CONFIDENTIAL

STATISTICAL ANALYSIS PLAN FOR PROTOCOL 207468

A Proof of Concept (POC) Clinical Study to Evaluate the appearance of fine lines and wrinkles on a Developmental Cosmetic Moisturising Cream in Healthy Subjects Presenting Visible Signs of Ageing.

BIOSTATISTICS DEPARTMENT

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PPD (Principal Statistician)

Table of Contents

Glossary

CI	Confidence Interval
ITT	Intent-to-Treat
PP	Per Protocol
AE	Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
TE	Treatment Emergent
TEWL	Transepidermal Water Loss

1 Introduction

This document describes the statistical methods and data presentations to be used in the summary and analysis of the final data from Protocol 207468.

2 Objectives

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

3 Study Design

- Evaluator-blind
- Single study centre
- Split-face design
- Healthy female subjects aged 30 to 65 with self-reported sensitive skin and visible signs of aging (visual wrinkles) on the face
- Study treatments: Positive- (Olay ProX Wrinkle Smoothing Cream) and Untreated-control
- Randomisation was to two of the 3 treatment arms (test product, positive control, no treatment) with treatment arm assignment further randomised to either the right side or left side of the face. Therefore, a subject was randomised to one of the 6 possible treatment groups:

Right Side of Face	**Left Side of Face**
Test Product	Positive Control
Test Product	No Treatment
Positive Control	No Treatment
Positive Control	Test Product
No Treatment	Test Product
No Treatment	Positive Control

4 Sample Size Determination

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

The sample size is based on clinical considerations. With 40 subjects, a difference between test product and untreated in the change from baseline in R_a of at least 46% of the magnitude of the within-subject standard deviation of the difference would be detectable at two-sided alpha=0.05 with approximately 80% power.

5 Data Considerations

5.1 Analysis Populations

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

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

- The Per Protocol (PP) population will consist of the subset of ITT subjects which excludes those subjects with significant protocol deviations. Protocol deviations will be identified prior to database unblinding and will include, but not be limited to, non-compliance with the protocol or product application and use of prohibited concomitant medications. Confirmatory analyses of at least the primary efficacy endpoint of DermaTOP R_a and key secondary objective relating to Fitzpatrick wrinkle score will be performed on the PP population.

  Subjects with a protocol violation that is deemed to affect facial skin assessments after a specific timepoint will be part of the PP population, but will have their data excluded from the assessment at which the protocol violation occurred.

  Violations that may lead to the exclusion of data for PP analysis include, but are not limited to, the following:

  - Violation of inclusion or exclusion criteria at screening or baseline that may affect facial skin assessments.
  - Non-compliance with assigned treatment regimen.
  - Use of prohibited treatment or medication before or during the study,

which it is felt will affect facial skin assessments.

Violations will be documented in the Population Definitions document. The content of this document will be agreed upon between the Biostatistician and Clinical Development Director or designee prior to database lock and breaking of the study blind.

A PP analysis will be performed on the primary and key secondary objective if there is more than 10% difference in the number of subjects evaluable in any of the treatment groups for the ITT and PP populations.

5.2 Subgroups/Stratification

There was no stratification in this study.

5.3 Time Windows

All data will be accepted for analysis. Deviations from the scheduled nominal visit days are not expected. Any deviations will be noted in the deviation log and visits may be considered for exclusion from the Per Protocol population.

5.4 Missing Data Handling

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

6 Demographics and Baseline Characteristics

6.1 Subject Disposition

The number of subjects screened, enrolled, randomised and completing the study will be presented by treatment arm (i.e. test product, positive control, no treatment) and overall as well as in a separate summary, by treatment group (i.e. each right side of body/left side of body treatment combinations to which subjects were randomised) and overall using frequency counts and percentages.

6.2 Demographics

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

7 Treatment Compliance and Concomitant Medications

7.1 Treatment Compliance

All deviations associated with the application of either the test product or positive control or the preservation of the lack of treatment, if so assigned, to the relevant side of the face will be listed.

7.2 Concomitant Medications

Any concomitant medication use will be listed.

8 Analysis

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

8.1 Primary Analysis

The primary endpoint of the study will be change from baseline in Derma TOP parameter R_a at 4 weeks.

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

If the assumption of normality is rejected, an appropriate transformation to the data

may be performed to facilitate the above method of analysis. Least square means from the ANCOVA model for the change from baseline will be presented for each treatment arm and pairwise treatment comparisons, together with the 95% confidence intervals. In the absence of an appropriate data transformation, non-parametric analyses may be performed. In the event of the use of non-parametric analysis, median differences will be presented, together with 95% confidence intervals based on the Hodges-Lehmann method.

8.2 Secondary Analysis

The same presentation and analysis methods, as outlined above, will be performed using change from baseline for other parameters; DermaTOP parameters Rz, S_a and $S_{tm,}$ clinical wrinkle assessment, TEWL values, Corneometer values and Cutometer parameters R5 and R7.

The texture assessment resulting from the ranking of photos will inherently be an assessment of change from baseline. As such, the data resulting from these rankings will be tabulated by treatment arm as proportions with baseline image better and Day 29 image better and analysed using a logistic regression with effects for treatment arm and side of face included in the model.

9 Safety Analysis

Treatment emergent AEs are defined as events that start on or after the first treatment date. Events occurring following the start of treatment which were also reported before treatment began with no change in severity or causality will however not be considered treatment emergent.

AEs will be tabulated according to the current version of the MedDRA. Frequencies and percentages will be presented by product group and overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related treatment-emergent AEs, AEs leading to discontinuation, and serious AEs will be completed.

10 Interim Analysis

Not Applicable

11 Topline Summary

The following tables will be produced for the topline summary:

Table No.	Description
9.1	Subject Disposition by Treatment Group – All Screened Subjects
9.3.1.1	Summary of DermaTOP Parameter R_a at 4 weeks – ITT Population
9.3.1.2	Analysis of DermaTOP Parameter R_a – Change from baseline at 4 weeks – ITT Population
9.4.1	Treatment-Emergent Adverse Events – Safety Population
9.4.2	Treatment-Emergent Treatment-Related Adverse events – Safety Population

12 Changes to Planned Analysis

There are no changes to the protocol-planned analyses.

13 References

None

Appendix 1 Study Schedule

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

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

Appendix 2 List of Tables, Figures & Listings

In all outputs, the treatment labels and order for presentation in tables and listings is:

1) Moisturising Cream
2) Olay ProX Cream
3) No Treatment

Table No.	Table Title (including population)	Standard	Template
9.1.1	Subject Disposition by Treatment Group – All Screened Subjects	X	
9.1.2	Subject Disposition by Treatment Arm – All Screened Subjects	X	
9.2.1.1	Demographics – ITT Population	X	
9.2.1.2	Demographics – Safety Population	X	
9.2.1.3	Demographics – PP Population *(if needed)*	X	
9.3.1.1	Summary of DermaTOP Parameter R_a at 4 weeks – ITT Population		Table 9.3.2.1
9.3.1.2	Analysis of DermaTOP Parameter R_a – Change from baseline at 4 weeks – ITT Population		Table 9.3.2.2
9.3.1.3	Summary of DermaTOP Parameters R_a at 4 weeks – PP Population *(if needed)*		Table 9.3.2.1
9.3.1.4	Analysis of DermaTOP Parameter R_a – Change from baseline at 4 weeks – PP Population *(if needed)*		Table 9.3.2.2
9.3.1.3	Summary of DermaTOP Parameters – ITT Population *(except primary endpoint)*		Table 9.3.2.1
9.3.1.4	Analysis of DermaTOP Parameters – Changes from baseline – ITT Population *(except primary endpoint)*		Table 9.3.2.2
9.3.2.1	Summary of TEWL – ITT Population		Appendix 3

9.3.2.2	Analysis of TEWL – Changes from Baseline – ITT Population		Appendix 3
9.3.3.1	Summary of Corneometry – ITT Population		Table 9.3.2.1
9.3.3.2	Analysis of Corneometry – Changes from Baseline – ITT Population		Table 9.3.2.2
9.3.4.1	Summary of Cutometer Parameters – ITT Population		Table 9.3.2.1
9.3.4.2	Analysis of Cutometer Parameters – Changes from Baseline – ITT Population		Table 9.3.2.2
9.3.5.1	Summary of Fitzpatrick Wrinkle Assessment Score – ITT Population		Table 9.3.2.1
9.3.5.2	Analysis of Fitzpatrick Wrinkle Assessment Score – Changes from Baseline – ITT Population		Table 9.3.2.2
9.3.5.3	Summary of Fitzpatrick Wrinkle Assessment Score – PP Population		Table 9.3.2.1
9.3.5.4	Analysis of Fitzpatrick Wrinkle Assessment Score – Changes from Baseline – PP Population		Table 9.3.2.2
9.3.6.1	Summary of Texture Rankings Based on USR-CliP Images – ITT Population		Appendix 3
9.3.6.2	Analysis of Texture Rankings Based on USR-CliP Images – Change from baseline – ITT Population		Appendix 3
9.4.1	Treatment-Emergent Adverse Events – Safety Population	X	

9.4.2	Treatment-Emergent Treatment-Related Adverse events – Safety Population	X	
9.4.3	Treatment-Emergent Adverse Events by Severity – Safety Population	X	
9.4.4	Treatment-Emergent Treatment-Related Adverse Events by Severity – Safety Population	X	

All listings to be generated are the standard set.

Appendix 3 Templates for Tables, Figures & Listings

Table 9.3.2.1
Summary of TEWL
ITT Population (N=xx)

Timepoint		Moisturising Cream	Olay ProX Cream	No Treatment
Baseline	N	XX	XX	XX
	Missing	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	95%CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
Day 15	N	XX	XX	XX
	Missing	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	95%CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
Day 15 Change from Baseline	N	XX	XX	XX
	Missing	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	95%CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
	LSMean (±SE)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
Day 29	N	XX	XX	XX
	Missing	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	95%CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX

Day 29 Change from Baseline	N	XX	XX	XX
	Missing	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	95%CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX
	LSMean (±SE)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)

An increase in TEWL shows damage to the skin barrier function.
* Baseline is measured prior to any test product application.
# LSMean and standard error (SE) derived from ANCOVA with subject as random effect, treatment arm and side of face as fixed effects, and baseline value as covariate.

Programmers Note: Same format for Tables 9.3.1.1, 9.3.1.3, 9.3.3.1, 9.3.4.1, 9.3.5.1 - Change the title, including adding the parameters as a BY group (DermaTOP has 4 parameters: R_a, R_z S_a and S_{tm}, and Cutometer has 2 parameters: R5 and R7) to match protocol.

Table 9.3.2.2
Analysis of TEWL Change from Baseline
ITT Population (N=xx)

Timepoint		Difference	95% Confidence Interval for the Difference	P-Value
Day 15	Moisturising Cream vs. No Treatment	X.XX	X.XX, X.XX	X.XXX
	Olay ProX Cream vs No Treatment	X.XX	X.XX, X.XX	X.XXX
	Moisturising Cream vs Olay Prox Cream	X.XX	X.XX, X.XX	X.XXX
Day 29	Moisturising Cream vs. No Treatment	X.XX	X.XX, X.XX	X.XXX
	Olay ProX Cream vs No Treatment	X.XX	X.XX, X.XX	X.XXX
	Moisturising Cream vs Olay Prox Cream	X.XX	X.XX, X.XX	X.XXX

Difference is the first named treatment adjusted (LS) mean change from baseline minus the second named treatment adjusted mean change from baseline.

Analysis model (ANCOVA) included subject as random effect, treatment arm and side of face as fixed effects, and baseline value as covariate.

PROGRAMMER'S NOTE: Same format for Tables 9.3.1.2, 9.3.1.4, 9.3.3.2, 9.3.4.2, 9.3.5.2 - Change the title, including adding the parameters as a BY group (DermaTOP has 4 parameters: R_a, R_z S_a and S_{tm}, and Cutometer has 2 parameters: R5 and R7) to match protocol.

Table 9.3.6.1

Summary of Texture Rankings Based on USR-CliP Images
ITT Population (N=xx)

Lay Reader ID		Moisturising Cream	Olay ProX Cream	No Treatment
1	N	XX	XX	XX
	Missing	XX	XX	XX
	Proportion Day 29 better than Baseline	X.XX	X.XX	X.XX
2	N	XX	XX	XX
	Missing	XX	XX	XX
	Proportion Day 29 better than Baseline	X.XX	X.XX	X.XX
etc		XX	XX	XX
24	N	XX	XX	XX
	Missing	XX	XX	XX
	Proportion Day 29 better than Baseline	X.XX	X.XX	X.XX
Total	N	XX	XX	XX
	Missing	XX	XX	XX
	Proportion Day 29 better than Baseline	X.XX	X.XX	X.XX
	95%CI	X.XX, X.XX	X.XX, X.XX	X.XX, X.XX

Table 9.3.6.2
Analysis of Texture Rankings Based on USR-CliP Images
ITT Population (N=xx)

Timepoint	Difference in Proportions of Day 29 Image Better than Baseline	95% Confidence Interval for the Difference	P-Value
Moisturising Cream vs. No Treatment	X.XX	X.XX, X.XX	X.XXX
Olay ProX Cream vs No Treatment	X.XX	X.XX, X.XX	X.XXX
Moisturising Cream vs Olay ProX Cream	X.XX	X.XX, X.XX	X.XXX

Difference is the first named treatment minus the second named treatment.

Analysis model (logistic regression) included treatment arm and side of face as fixed effects.

SIGNATURE PAGE

Statistical Analysis CCI [redacted] 207468.docx

Date	Signed By
10-Apr-2017 02:06:40	PPD
Justification	Biostatistics Approval

Date	Signed By
10-Apr-2017 13:34:16	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	

CONFIDENTIAL

AMENDMENT TO STATISTICAL ANALYSIS PLAN FOR PROTOCOL 207468

A Proof of Concept (POC) Clinical Study to Evaluate the appearance of fine lines and wrinkles on a Developmental Cosmetic Moisturising Cream in Healthy Subjects Presenting Visible Signs of Ageing.

Biostatistics Department
GlaxoSmithKline Consumer Health

PPD (Statistician)

Timing of Amendment: ☒ Before unblinding ☐ After unblinding

Section: 6.1 Subject Disposition

Reason for amendment: Clarification of the extent of reporting.

Original text:. The number of subjects screened, enrolled, randomized and completing the study will be presented by treatment arm (i.e. test product, positive control, no treatment) and overall as well as in a separate summary, by treatment group (i.e. each right side of body/left side of body treatment combinations to which subjects were randomized) and overall using frequency counts and percentages.

Amendment: The number of subjects screened, enrolled, randomized and completing the study will be presented by treatment **combination** arm (i.e **the pair of treatments received**~~. test product, positive control, no treatment~~) **with no account being made for side specific combinations – hence 3 columns**. ~~and overall as well as in a separate summary, by treatment group (i.e. each right side of body/left side of body treatment combinations to which subjects were randomized) and overall using frequency counts and percentages.~~

Section: 9 Safety Analysis

Reason for amendment: Reference to additional pre-unblind step of assigning application site(s) AE's to treatment at that site(s).

Original text: Treatment emergent AEs are defined as events that start on or after the first treatment date. Events occurring following the start of treatment which were also reported before treatment began with no change in severity or causality will however not be considered treatment emergent.

AEs will be tabulated according to the current version of the MedDRA. Frequencies and percentages will be presented by product group and overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related treatment-emergent AEs, AEs leading to discontinuation, and serious AEs will be completed.

Amendment: Treatment emergent AEs are defined as events that start on or after the first treatment date. Events occurring following the start of treatment which were also

reported before treatment began with no change in severity or causality will however not be considered treatment emergent.

AEs will be tabulated according to the current version of the MedDRA. Frequencies and percentages will be presented by product group and overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related treatment-emergent AEs, AEs leading to discontinuation, and serious AEs will be completed.

A further step will take place pre-unblind to flag the AEs by application site if appropriate so that attribution to applied treatment is preserved. This will involve review of all application site AEs and addition of a flag to indicate which site(s) it is applicable to.

SIGNATURE PAGE

SAP Amendment 207648.doc

Date	Signed By
12-Jun-2017 06:39:36	PPD
Justification	Approved

Date	Signed By
12-Jun-2017 07:04:18	PPD
Justification	Biostatistics Approval

Date	Signed By
Justification	

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Justification	

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Justification	