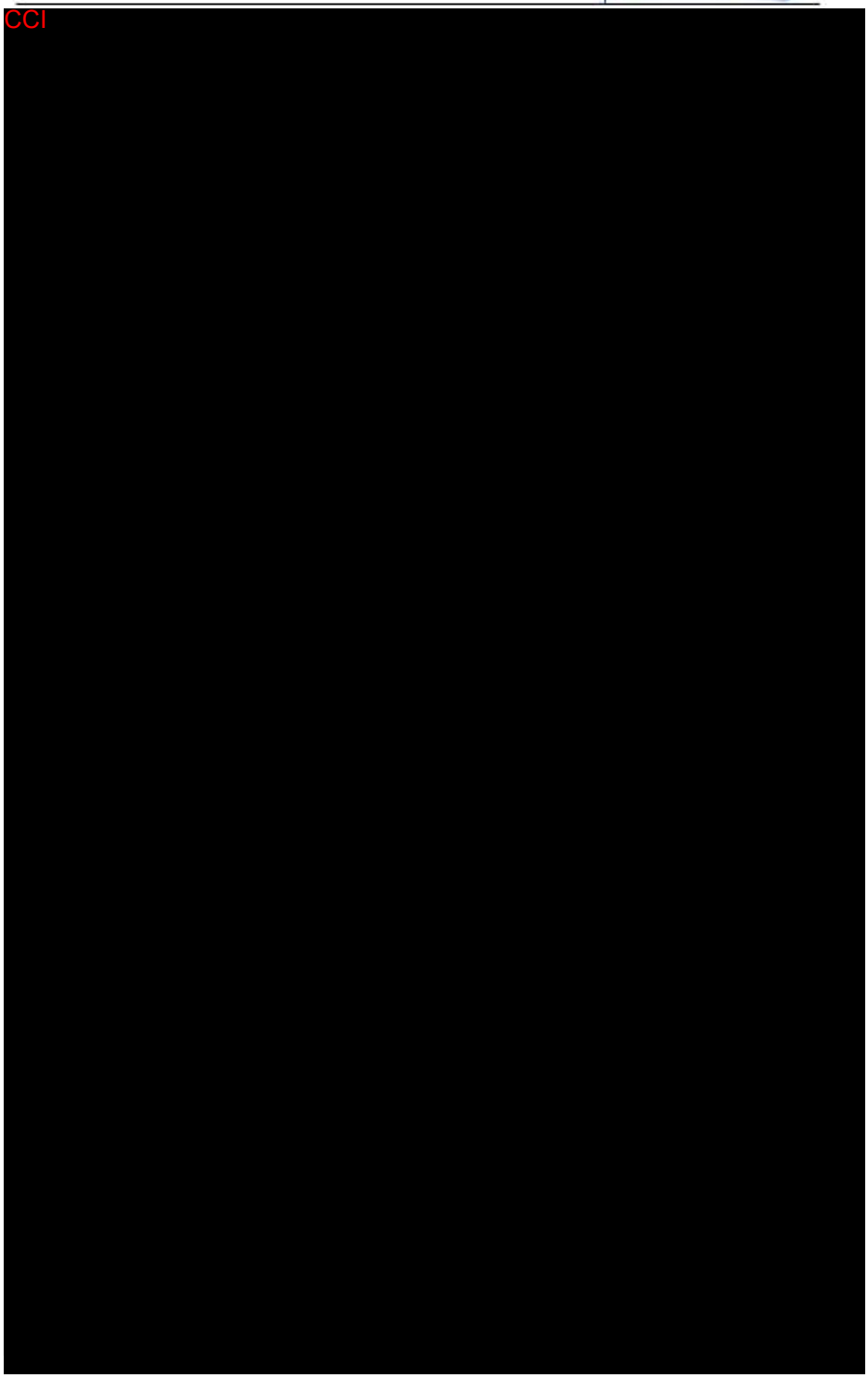
CCI

12.3. Appendix 3 – Fitzpatrick Wrinkle Score (Crow's Feet Area)

Fitzpatrick Wrinkle Score
CCI 

proDERM

CCI



12.4. Appendix 4 – Texture Ranking Scale

12.5. Appendix 5 DermaTOPV3 Calculated Parameters

dermaTOP-V3 SOFTWARE
CALCULATED PARAMETERS

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SIGNATURE PAGE

Clinical Protocol 207468.doc

Date	Signed By
22-Mar-2017 09:34:38	PPD
Justification	Clinical Operations Approval

Date	Signed By
22-Mar-2017 10:04:09	PPD
Justification	Approved

Date	Signed By
22-Mar-2017 11:13:21	PPD
Justification	Biostatistics Approval

Date	Signed By
24-Mar-2017 07:31:25	PPD
Justification	Approved

Date	Signed By
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