Clinical Protocol

207196

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A randomised, parallel-group, evaluator-blind, no-treatment and positive controlled, single-site, proof of concept clinical study to evaluate the cosmetic benefit provided by 8 weeks of twice-daily topical application of a developmental moisturising cream with niacinamide in healthy subjects with sensitive, oily, blemish-prone skin.
Protocol Number:	207196
Sponsor:	GlaxoSmithKline (GSK) Rua Hungria, 1.240 - 4^{0} andar Jardim Europa - Sao Paulo - SP CEP: 01455-000, Brazil Tel: PPD
Product Name:	Moisturising Cream with Niacinamide
Development Phase:	Not Applicable

Expert Advice Outside of Normal Working Hours:	Tel: PPD

Key Protocol Authors:	
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Study Site Name & Address:	Azidus Brasil - Rua General Osório, 507, Vila Martina, Valinhos, São Paulo, Brazil
Study Site Telephone Number:	PPD
Study Examiner(s):	Study examiners will be assigned and their details recorded prior to study start

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

1. I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

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

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

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

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

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 GlaxoSmithKline Consumer Healthcare (GSKCH) and the investigator.

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

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

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

PROTOCOL AMENDMENT PAGE

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

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1	Non-Substantial/Minor ☒	To correct an error pertaining to the location of the Fitzpatrick assessment scale.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	4.1 Inclusion Criteria (page 30)	Signature: PPD
Protocol Version No.: 2	Substantial/ Major ☐				Date: PPD
Amendment No.: 2	Non-Substantial/Minor ☒	To remove the sub-totals for the blemish counts, which will no longer be collected on the CRF. To add text clarifying that a grand total of blemish counts will be automatically calculated on the CRF at Visits 1 and 2.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	6.1.5. Evaluator Assessment of Blemish Counts (page 40)	Signature: PPD
Protocol Version No.: 2	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.: 3 **Protocol Version No.: 2**	Non-Substantial/Minor ☒ Substantial/ Major ☐	To clarify that Corneometer measurements will only be taken in triplicate at the left cheek and not both the right and left cheeks.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	6.2.10. Corneometry Measurements (Page 43)	Signature: PPD Date: PPD
Amendment No.: 4 **Protocol Version No.: 3**	Non-Substantial/Minor ☒ Substantial/ Major ☐	To add time windows for the Corneometer and Sebumeter Kinetic measurements	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	Schedule of Events (Page 14); Study Design (Page 17-19); 3.2 Study Design (Page 25-26); 6.2.11 (Page 43); 6.2.14 (Page 44)	Signature: PPD Date: PPD
Amendment No.: 5 **Protocol Version No.: 4**	Non-Substantial/Minor ☒ Substantial/ Major ☐	To reduce the minimum number of blemishes at screening from 10 to 8 and to permit rescreening of screen-failed subjects due to this inclusion criterion in order to address recruitment challenges. Contact information for GSK Statistician and Clinical Study Manager have also been	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☒ Yes ☐ No	Screening (Page 32); Study Design and dose justification (Page 27); Inclusion criteria (Page 30, Page 68)	Signature: PPD Date: PPD

		updated.			

SCHEDULE OF EVENTS

Procedure/Assessment	Visit 1 Day -5 to -7	Visit 2 Day 1	Visit 3 Day 8 +/- 1 Day	Visit 4 Day 29 +/- 2 Days	Visit 5 Day 57 +/- 2 Days
	Screening / Washout	Baseline	1 Week of Application	4 Weeks of Application	8 Weeks of Application
Informed Consent	X				
Demographics	X				
Medical History	X				
Current / Concomitant Medication	X	X	X	X	X
Adverse Events		X	X	X	X
Diary Review (Compliance)[1]		X	X	X	X
Continued Eligibility		X	X	X	X
Fitzpatrick Skin Type Assessment	X				
Evaluator Assessment of Blemish Counts[2]	X	X[4]	X	X	X
Forehead Sebumeter Measurement[3]	X	X[4]	X	X	X
Inclusion / Exclusion Criteria	X	X[5]			
Subject Eligibility	X	X			
Washout Cleanser and Diary Dispensing	X				
Randomisation		X			
Corneometer Measurements[3]		X[4]	X	X	X
Image Capture		X[4]			X
Washout Cleanser Return and Products Dispensing		X			
Sebumeter Kinetic Measurements[3,9]		X	X	X	X
Supervised Product Application[6]		X	X	X	
Acute Corneometer Measurements		X[7]			
Products and Diary Return					X
Subject Discharge from Study					X
Lay Person Assessment of Overall Appearance of Blemishes (Photographs)[8]					X

1. Evaluators must be blinded to diary review.
2. Blind evaluator assessment of papules and pustules, to be counted separately for the face, chin and cheeks.
3. Subjects must also acclimatize for a minimum of 30 minutes in a temperature (20 ± 1 degrees Celsius (°C)) and humidity (50 ± 10% Relative Humidity (RH)) controlled room prior to any instrumental measurement being taken.
4. Baseline measurements (prior to any product application).
5. Only the inclusion and exclusion criteria in Appendix 2 will be reviewed at this visit.
6. Subjects randomised to positive control regimen will apply the positive control cleanser and positive control cream. Subjects randomised to the test product regimen will apply the standard cleanser and test product. Subjects randomised to the no treatment regimen will apply the standard cleanser, only. Test product application will be overseen by a member of the study team who must not be involved in any clinical or instrumental assessment which could influence the study outcome.
7. Acute Corneometer assessments will be taken 1 hour ± **15 MINUTES**, 3 hours ± **15 MINUTES** and 8 hours ± **15 MINUTES** after application of the cream for subjects randomised to the test product and positive control regimens and after cleansing for subjects randomised to the untreated regimen.
8. Lay person assessment of overall appearance of blemishes (Photographs) will take place after the completion of the clinical study.
9. **SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

PROTOCOL SYNOPSIS FOR STUDY 207196

Brief Summary

A randomised, parallel-group, evaluator-blind, no-treatment and positive controlled, single-site, proof of concept clinical study to evaluate the cosmetic benefit provided by 8 weeks of twice-daily topical application of a developmental moisturising cream with niacinamide in healthy subjects with sensitive, oily, blemish-prone skin.

Cosmetic creams containing niacinamide have been shown to help improve the moisturisation of the stratum corneum, improve the rate of desquamation, normalize sebum levels and reduce the appearance of blemishes.

It is therefore hypothesized that the test product, which is also formulated as a cosmetic cream containing niacinamide, will help moisturise the skin, support efficient desquamation of the stratum corneum and prevent excessive aggregation of corneocytes in the follicles, a known trigger implicated in the development of blemishes. These cosmetic benefits should translate to an overall improvement in the appearance of the complexion of people with blemish-prone skin.

Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
Evaluation of skin moisturisation (change from baseline) compared to no treatment	Corneometer values at 8 hours on Day 1
Secondary	
Evaluation of skin moisturisation (change from baseline) compared to no treatment	Corneometer values at 1 hour on Day 1, 3 hours on Day 1, 1 week, 4 weeks and 8 weeks
Evaluation of the overall appearance of blemishes (change from baseline) compared to no treatment	Lay person assessment of the appearance of blemishes by photographic assessment at 8 weeks Evaluator assessment blemish count (sum of papules and pustules at forehead, chin and cheeks) at 1, 4 and 8 weeks Evaluator assessment of individual blemish count (individual count of papules and pustules at the forehead, chin and cheeks) at 1, 4 and 8 weeks
Evaluation of skin oiliness improvement (change from baseline) compared to no treatment	Sebumeter values at 1, 4 and 8 weeks Sebum excretion rate at 1, 4 and 8 weeks
To evaluate the safety of the test product	Frequency and severity of adverse events

Study Design

Overall Design
A randomised, parallel-group, evaluator-blind, no-treatment and positive controlled, single-site, proof of concept clinical study to evaluate the cosmetic benefit provided by 8 weeks of twice-daily topical application of a developmental moisturising cream with niacinamide in healthy subjects with sensitive, oily, blemish-prone skin.
Visit 1 (Day -5 to -7) – Screening / Washout Visit
The following assessments will be conducted: 1. Informed Consent 2. Demographics 3. Medical History 4. Current / Concomitant Medication 5. Fitzpatrick Skin Type Assessment 6. Evaluator Assessment of Blemish Counts 7. Forehead Sebumeter Measurements 8. Inclusion / Exclusion Criteria 9. Subject Eligibility 10. Washout Cleanser and Diary Dispensing
Visit 2 / Day 1 – Baseline Visit
The following assessments will be conducted: 1. Current / Concomitant Medication 2. Diary Review (Compliance) 3. Continued Eligibility 4. Evaluator Assessment of Blemish Counts 5. Inclusion / Exclusion Criteria* 6. Subject Eligibility 7. Randomisation 8. Image Capture 9. Forehead Sebumeter Measurements 10. Corneometer Measurements 11. Sebumeter Kinetic Measurements** 12. Washout Cleanser Return and Test Product Dispensing 13. Supervised Test Product Application 14. Acute Corneometer Measurements*** 15. Adverse Events *To include a review of the inclusion and exclusion criteria specified in Appendix 2 **SEBUMETER MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90

± 5 MINUTES AFTER FOREHEAD CLEANSING.

***Acute Corneometer measurements to be taken 1 **HOUR ± 15 MINUTES**, 3 **HOURS ± 15 MINUTES** and 8 hours **± 15 MINUTES** after test product or positive control application for subjects randomised to the test product and positive control regimens and after cleansing for subjects randomised to the untreated regimen.

Visit 3 / Day 8 ± 1 Day – 1 Week of Application

The following assessments will be conducted:

1. Current / Concomitant Medication
2. Diary Review (Compliance)
3. Continued Eligibility
4. Evaluator Assessment of Blemish Counts
5. Forehead Sebumeter Measurements
6. Corneometer Measurements
7. Sebumeter Kinetic Measurements*
8. Supervised Test Product Application
9. Adverse Events

***SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

Visit 4 / Day 29 ± 2 Days – 4 Weeks of Application

The following assessments will be conducted:

1. Current / Concomitant Medication
2. Diary Review (Compliance)
3. Continued Eligibility
4. Evaluator Assessment of Blemish Counts
5. Forehead Sebumeter Measurements
6. Corneometer Measurements
7. Sebumeter Kinetic Measurements*
8. Supervised Test Product Application
9. Adverse Events

****SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

Visit 5 / Day 57 ± 2 Days – 8 Weeks of Application

The following assessments will be conducted in the order written:

1. Current / Concomitant Medication
2. Diary Review (Compliance)
3. Continued Eligibility
4. Evaluator Assessment of Blemish Counts
5. Image Capture
6. Forehead Sebumeter Measurements

7. Corneometer Measurements
8. Sebumeter Kinetic Measurements*
9. Test Product, Cleanser and Diary Return
10. Adverse Events
11. Subject Discharge from Study
12. Lay Person Assessment of Overall Appearance of Blemishes (Photographs)**

***SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

**This procedure will take place after all the subjects have been discharged from the study.

Type and Planned Number of Subjects

Approximately 200 female subjects aged 18-45 with self-assessed sensitive skin and a minimum of ~~10~~ **8** and a maximum of 25 facial blemishes (papules and pustules, excluding the nose) will be screened to randomise 132 healthy subjects, to ensure approximately 40 subjects in the test product regimen, 40 subjects in the no treatment regimen and 40 subjects in the positive control regimen complete the study (assuming a 10% dropout rate). Randomisation will be stratified by age (<21 years old, ≥21 years of age).

The sample size was based on clinical considerations. In a previous study of a cosmetic product, counts of papules and pustules decreased from a baseline mean of 27.6 to a mean of 13.5 at Week 8 (ref. Shalita 1995 IJD). With 40 subjects in both the test product and no-treatment regimens, a difference between groups at least 60% the magnitude of the standard deviation (assumed equal for both groups) would be detectable at two-sided alpha=0.05 with approximately 80% power.

Main Criteria for Inclusion

Healthy female subjects aged 18-45 with oily, self-assessed sensitive skin and a minimum of ~~10~~ **8** blemishes (papules and pustules) and a maximum of 25 blemishes on the face will be recruited for this study. Subjects must not currently have acne conglobate, fulminans, secondary acne (drug induced acne) nodular lesions or any acne requiring systemic or topical treatment. Subjects must not have a history of using a medicated acne treatment within the last 12 months.

Product Information

	Washout / Standard Cleanser	Test Product	Positive Control Cleanser	Positive Control Moisturiser
Product Name	Simple Kind to Skin Moisturising Facial Wash	Moisturising Cream with Niacinamide	Neutrogena Visibly Clear Spot Clearing Facial Wash	Vivatinell Acnecinamide Gel Cream
Product Formulation Code (MFC)	Commercially Available (UK)	CCI	Commercially Available (UK)	Commercially Available (Turkey)
Application Quantity	Approx. 0.6 g	Approx. 0.6 g	Approx. 0.6 g	Approx. 0.6 g
Application Instructions	Use twice daily (morning and night) with at least 8 hours between product applications. Wet your face and hands with water. Dispense the product into your hands and apply to the face. Massage gently. Rinse with water and pat dry. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.	Use twice daily (morning and night) with at least 8 hours between product applications. Dispense two pumps of product onto your fingertips and apply to your whole face, covering all blemishes. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.	Use twice daily (morning and night) with at least 8 hours between product applications. Wet your face and hands with water. Dispense the product into your hands and apply to the face. Massage gently. Rinse with water and pat dry. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.	Use twice daily (morning and night) with at least 8 hours between product applications. Apply a pea-sized quantity to your whole face, covering all blemishes. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.

Statistical Methods

A formal statistical analysis plan will be prepared prior to database finalization.

All efficacy analyses will be performed on the ITT population defined as all subjects randomized with at least one post-baseline study assessment. Safety analyses will be based on the safety population defined as all treated subjects. For the no treatment

regimen, treatment is defined as at least one use of the washout cleanser post-randomisation. No statistical comparison between the positive control regimen and the test product regimen is planned.

The change from baseline in Corneometer measurement at 8 hours post-treatment on Day 1 (primary endpoint) will be summarized by age stratum, treatment regimen and study visit using means and 95% confidence intervals and compared between treatment regimen using analysis of covariance (ANCOVA) with treatment main effect, age stratum (<21, ≥21 years of age) and baseline measurement as covariate or Wilcoxon rank sum test, depending on the data distribution. Differences between least squares means for the test product and no treatment regimen will be presented, together with 95% confidence intervals. While for this proof of concept study statistical significance ($p<0.05$) may not be achieved, these results will drive sample size projections for future studies.

The secondary Corneometer and Sebumeter changes from baseline will be summarized by age stratum, treatment regimen and study visit and analysed using the ANCOVA model described above.

Clinical assessment of blemish counts (papules and pustules) will be summarized by age group stratum (<21, ≥21 years of age), treatment regimen and study visit and compared between treatment regimens using means and 95% confidence intervals and compared between treatment regimen using analysis of covariance (ANCOVA) with treatment main effect, age stratum (<21, ≥21 years of age) and baseline count as covariate or Wilcoxon rank sum test, depending on the data distribution. Differences between least squares means for the test product and no treatment regimen will be presented, together with 95% confidence intervals.

The lay person assessment resulting from the ranking of images will inherently be an assessment of change from baseline. As such, the data resulting from these rankings will be tabulated by treatment regimen as proportions with baseline image better and Day 57 image better and analysed using a logistic regression.

Adverse events will be tabulated by age stratum and treatment regimen and displayed.

1. INTRODUCTION

This randomised, parallel-group, evaluator-blind, no-treatment and positive controlled, single-site, proof of concept clinical study is designed to evaluate the cosmetic benefit provided by 8 weeks of twice-daily topical application of a developmental moisturising cream with niacinamide in healthy subjects with sensitive, oily, blemish-prone skin.

The process by which facial blemishes appear usually begins with blocked follicles, which can be caused by inefficient desquamation of dead skin cells in the stratum corneum. Once blocked, sebum and additional dead skin cells can build up behind the blockage to create a comedone, commonly referred to as a blackhead or whitehead. In addition, the environment inside the blocked follicle is anaerobic, which promotes the propagation of bacteria that can trigger the redness associated with the appearance of blemishes, commonly referred to as papules and pustules.

It is well established that regular use of cosmetic creams containing niacinamide can help moisturise the skin, ensure efficient desquamation of the stratum corneum and normalize sebum levels. It is therefore expected that the test product will help promote efficient desquamation and prevent follicles from becoming blocked, thereby preventing the formation of new blemishes. These cosmetic benefits should translate to an overall improvement in the appearance of the complexion of people with blemish-prone skin.

The inclusion of a positive control regimen (Neutrogena Visibly Clear Spot Clearing Facial Wash and Vivatinell Acnecinamide Gel Cream) will help to validate the design of the trial by confirming the detectable cosmetic benefits of moisturisation and overall appearance of blemishes.

2. OBJECTIVE(S) AND ENDPOINT(S)

Objective(s)	Endpoint(s)
Primary	
Evaluation of skin moisturisation (change from baseline) compared to no treatment	Corneometer values at 8 hours on Day 1
Secondary	
Evaluation of skin moisturisation (change from baseline) compared to no treatment	Corneometer values at 1 hour on Day 1, 3 hours on Day 1, 1 week, 4 weeks and 8 weeks
Evaluation of the overall appearance of blemishes (change from baseline) compared to no treatment	Lay person assessment of the appearance of blemishes by photographic assessment at 8 weeks Evaluator assessment blemish count (sum of papules and pustules at forehead, chin and cheeks) at 1, 4 and 8 weeks Evaluator assessment of individual blemish count (individual count of papules and pustules at the forehead, chin and cheeks) at 1, 4 and 8 weeks
Evaluation of skin oiliness improvement (change from baseline) compared to no treatment	Sebumeter values at 1, 4 and 8 weeks Sebum excretion rate at 1, 4 and 8 weeks
To evaluate the safety of the test product	Frequency and severity of adverse events

3. STUDY PLAN

3.1. Study Design

Overall Design
A randomised, parallel-group, evaluator-blind, no-treatment and positive controlled, single-site, proof of concept clinical study to evaluate the cosmetic benefit provided by 8 weeks of twice-daily topical application of a developmental moisturising cream with niacinamide in healthy subjects with sensitive, oily, blemish-prone skin.
Visit 1 (Day -5 to -7) – Screening / Washout Visit
The following assessments will be conducted: 11. Informed Consent 12. Demographics 13. Medical History 14. Current / Concomitant Medication 15. Fitzpatrick Skin Type Assessment 16. Evaluator Assessment of Blemish Counts 17. Forehead Sebumeter Measurements 18. Inclusion / Exclusion Criteria 19. Subject Eligibility 20. Washout Cleanser and Diary Dispensing
Visit 2 / Day 1 – Baseline Visit
The following assessments will be conducted: 16. Current / Concomitant Medication 17. Diary Review (Compliance) 18. Continued Eligibility 19. Evaluator Assessment of Blemish Counts 20. Inclusion / Exclusion Criteria* 21. Subject Eligibility 22. Randomisation 23. Image Capture 24. Forehead Sebumeter Measurements 25. Corneometer Measurements 26. Sebumeter Kinetic Measurements** 27. Washout Cleanser Return and Test Product Dispensing 28. Supervised Test Product Application 29. Acute Corneometer Measurements*** 30. Adverse Events

*To include a review of the inclusion and exclusion criteria specified in Appendix 2
**SEBUMETER MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.
***Acute Corneometer measurements to be taken 1 **HOUR ± 15 MINUTES**, 3 **HOURS ± 15 MINUTES** and 8 hours **± 15 MINUTES** after test product or positive control application for subjects randomised to the test product and positive control regimens and after cleansing for subjects randomised to the untreated regimen.

Visit 3 / Day 8 ± 1 Day – 1 Week of Application

The following assessments will be conducted:

10. Current / Concomitant Medication
11. Diary Review (Compliance)
12. Continued Eligibility
13. Evaluator Assessment of Blemish Counts
14. Forehead Sebumeter Measurements
15. Corneometer Measurements
16. Sebumeter Kinetic Measurements*
17. Supervised Test Product Application
18. Adverse Events

***SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

Visit 4 / Day 29 ± 2 Days – 4 Weeks of Application

The following assessments will be conducted:

10. Current / Concomitant Medication
11. Diary Review (Compliance)
12. Continued Eligibility
13. Evaluator Assessment of Blemish Counts
14. Forehead Sebumeter Measurements
15. Corneometer Measurements
16. Sebumeter Kinetic Measurements*
17. Supervised Test Product Application
18. Adverse Events

****SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

Visit 5 / Day 57 ± 2 Days – 8 Weeks of Application

The following assessments will be conducted in the order written:

13. Current / Concomitant Medication
14. Diary Review (Compliance)
15. Continued Eligibility

16. Evaluator Assessment of Blemish Counts
17. Image Capture
18. Forehead Sebumeter Measurements
19. Corneometer Measurements
20. Sebumeter Kinetic Measurements*
21. Test Product, Cleanser and Diary Return
22. Adverse Events
23. Subject Discharge from Study
24. Lay Person Assessment of Overall Appearance of Blemishes (Photographs)**

***SEBUMETER KINETIC MEASURMENTS WILL BE TAKEN 5 ± 1 MINUTE AND 90 ± 5 MINUTES AFTER FOREHEAD CLEANSING.**

**This procedure will take place after all the subjects have been discharged from the study.

3.2. Subject Restrictions

Lifestyle/ Dietary
During the entire study (screening – Last Subject Last Visit (LSLV)); 1. Subjects must not take holiday outside of their home country. 2. Subjects must avoid water sports including sailing, diving, swimming and winter sports including skiing and snowboarding.
Medications and Treatments
On the day of site visit; 1. Subjects must cleanse their face with water (only). 2. Subjects must not apply any other cosmetic or medicated treatment on the face, including the test products provided.
During the entire study (screening – LSLV); 1. Subjects must not apply any other cosmetic or medicated treatment on the face, other than the test products provided. 2. Subjects may continue to wear their current brand of mascara and lipstick but must not use any facial cosmetics (e.g. blusher, foundation, tinted moisturiser, eyeshadow). 3. Subjects must not change their brand or usage of shampoo, shower gel, hand soap and other cosmetic products otherwise used on the body. 4. Female subjects of child-bearing potential must use effective contraception. 5. 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. 6. Subjects must not undergo any aesthetic, cosmetic or dermatological

treatment in the treatment area (face or eyes)

7. Subjects must not use any study prohibited medication as specified in the exclusion criteria.
8. Subjects must avoid photodynamic therapy, laser therapy, microdermabrasion for acne.
9. Subject must avoid sunbathing, ultraviolet (UV) treatments and tanning salons.
10. The use of sunscreen on the face is not permitted.

3.3. Type and Planned Number of Subjects

Approximately 200 female subjects aged 18-45 with self-assessed sensitive skin and a minimum of ~~10~~ **8** and a maximum of 25 facial blemishes (papules and pustules, excluding the nose) will be screened to randomise 132 healthy subjects, to ensure approximately 40 subjects in the test product regimen, 40 subjects in the no treatment regimen and 40 subjects in the positive control regimen complete the study (Assuming a 10% dropout rate). Randomisation will be stratified by age (<21 years old, ≥21 years of age).

The sample size was based on clinical considerations. In a previous study of a cosmetic product, counts of papules and pustules decreased from a baseline mean of 27.6 to a mean of 13.5 at Week 8 (ref. Shalita 1995 IJD). With 40 subjects in both the test product and no-treatment regimens, a difference between groups at least 60% the magnitude of the standard deviation (assumed equal for both groups) would be detectable at two-sided alpha=0.05 with approximately 80% power.

3.4. Study Design and Dose Justification

This proof of concept study is part of a broader development program to bring to market a range of cosmetic products targeted at female adults with sensitive, blemish-prone skin. The study is designed as a randomised, parallel-group, evaluator-blind, positive and no-treatment controlled, single-site, clinical study to evaluate the cosmetic benefits provided by 8 weeks of twice-daily topical application of a developmental moisturising cream with niacinamide in healthy subjects with sensitive, oily, blemish-prone skin.

For the purpose of this clinical study a steady state approximation is assumed, i.e. that the rate at which new blemishes appear is equal to the rate at which blemishes disappear. As this product is designed to prevent new blemishes from forming by

ensuring the skin is well moisturised to facilitate efficient desquamation, it is expected that there will be a preventative effect on the rate at which new blemishes appear. To account for natural fluctuations in blemish counts, subjects will only be enrolled into the washout phase if they have a minimum of ~~10~~ **8** and a maximum of 25 facial blemishes (papules and pustules), excluding the nose.

NOTE: ON 9 MAY 2017 THE SPONSOR AGREED TO RELAX THE SCREENING CRITERIA TO ENABLE INCLUSION OF SUBJECTS WITH A MINIMUM OF 8 FACIAL BLEMISHES IN ORDER TO FACILITATE RECRUITMENT. THIS AMENDMENT HAS NO IMPACT ON THE STATISTICAL POWER OF THE STUDY AS THE INCLUSION/EXCLUSION CRITERIA FOR RANDOMISATION ARE UNCHANGED.

Male subjects are excluded from this study to avoid the confounding impact of facial shaving on clinical assessments. Adolescent subjects and subjects older than 45 years are excluded as they do not represent the target population for the product.

Subjects with a history of using a medicated acne treatment within the last 24 months and subjects who, in the opinion of the investigator, require medicated acne treatment will not be enrolled in the study as they do not represent the target population for the cosmetic products.

Therefore, approximately 200 female subjects aged 18-45 with self-assessed sensitive skin and a minimum of ~~10~~ **8** and a maximum of 25 facial blemishes (papules and pustules, excluding the nose) will be screened to randomise 132 healthy subjects, to ensure approximately 40 subjects in the test product regimen, 40 subjects in the no treatment regimen and 40 subjects in the positive control regimen complete the study (assuming a 10% dropout rate). Randomisation will be stratified by age (<21 years old, ≥21 years of age).

A 5-7 day washout period is included to standardize subjects' cleansing and skin care regimens prior to entering the test phase. Subjects will be instructed not to use any skin care or cosmetic product during the washout phase and to cleanse twice a day (morning and night) with the washout facial cleanser provided (Simple Kind to Skin Moisturising Facial Wash; Commercially Available (UK)). To remain eligible for this study, subjects must complete the washout period (assessed at Visit 2) with at least 8 blemishes (papules and pustules, excluding the nose).

Following the washout period, subjects who continue to be eligible for the study will be randomised to one of three treatment regimens (no treatment + standard cleanser, test product + standard cleanser, or positive control cream + positive control cleanser). Due to the natural fluctuations of facial blemishes, the negative control, no-treatment regimen, is included to provide an anchor for efficacy assessments. All efficacy comparisons of the test product will be to the no-treatment regimen.

A cosmetic moisturising cream with niacinamide reported efficacious in subjects with blemish-prone skin (Vivatinell Acnecinamide Gel Cream) and a cosmetic cleanser containing 2% Salicylic Acid for exfoliation (Neutrogena Visibly Clear Spot Clearing Facial Wash) comprise a positive control regimen to support validation of the clinical study. No statistical comparison between the positive control regimen and the test product is planned.

The test product and no treatment regimens include a standard cleanser (Simple Kind to Skin Moisturising Facial Wash) that has not been designed to deliver improvements in the appearance of blemishes to enable the efficacy of the test product to be accurately evaluated.

During the test phase, subjects randomised to test product or positive control regimen will be instructed to use the cleanser and test/control products twice a day (morning and night). Subjects randomised to the no treatment regimen will use the standard cleanser (only) twice a day. The first application of the standard cleanser or positive control cleanser will be at the site, under supervision of the Investigator or designee who will provide instruction on how to correctly apply the product. The first application of test product or positive control will be conducted by the subject at the site, after cleansing, under the supervision of the Investigator or designee who will provide instruction on how to correctly apply the product.

Blinded evaluator and instrumental assessments will be taken after the washout period (baseline) and after 7, 28 and 56 days of twice-daily product use. All reasonable efforts will be made to ensure the same Evaluator assesses the same subject at each visit.

The Investigator or designee will dispense a diary to all subjects to monitor and encourage compliance. This diary will be reviewed at each site visit by the Investigator or designee and missed/extra applications recorded as deviations. The Investigator or designee will observe the subject applying the products and, if needed, will instruct the subject how to correctly apply them.

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. SEX / AGE
Female aged between 18 and 45 years inclusive.

3. 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.

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

5. SKIN TYPE
A. Minimum of ~~10~~ **8** and maximum of 25 blemishes (papules and pustules) at Visit 1 and a minimum of 8 blemishes (papules and pustules) at Visit 2. B. Fitzpatrick photo-type I-V (~~Appendix 1~~ **SECTION 6.1.4**). C. Sebumeter score of >66 µg / cm^2 at the forehead.

6. 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.

7. Cleansing Routine
Cleanses their face at least once a day.

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. Medical history of using a medicated acne treatment (e.g. Benzoyl Peroxide, Clindamycin, isotretinoin) within the last 12 months. B. Change in contraception within the last 3 months. C. Active skin disease in the test area. D. Medical history of dysplastic nevi or melanoma on the face. E. Moles, cysts, tattoos, scars, irritated skin, hairs, etc. at the test area that could influence the investigation. F. Systemic therapy with immuno-suppressive drugs (e.g. corticosteroids) and/or antihistamines within 7 days prior to the start of the study and/or throughout the entire course of the study. G. Systemic use of anti-microbials within the last month. H. Systemic use of over-the-counter (OTC) analgesics or anti-inflammatory drugs 24 hours prior to dosing at the first assessment visit. I. One of the following illnesses that might require regular systemic medication: Insulin-dependent diabetes, cancer. J. One of the following illnesses if not medicated: Asthma, hypertension K. Medical history of abnormal response to sunlight.

L. History of mental illness.
M. Medically diagnosed acne vulgaris, acne conglobate, fulminans, secondary acne (drug induced acne) or any acne requiring systemic or topical treatment.
N. No aesthetic, cosmetic or dermatological treatment in the treatment area (face) within the last month.
O. No intense sun exposure, UV-treatments or tanning salon visit within the last 2 weeks.

4. ALLERGY/ INTOLERANCE
A. Known or suspected intolerance, allergy or hypersensitivity to study materials (or closely related compounds) or any of their stated ingredients. B. History of allergies to cosmetic products or medicated acne treatments.

5. CLINICAL STUDY/ EXPERMENTAL PRODUCT
A. Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 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.

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 (SAEs) Events. Re-screening of subjects will not be allowed in this study.

ON 5 MAY 2017 THE SPONSOR AGREED TO RELAX THE SCREENING CRITERIA TO ENABLE THE INCLUSION OF SUBJECTS WITH A MINIMUM OF 8 FACIAL BLEMISHES TO FACILITATE RECRUITMENT. SUBJECTS WHO PREVIOUSLY SCREEN-FAILED BECAUSE OF THIS CRITERIA WILL BE ELIGIBLE FOR RE-SCREENING. SUBJECTS WHO WERE SCREEN FAILURES FOR OTHER REASONS WILL NOT BE ELIGIBLE FOR RE-SCREENING.

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

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

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

4.5. Subject Replacement

Subjects who withdraw from the study post-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 completion of the photographic assessments by lay graders, which will occur no sooner than the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

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

	Washout / Standard Cleanser	Test Product	Positive Control Cleanser	Positive Control Moisturiser
Product Name	Simple Kind to Skin Moisturising Facial Wash	Moisturising Cream with Niacinamide	Neutrogena Visibly Clear Spot Clearing Facial Wash	Vivatinell Acnecinamide Gel Cream
Product Formulation Code (MFC)	Commercially Available (UK)	CCI	Commercially Available (UK)	Commercially Available (Turkey)
Application Quantity	Approx. 0.6 g	Approx. 0.6 g	Approx. 0.6 g	Approx. 0.6 g
Application Instructions	Use twice daily (morning and night) with at least 8 hours between product applications. Wet your face and hands with water. Dispense the product into your hands and apply to the face. Massage gently. Rinse with water and pat dry. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.	Use twice daily (morning and night) with at least 8 hours between product applications. Dispense two pumps of product onto your fingertips and apply to your whole face, covering all blemishes. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.	Use twice daily (morning and night) with at least 8 hours between product applications. Wet your face and hands with water. Dispense the product into your hands and apply to the face. Massage gently. Rinse with water and pat dry. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.	Use twice daily (morning and night) with at least 8 hours between product applications. Apply a pea-sized quantity to your whole face, covering all blemishes. Avoid contact with eyes. If contact occurs, rinse thoroughly with water.

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

Name of Item	Purpose
N/A	N/A

5.2. Application Schedule

A 5-7 day washout period is included to standardize subjects' cleansing and skin care regimens prior to entering the test phase. Subjects will be instructed not to use any skin care or cosmetic product during the washout phase and to cleanse twice a day (morning and night) with the washout facial cleanser provided (Simple Kind to Skin Moisturising Facial Wash; Commercially Available (United Kingdom (UK)). Morning applications should occur prior to Noon (12:00) and evening applications should occur prior to midnight (00:00). Morning and evening applications should be separated by at least 8 hours. To remain eligible for this study, subjects must complete the washout period (assessed at Visit 2) with at least 8 blemishes (papules and pustules, excluding the nose).

Following the washout period, subjects who continue to be eligible for the study will be randomised to one of three treatment regimens (no-treatment + standard cleanser, test product + standard cleanser, or positive control cream + positive control cleanser).

During the test phase, subjects randomised to test product or positive control regimen will be instructed to use the cleanser and test/control products twice a day (morning and night). Morning applications should occur prior to Noon (12:00) and evening applications should occur prior to midnight (00:00). Morning and evening applications should be separated by at least 8 hours. Subjects will be instructed to apply the test product or positive control cream immediately after cleansing. Subjects randomised to the no treatment regimen will use the standard cleanser (only) twice a day. The first application of the standard cleanser or positive control cleanser will be at the site, under supervision of the Investigator or designee who will provide instruction on how to correctly apply the product. The first application of test product or positive control will be conducted by the subject at the site, after cleansing, under the supervision of the Investigator or designee who will provide instruction on how to correctly apply the product.

5.3. Application Modification

No modification of product application is permitted in this study.

5.4. Product Compliance

A daily dairy will be used to monitor and promote compliance. Subjects will not be excluded due to missed applications, but will be reminded to use the products as per the instructions provided and to complete the diary card on a daily basis. The number of missed or additional product applications will be recorded by the Investigator or designee as deviations on the electronic Case Report Form (eCRF).

5.5. Precautions

No special precautions are required providing the study is carried out in accordance with this protocol.

5.6. Rescue Therapy

No rescue therapy is required in this study.

5.7. Product Assignment

Subjects will be assigned to study product in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.7.1 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.

5.7.2 Blinding

This is an evaluator-blind clinical study. Therefore, all personnel and evaluators who may influence study outcomes are blinded to the product allocation of subjects and their diaries. The Investigator or their designees who are not involved in procedures or processes which may influence study outcomes are not required to be blinded to the product allocation of subjects and will have visibility of the subject diary.

5.7.3 Code Breaks

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

blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

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

5.8. 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 Washout Cleanser (Simple Kind to Skin Moisturising Facial Wash) will be over-wrapped in opaque vinyl and any branding on the commercial products will be obscured. 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 Standard Cleanser (Simple Kind to Skin Moisturising Facial Wash) and Positive Control Moisturiser (Vivatinell Acnecinamide Gel Cream) will be over-wrapped in opaque vinyl and any branding on the commercial products will be obscured. 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, study regimen code and directions for storage.

The Test product ([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, study regimen code and directions for storage.

The Positive Control Cleanser (Neutrogena Visibly Clear Spot Clearing Facial Wash) will be supplied in commercial packs that will be over-wrapped with opaque vinyl to obscure any commercial branding as much as possible. The bottles will be supplied with a study label affixed by the Sponsor. Each study label will contain, but not be limited to, protocol number, study regimen code and directions for storage.

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

5.8.1. Accountability of Product

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

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

1. The identification of the subject to whom the study product was dispensed.
2. The date(s) and quantity of the study product dispensed to the subject.
3. 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.

5.8.2. 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 / Day -7 to Day -5 – Screening/Washout Visit

6.1.1. Informed Consent

Prior to execution of any study procedure, 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. To be considered eligible for this study, subjects must provide their consent to permit use of photographic images of their face for assessment/grading after their final visit to the study site.

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

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

6.1.2. Demographics

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

6.1.3. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or designee. Details of any relevant medical or surgical history within the last year, including allergies or drug sensitivity, will be recorded on the eCRF.

Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.4. Fitzpatrick Skin Type Assessment

Fitzpatrick skin type assessment will be conducted by a trained and qualified investigator and recorded on the eCRF using the scale below.

CCI

[redacted]

6.1.5. Evaluator Assessment of Blemish Counts

The following assessment will be conducted by a trained and qualified evaluator reflective of the subject's facial skin condition at the time of the evaluation and recorded on the eCRF. All practical efforts will be made to ensure the same blinded evaluator assesses the same subject through the entire study.

	Forehead	Cheeks	Chin	~~Sub Total~~
Papules	#	#	#	#
Pustules	#	#	#	#
~~Sub Total~~	~~#~~	~~#~~	~~#~~	~~#~~

= Number of papules or pustules

THE GRAND TOTAL OF THE NUMBER OF PAPULES AND PUSTULES AT THE FOREHEAD, CHEEKS AND CHIN WILL BE AUTOMATICALLY CALCULATED ON THE CRF AT VISITS 1 AND 2 TO PROVIDE CLARITY ON SUBJECT COMPLIANCE WITH INCLUSION CRITERION 5A.

6.1.6. Forehead Sebumeter Measurements

A blind, trained and qualified evaluator will conduct instrumental measurements of skin sebum levels. Subjects will first acclimatize to the controlled room temperature

(21±1 ºC) and humidity (50±10% RH) for at least 30 minutes prior to instrumental assessment. Subject visits should be scheduled at similar times of day.

6.1.7. Inclusion / Exclusion Criteria

Inclusion/exclusion criteria will be assessed by the Investigator or designee and recorded on the eCRF.

6.1.8. Subject Eligibility

Subjects meeting the inclusion and exclusion criteria, whom provide their informed consent and who are otherwise considered eligible for enrollment in the study by the Investigator or medically qualified designee will be enrolled into the study. Confirmation of whether a subject was enrolled, or not, will be recorded on the eCRF.

6.1.9. Washout Product and Diary Dispensing

Dispensing of washout product and diary to subjects to standardize skin care regimen and usage instructions will be recorded on the eCRF.

6.2. Visit 2 / Day 1 – Baseline Visit

6.2.1. Current / Concomitant Medication

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

6.2.2. Diary Review (Compliance)

Subject diaries will be reviewed by the Investigator or their designee. The total number of missed and additional washout cleanser applications will be recorded on the eCRF. Subjects who apply the washout cleanser more or less frequently than

twice a day will be considered to have deviated from the protocol and additional/missed applications will recorded on the Deviations Log on the eCRF.

6.2.3. Continued Eligibility

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

6.2.4. Evaluator Assessment of Blemish Counts

Assessment will be conducted as per 6.1.5

6.2.5. Inclusion / Exclusion Criteria

Inclusion/exclusion criteria detailed in Appendix 2 will be assessed by the Investigator or designee to confirm subject eligibility and recorded on the eCRF. Subjects who trigger any of the exclusion criteria will be discharged from the study.

6.2.6. Subject Eligibility

Subjects meeting the inclusion and exclusion criteria detailed in Appendix 2 and who are otherwise considered eligible to continue in the study by the Investigator or medically qualified designee will be randomised. Confirmation of whether a subject was randomised, or not, will be recorded on the eCRF.

6.2.7. Randomisation

Subject randomisation will be conducted as per the process detailed in Section 5.7.1 and documented on the eCRF.

6.2.8. Image Capture

High resolution colour photographs of the front of each subject's face will be taken using a Canfield Visia imaging system, using polarised and non-polarised lighting. Jewelry will be removed and hair loosely tied back and covered with a black veil so that it does not interfere with the photograph. Subjects will be asked to maintain a relaxed, neutral expression with their eyes closed. The imaging system will be calibrated to ensure consistent image illumination and capture. The technician responsible for taking photographs must have sufficient experience and/or training to be capable of ensuring consistent alignment of subjects between visits. Photographic data will be stored in raw, uncompressed file format. The same imaging system will be used to take all photographs.

Photographic images of subjects are considered personal identifiable information (PII) and will be transferred securely from the site to GSK. Prior to transfer to GSK, the site will anonymize all images by placing a black box over the eyes of the subjects without obscuring any facial blemishes (excluding the nose).

6.2.9. Forehead Sebumetry Measurements

Sebumetry measurements will be taken as per 6.1.6.

6.2.10. Corneometry Measurements

PPD

6.2.11. Sebumeter Kinetic Measurements

PPD

6.2.12. Washout Cleanser Return and Test Product Dispensing

The washout cleanser will be returned by all subjects. Subjects randomised to the test product regimen will be dispensed the standard cleanser (Simple Kind to Skin Moisturising Facial Wash) and the test product. Subjects randomised to the positive

control regimen will be dispensed the positive control facial wash (Neutrogena Visibly Clear Spot Clearing Wash) and cream (Vivatinell Acnecinamide Gel Cream). Subjects randomised to the no-treatment regimen will be dispensed standard cleanser (Simple Kind to Skin Moisturising Facial Wash) only. The time and date of washout cleanser return and products dispensing will be documented on the eCRF. The Investigator or designee involved in product dispensing must not be involved in any assessments in order to protect the blind.

6.2.13. Supervised Product Application

Subjects randomised to the test product regimen will undergo supervised application of the standard cleanser and test product. Subjects randomised to the positive control regimen will undergo supervised application of the positive control cleanser and positive control cream. Subjects randomised to the no-treatment regimen will undergo supervised application of the standard cleanser, only. The Investigator or designee will oversee application of the product. Product application will be recorded on the eCRF and subject diary. The Investigator or designee involved in this step must not be involved in any assessments in order to protect the blind.

6.2.14. Acute Corneometer Measurements

Corneometer measurements will be taken as per 6.2.10, 1 hour **± 15 MINUTES**, 3 hours **± 15 MINUTES** and 8 hours **± 15 MINUTES** after test product or positive control cream application for subjects randomised to the test product or positive control regimen. Subjects randomised to the no treatment regimen will undergo Corneometer measurements 1 hour **± 15 MINUTES**, 3 hours **± 15 MINUTES** and 8 hours **± 15 MINUTES** after application of the standard cleanser.

6.2.15. Adverse Events

Adverse events will be assessed by a blinded investigator and recorded on the eCRF, as per the process detailed in Section 7.

6.3. Visit 3 / Day 8 – 1 Week of Application

6.3.1. Current / Concomitant Medication

To be completed as per 6.2.1

6.3.2. Diary Review (Compliance)

Subject diaries will be reviewed by the Investigator or their designee. The total number of missed and additional standard cleanser, positive control cleanser, test product and/or positive control applications, as appropriate per subject randomisation, will be recorded on the eCRF. Subjects who apply each of their allocated products

more or less frequently than twice a day will be considered to have deviated from the protocol and additional/missed applications will recorded on the Deviations Log on the eCRF.

6.3.3. Continued Eligibility

To be completed as per 6.2.3

6.3.4. Evaluator Assessment of Blemish Counts

Assessment will be conducted as per 6.1.5

6.3.5. Sebumetry Measurements

Measurements will be taken as per 6.1.6

6.3.6. Corneometry Measurements

Measurements will be taken as per 6.2.10

6.3.7. Sebumeter Kinetic Measurements

Measurements will be taken as per 6.2.11

6.3.8. Supervised Product Application

To be completed as per 6.2.13

6.3.9. Adverse Events

To be completed as per 6.2.15

6.4. Visit 4 / Day 29 – 4 Weeks of Application

6.4.1. Current / Concomitant Medication

To be completed as per 6.2.1

6.4.2. Diary Review (Compliance)

To be completed as per 6.3.2

6.4.3. Continued Eligibility

To be completed as per 6.2.3

6.4.4. Evaluator Assessment of Blemish Counts

Assessment will be conducted as per 6.1.5

6.4.5. Sebumetry Measurements

Measurements will be taken as per 6.1.6

6.4.6. Corneometry Measurements

Measurements will be taken as per 6.2.10

6.4.7. Sebumeter Kinetic Measurements

Measurements will be taken as per 6.2.11

6.4.8. Supervised Product Application

To be completed as per 6.2.13

6.4.9. Adverse Events

To be completed as per 6.2.15

6.5. Visit 5 / Day 57 – 8 Weeks of Application

6.5.1. Current / Concomitant Medication

To be completed as per 6.2.1

6.5.2. Diary Review (Compliance)

To be completed as per 6.3.2

6.5.3. Continued Eligibility

To be completed as per 6.2.3

6.5.4. Evaluator Assessment of Blemish Counts

Assessment will be conducted as per 6.1.5

6.5.5. Image Capture

Measurement will be taken as per 6.2.8

6.5.6. Sebumetry Measurements

Measurements will be taken as per 6.1.6

6.5.7. Corneometry Measurements

Measurements will be taken as per 6.2.10

6.5.8. Sebumeter Kinetic Measurements

Measurements will be taken as per 6.2.11

6.5.9. Test Product, Cleanser and Diary Return

Standard cleanser, positive control cleanser, positive control cream, test product and subject diary will be returned to the Investigator or designee and documented on the eCRF.

6.5.10. Adverse Events

To be completed as per 6.2.15

6.5.11. Lay Person Assessment of Overall Appearance of Blemishes (Photographs)

The baseline and week 8 photographs of test subjects will be displayed side by side on a high resolution, colour-calibrated display screen in a room with neutral wall colours and standardised lighting and all practical efforts will be made to minimize glare. The relative positioning (left and right) of the baseline and week 8 photographs will be blinded to the evaluator and randomised. The randomisation schedule for the image pair assessments will be generated by GSK. A technician will use the randomisation schedule to display each pair of images to each lay evaluator. Both the polarised and non-polarised image pairs will be assessed for every subject by every lay evaluator. Lay evaluators will be blind to the identity of each image.

24 blinded, lay evaluators will assess the baseline and week 8 images to judge the magnitude of improvement in overall appearance of blemishes using the below scale. The evaluators' scores will be recorded on the eCRF.

Score	Description
Left	The blemishes in the image on the left are more obvious than those in the image on the right
Right	The blemishes in the image on the right are more obvious than those in the image on the left

The lay evaluators 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). The lay evaluators will have subject identification numbers (IDs) and their participation in the study will be recorded.

The lay evaluators will be recruited by the site. Once the 'lay evaluator' Informed Consent is signed, the site will explain the imaging assessment process (2 images on the same screen that have to be ranked). A paper source document will be used to record the lay evaluator response for each image pair and this will be transcribed into the eCRF by the Investigator or designee.

6.5.12. Discharge from Study

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 eCRF by selecting one of the options below.

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

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

Adverse Event Definition:
1. An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout product. 2. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational or washout product.

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

Events NOT meeting definition of an AE include:
1. Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. 2. The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.. 3. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

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

7.1.2. Serious Adverse Events

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

A. Results in death

B. Is life-threatening

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

C. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

E. Is a congenital anomaly/birth defect

F. Other Situations

1. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be

considered serious.

2. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

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

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

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

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

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

Assessment of Causality:

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

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

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

follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***

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

SAE Reporting to GSKCH:

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

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

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

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

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

Fax Serious Adverse Events to:
PPD

The GSKCH SAE Coordinator 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.

Brazil SAE Coordinator (PPD**):**

Tel: PPD
E-mail: PPD

Brazil backup contact (PPD):
Tel: PPD
Email: PPD

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

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

Follow-up of AEs and SAEs:

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

Regulatory and ethics reporting requirements for SAEs:

1. The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
2. GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
3. Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

4. An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IEC, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

1. Pregnancy information will be collected on all pregnancies reported following administration of any 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:

1. 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.
2. While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.
3. A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK.
4. While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
5. There is no requirement for the subject to be withdrawn from the study as a result of the pregnancy. However if they are withdrawn, this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

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

8.1. Source Documents/ Data

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

An eCRF is an 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, an eCRF 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 (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 eCRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm™).

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

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

8.3. Data Handling

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

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the eCRF 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 eCRFs 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 eCRFs, to raise manual queries as needed for site clarification or correction.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Approximately 200 female subjects aged 18-45 with self-assessed sensitive skin and a minimum of ~~10~~ **8** and a maximum of 25 facial blemishes (papules and pustules, excluding the nose) will be screened to randomise 132 healthy subjects, to ensure approximately 40 subjects in the test product regimen, 40 subjects in the no treatment regimen and 40 subjects in the positive control regimen complete the study (Assuming a 10% dropout rate). Randomisation will be stratified by age (<21 years old, ≥21 years of age).

The sample size was based on clinical considerations. In a previous study of a cosmetic product, counts of papules and pustules decreased from a baseline mean of 27.6 to a mean of 13.5 at Week 8 (ref. Shalita 1995 IJD). With 40 subjects in both the test product and no-treatment regimens, a difference between groups at least 60% the magnitude of the standard deviation (assumed equal for both groups) would be detectable at two-sided alpha=0.05 with approximately 80% power.

9.2. General Considerations

Statistical testing for the endpoints in this study will be conducted at unadjusted two-sided alpha=0.05. While for this proof of concept study statistical significance ($p<0.05$) may not be achieved, these results will drive sample size projections for future studies. Due to the exploratory nature of the study, no adjustment to the alpha level for multiple comparisons will be made. P-values resulting from inferential testing will be considered primarily as summary statistics.

No statistical comparisons between the positive control regimen and the test product regimen are planned. The positive control is included to provide internal validation to the trial and to provide a reference point for estimates of effect size.

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 measurement 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 will be performed on the PP population.

The Safety population will include all subjects who applied any of the study products. All safety analyses will be performed using the Safety population. For the no treatment regimen, this will include any use of the cleanser post-randomisation.

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 assess the skin moisturisation potential of the test product formulation compared to no treatment based on change from baseline in corneometry 8 hours after the first application of test product. Given this proof of concept study, the study will be considered a success if at least a trend in favor of the test product is observed. Other efficacy evaluations will be similarly assessed for success.

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 finalization of the protocol and prior to study unblinding / analysis (as appropriate).

9.3.1. Demographic and Baseline Characteristics

Age and baseline characteristics (corneometry, blemish counts, sebumetry) will be summarised descriptively by treatment regimen (test product, positive control, no treatment) using means, medians and standard deviations. Race and Fitzpatrick Skin Type will be summarised by treatment regimen using frequency counts and percentages.

9.3.2. Primary Analysis(es)

The primary endpoint is the change from baseline in Corneometer measurement at 8 hours following the first product application (use of cleanser for the no treatment regimen). Data for the endpoint will be summarized by age stratum and treatment

regimen using means and 95% confidence intervals and compared between treatment regimens using analysis of covariance (ANCOVA) with treatment main effect, age stratum (<21, ≥21 years of age) and baseline measurement as covariate or Wilcoxon rank sum test, depending on the data distribution. Differences between least squares means for the test product and no treatment regimen will be presented, together with 95% confidence intervals.

9.3.3. Secondary Analysis(es)

The change from baseline in Corneometer measurements at 1 and 3 hours following the first product application as well as at Weeks 1, 4 and 8 will be summarized by age stratum, treatment regimen and study visit using means and 95% confidence intervals and compared between treatment regimens using the ANCOVA model described above for the primary endpoint. Wilcoxon rank sum test may also be performed depending on the data distribution. Differences between least squares means for the test product and no treatment regimen will be presented, together with 95% confidence intervals.

Sebumetry and sebum excretion rate changes from baseline at Weeks 1, 4 and 8 will be summarized by age stratum, treatment regimen and study visit and analyzed using the ANCOVA model described above for corneometry. Wilcoxon rank sum test may also be performed depending on the data distribution. Differences between least squares means for the test product and no treatment regimen will be presented, together with 95% confidence intervals.

Clinical assessment of blemish counts (papules and pustules) will be summarized by age group stratum, treatment regimen and study visit and compared between treatment regimens using means and 95% confidence intervals and compared between treatment regimens using the ANCOVA model described above for corneometry. Wilcoxon rank sum test may also be performed depending on the data distribution. Differences between least squares means for the test product and no treatment regimen will be presented, together with 95% confidence intervals.

The lay person assessment resulting from the ranking of images will inherently be an assessment of change from baseline. As such, the data resulting from these rankings will be tabulated by treatment regimen as the proportion of evaluations where the baseline image had blemishes most obvious compared to the proportion of evaluations where the Week 8 image had blemishes most obvious. Data will be analysed using a logistic regression which will include effects of age stratum and treatment regimen.

9.3.4. Safety Analysis(es)

Adverse Events (AEs) will be tabulated according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Frequencies and percentages will be presented by treatment regimen overall, for each system organ class, and for each preferred term. Events specific to the face will be tabulated separately. Summaries of treatment-emergent AEs, 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 enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

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

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

1. Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the Independent Ethics Committee (IEC) for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
2. Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
3. Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)
4. GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

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

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

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

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

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

10.4. Quality Assurance

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

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

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

10.5. Conditions for Terminating the Study

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

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/

follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).
In addition:

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

10.6. Records Retention

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

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

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

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

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

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

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

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

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

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

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

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

11. REFERENCES

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28
ICH Topic 6 Guideline for Good Clinical Practice CPMP/ICH/135/95 17th July 1996
World Medical Association Declaration of Helsinki, 59th General Assembly, Seoul 2008
Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28
ICH Topic 6 Guideline for Good Clinical Practice CPMP/ICH/135/95 17th July 1996
World Medical Association Declaration of Helsinki, 59th General Assembly, Seoul 2008
Berardesca E, Skin Research and Technology 1997;3(2):126-132
Fitzpatrick, TB, The validity and practicability of sun-reactive skin types I through VI, Arch Dermatol. 1988; 124: 869-871
Griffiths CEM, Nicotinamide 4% gel for the treatment of inflammatory acne vulgaris, Journal of Dermatological Treatment. 1995;6(1): S8-S10
Kaymak Y, Önder M, An Investigation of Efficacy of topical niacinamide for the treatment of mild and moderate acne vulgaris, J Turk Acad Dermatol. 2008; 2(4)
Khodaeiani E, Fouladi RF, Amirnia M, Saeidi M, Karimi ER, Topical 4% nicotinamide vs. 1% clindamycin in moderate inflammatory acne vulgaris. International Journal of Dermatology. 2013; 52(8): 999-1004
Rogiers V, Skin Pharmacol Appl Skin Physiol 2001;14:117–128
Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. Topical Nicotinamide Compared with Clindamycin Gel in the Treatment of Inflammatory Acne Vulgaris. International Journal of Dermatology. 1995; 34(6):434-7

12. APPENDICES

Appendix 1 - Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
°C	Degrees Celsius
CD	Compact Disc
cm^2	Square Centimeters
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEMCO	European Group on Efficacy Measurement of Cosmetics and other Topical Products
g	Grams
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ITT	Intention to Treat
LSLV	Last Subject Last Visit
mg	Milligrams
PII	Personally Identifiable Information
POC	Proof of Concept
PP	Per Protocol
RH	Relative Humidity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
µg	Micrograms
UV	Ultraviolet

Trademark Information

Trademarks not owned by the GlaxoSmithKline group of companies:
Neutrogena
Vivatinell
Simple

Appendix 2 – Inclusion / Exclusion Criteria for Review at Visit 2

Inclusion Criteria

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

5. SKIN TYPE
A. Minimum of ~~10~~ **8** and maximum of 25 blemishes (papules and pustules) at Visit 1 and a minimum of 8 blemishes (papules and pustules) at Visit 2.

Exclusion Criteria

A subject will not be considered still 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.

3. CONCURRENT MEDICATION/ MEDICAL HISTORY
C. Active skin disease in the test area. E. Moles, cysts, tattoos, scars, irritated skin, hairs, etc. at the test area that could influence the investigation.

SIGNATURE PAGE

Rainbow Clinical Protocol.doc

Date	Signed By
23-May-2017 06:19:06	PPD
Justification	Approved

Date	Signed By
23-May-2017 06:51:30	PPD
Justification	Biostatistics Approval

Date	Signed By
23-May-2017 08:32:51	PPD
Justification	Clinical Operations Approval

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	