STATISTICAL ANALYSIS PLAN

Sponsor: GlaxoSmithKline Consumer Healthcare (UK) Trading Limited

Protocol No.: 216953

PPD Code: GSK-001

Title: A REAL-WORLD EVIDENCE STUDY EVALUATING ORAL HEALTH RELATED QUALITY OF LIFE FOLLOWING THE USE OF ANTI-SENSITIVITY TOOTHPASTE FOR DENTINE HYPERSENSITIVITY MANAGEMENT

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Statistical Analysis Plan Signature Page

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Abbreviations

Abbreviation	Definition
ADS	Analysis Dataset
AE	Adverse Event
ANOVA	Analysis of Variance
CSR	Clinical study report
DH	Dentin hypersensitivity
DHEQ	Dentin hypersensitivity experience questionnaire
eIC	Electronic Informed Consent
FCS MI	Fully Conditional Specification Multiple imputation
GSKCH	GlaxoSmithKline Consumer Healthcare
ITT	Intent To Treat
MAR	Missing At Random
MCAR	Missing Completely At Random
MedDRA	Medical dictionary for regulatory activities
mITT	Modified Intent To Treat
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
OHrQoL	Oral health related quality of life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
VAS	Visual analogue scale

Scope

This document describes the analysis plan for the statistical analysis of the study GSK-001, study explanation.

This Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods as outlined in the study protocol and describe the analysis conventions to guide the statistical programming work.

Study Introduction

3.1 Study Background

Dentin hypersensitivity (DH) has been defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease' (Addy *et al*, 1985; Canadian Advisory Board on Dentin Hypersensitivity, 2003). The hydrodynamic theory of DH hypothesizes that a stimulus external to the tooth (for example, a temperature/osmotic differential, pressure) causes movement of the fluid resident within exposed dentinal tubules (Brännström, 1963). This movement may stimulate nerve processes in the dental pulp (Addy, 2002; Hall *et al*, 2000), resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches for the management of DH: nerve desensitization and the occlusion of exposed dentin tubules. Nerve depolarising agents, typically potassium salts, generally require a period of use (14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) via dentinal tubules is believed to result in depolarisation of the afferent nerve membrane thereby blocking the pain response. The second approach uses tubule occluding agents which physically block the exposed end of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Tubule occluding agents such as strontium and stannous salts, bioglasses, silicas or oxalates serve to seal or block the dentine tubules and thereby reduce the effect of external stimuli. Such agents are believed to function by precipitating insoluble materials onto the dentine surface and/or within the dentinal tubules to reduce dentinal fluid transport.

Recently, there have been a wider consideration to the psychosocial impacts of DH on everyday life (Gibson *et al*, 2015). One qualitative study showed that DH can be triggered by several stimuli and responses, not always described as pain, can affect everyday activities such as eating, drinking, tooth brushing, talking and social interactions (Gibson *et al*, 2015).

Oral health-related quality of life (OHrQoL) questionnaires are tools increasingly used in dentistry to capture the impact of clinical interventions on OHrQoL, however these measures cover a number of oral health conditions which lead to limitations of these tools and may not detect the nuances of a specific condition (Bekes *et al*, 2009). The Dentine Hypersensitivity Experience Questionnaire (DHEQ) is a validated, condition specific measure of OHrQoL in relation to DH (Baker *et al*, 2014) (Boiko *et al*, 2010). It was developed by GSKCH in

collaboration with Sheffield University through a robust theoretical framework, specific for DH (Boiko *et al,* 2010), and has shown reliability and validity in both a general population (Porritt *et al,* 2016) and in clinical studies (Boiko 2010, Gibson *et al,* 2015). The conception, development, validation, and initial usage of the DHEQ has been published (Robinson, 2014). The measure has been validated with both long- and short-form versions, comprising 48 (Baker *et al,* 2014; Boiko *et al,* 2010) and 15 (Machuca *et al,* 2014) questions respectively, and has been translated into multiple languages (e.g., Chinese, Turkish, Portuguese) confirming its global relevance (Başaran and Celik, 2018) (Douglas-De-Oliveira *et al,* 2018) (He and Wang, 2015a) (He and Wang, 2015b).

Data generated as part of GSKCH efficacy clinical studies, showed robust and positive results on the relief and management of DH in clinical measurements and OHrQoL. However, these results have been obtained from randomized controlled trials which include strict study procedures and controlled, but contrived DH stimuli. These studies may not necessarily fully reflect the general dental population when challenged with real world sensitivity stimuli.

Based on these assumptions, this will be a real-world evidence study which will include subjects among a general population who suffer from DH (self-reported symptoms). This study will aim to evaluate the impact of a recommended daily use of desensitizing toothpaste on oral health related quality of life. Data generated will give real world information on the impact of a daily use DH treatment on oral health related quality of life.

3.2 Study Objectives

3.2.1 Primary Objective

To describe subjects' oral health related quality of life over a 24-week period following the use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the DHEQ-48 in a population of DH sufferers.

3.2.2 Exploratory Objectives

- To explore subjects' oral health related quality of life over a 24-week period following the use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the DHEQ-48 in further characterisation of DH sufferers by subgroups.
- To characterise subjects' change in oral health related quality of life over 24 weeks compared to baseline, following use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the DHEQ-48, in the overall population of DH sufferers and in 4 subgroups
- To identify the DHEQ domain items important to the overall population of DH sufferers following 24 weeks use of the sensitivity toothpaste.

- To explore the potential impact a sensitivity toothpaste containing 5% potassium nitrate has on subjects' reported pain in relation to DH in the overall population of DH sufferers and in 4 sub-groups.
- To explore subjects' overall satisfaction with DH treatment in the overall population of DH sufferers and in 4 sub-groups.
- To describe oral hygiene habits of DH sufferers according to oral hygiene questionnaire.

3.3 Study Design

3.3.1 Study Population

Sufficient number of subjects will be screened (estimated 50% failure rate) to enroll approximately 650 subjects. This will ensure approximately 400 evaluable subjects complete the entire study (estimated 40% drop out). An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly and successfully met eligibility criteria to proceed beyond screening as applicable for the protocol design.

3.3.2 Study Product/Treatment

The study product is Sensodyne Fresh Mint (USA marketplace toothpaste).

3.3.3 Study Period

The duration of the study is defined for each subject as the date that the signed electronic informed consent (eIC) is provided through the end of the study follow-up period (168 days [+ 7days] post-baseline), subject death, early withdrawal from the study, lost to follow-up or overall study termination.

Statistical Analysis

4.1 Sample Size Calculation

No formal sample size calculation has been performed for this study however sufficient subjects will be screened (estimated screen failure 50%) to have approximately 650 subjects enrolled and 400 completers (estimated 40% drop-out).

There is no prior information for the use of DHEQ in DH sufferers in a RWE setting. It is believed that for this study 400 subjects are deemed sufficient to observe a trend over time from baseline at 24 weeks in total score.

4.2 Endpoints

4.2.1 Primary Endpoints

For the primary endpoints, plots of the mean values for section 1 questions Q1-3, and questions in section 2 for total DHEQ score – section 2 (sum Q1-34), each of the domain's mean values (Restrictions – sum Q1-4, Adaptation – sum Q5-16, Social Impact – sum Q17-21, Emotional Impact – sum Q22-29, Identity – sum Q30-34), Global oral health (Q35) and Effect of life overall (sum Q36-39) over 24 weeks to assess QoL over time.

4.2.2 Exploratory/Safety Endpoints

- Plot over time in DHEQ mean scores for each sub-group
- DHEQ Mean scores over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall DH sufferers and each sub-group
- Percentage of DH sufferers who agree (score 5-7) to items in each respective domain at baseline and week 24
- Numeric Pain Rating Scale (NPRS) Mean scores over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall DH sufferers and each sub-group
- Plot over time in NPRS mean scores (0, 4, 8, 12, 16, 20 and 24 weeks) for overall DH sufferers and each sub-group
- Percentage of DH sufferers who achieve pain reduction identified as clinically important (pain reduction NPRS > 30%) for overall DH sufferers and each sub-group
- Satisfaction Numerical rating scale (NRS) for overall DH sufferers and each sub-group
- Summary of oral hygiene habits of DH sufferers according to oral hygiene questionnaire

4.3 Analysis

4.3.1 Population to be Analyzed

The Screened population will include subjects who sign the eIC and enter the screening process of assessment of inclusion and exclusion criteria.

The Enrolled population will include all subjects who meet the inclusion/exclusion criteria and identified by the screening questionnaire

The Safety population will include all subjects who receive at least one dose of study product. Safety population will be used of safety variables.

The modified Intent-To-Treat (mITT) population will include all subjects who receive at least one dose of study product and have at least one post baseline DHEQ-48 questionnaire data. Efficacy data will be summarized using the mITT population only.

4.3.2 Sub-group Classification

A total of 4 different groups will be identified at screening for the purposes of sub-group analyses:

- Age group
  - ≤ 40 years old
  - > 40 years old
- Diagnosis
  - self-reported DH without previous diagnosis by a dentist
  - self-reported DH with previous diagnosis by a dentist
- Use of sensitivity toothpaste
  - Non-users – will include subjects who are not currently using a sensitivity toothpaste e.g., first-time user
  - Intermittent users – will include subjects who sometimes use a sensitivity toothpaste
  - current users – will include subjects who regularly (daily) use a sensitivity toothpaste
- Self-reported DH frequency
  - frequent = Several times a day, Once a day, Several times a week
  - less frequent = Once a week, Several times a month, once a month, less than once a month

4.3.3 Demographics

Age and other continuous demographic and baseline variables will be summarized using descriptive statistics such as mean, range, median and standard deviation. Gender, race, ethnicity and other categorical demographic and baseline variables will be summarized using frequency counts and percentages for the safety and mITT populations.

4.3.4 Compliance

Study product compliance and compliance to the study schedule will be tabulated and summarized for the safety population.

Summaries will include a simple yes/no frequency (and percent) count at each timepoint:

- Summary of completion to study schedule and assessments (yes/no)
- Summary of product usage according to product instructions (yes/no)
- Summary of number of tubes remaining at the end of the study (number remaining) into three categories: 2 or less tubes, 3 to 6 tubes, and more than 6 tubes.

A listing of number of tubes remaining per subject will also be produced.

4.3.5 Prior and Concomitant Medications

Concomitant medications taken during the study will be listed for the safety population.

4.3.6 Primary Objective Analysis

For the primary objective, plots of the mean values for section 1 questions Q1-3, and questions in section 2 for total DHEQ score – section 2 (sum Q1-34), each of the domain's mean values (Restrictions – sum Q1-4, Adaptation – sum Q5-16, Social Impact – sum Q17-21, Emotional Impact – sum Q22-29, Identity – sum Q30-34), Global oral health (Q35) and Effect of life overall (sum Q36-39) will be presented over 24 weeks to assess QoL over time in the overall population of DH sufferers, graphically.

4.3.7 Exploratory/Safety Objectives Analysis

4.3.7.1 Safety of the Study Product

All AEs will be coded using MedDRA. AEs will be categorized as oral and non-oral by PPD prior to database lock. The number of AEs/SAEs and number of subjects with AEs/SAEs will be listed and tabulated.

Adverse events will be listed individually with indicators as to the event's description, start and end time, severity, and relatedness to product.

4.3.7.2 Exploratory Objective 2

Plot over time in DHEQ mean scores for each sub-group

For the exploratory objective relating to sub-groups, plots of the mean values for section 1 questions Q1-3, and questions for section 2 total DHEQ score – section 2 (sum Q1-34), each of the domain's mean values (Restrictions – sum Q1-4, Adaptation – sum Q5-16, Social Impact –

sum Q17-21, Emotional Impact – sum Q22-29, Identity – sum Q30-34), Global oral health (Q35) and Effect of life overall (sum Q36-39) will be presented over 24 weeks to assess QoL over time in the further characterisation of DH sufferers by sub-group classification, graphically.

4.3.7.3 Exploratory Objective 3

DHEQ Mean scores over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall DH sufferers and each sub-group

The exploratory response variable is the DHEQ mean scores at 0, 4, 8, 12, 16, 20 and 24 weeks respectively in total score, each of the DHEQ domain scores, questions Q1-3, Global oral health, and Effect of life overall.

An Analysis of Variance (ANOVA) model will be used to analyze the DHEQ score as the response variable and timepoint as the dependent variable. Subject will be included as a random effect. Each post baseline timepoint will be compared to baseline using the adjusted means from the time variable from the model.

For the analysis of the 4 subgroups, an extra factor for the subgroup will be included along with the subgroup*timepoint interaction. This will enable to look at the differences between sub-group and the interaction term will enable adjusted means of each subgroup over time.

For the ANOVA if the underlying assumptions are not met, alternative methods will be sought, including transformations or non-parametric methods.

Each of the DHEQ items were summarized by time point (Baseline, Week 4, 8, 12, 16, 20 and 24).

4.3.7.4 Exploratory Objective 4

Percentage of DH sufferers who agree (score 5-7) to items in each respective domain at baseline and week 24

A table for percentage of consumers who agree (score 5-7) to items in each domain at baseline and at week 24 respectively will also be presented as part of this objective. Percentage will be presented per each question.

4.3.7.5 Exploratory Objective 5

Numeric Pain Rating Scale (NPRS) Mean scores over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall DH sufferers and each sub-group

The exploratory response variable is the NPRS mean score at 0, 4, 8, 12, 16, 20 and 24 weeks. An Analysis of Variance (ANOVA) model will be used to analyze the NPRS score as the response variable and timepoint as the dependent variable. Subject will be included as a

random effect. Each post baseline timepoint will be compared to baseline using the adjusted means from the time variable from the model.

For the analysis of the 4 subgroups, an extra factor for the subgroup will be included along with the subgroup*timepoint interaction. This will enable to look at the differences between sub-group and the interaction term will enable adjusted means of each subgroup over time.

For the ANOVA analyses if the underlying assumptions are not met, alternative methods will be sought, including transformations or non-parametric methods.

A plot of NPRS mean scores at each timepoint will also be presented along with a table reporting the percentage of participants who achieve pain reduction identified as clinically important (pain reduction NPRS > 30%).

4.3.7.6 Exploratory Objective 6

Satisfaction Numerical rating scale (NRS)

The satisfaction Numerical rating scale will be summarized using frequencies at week 24. Similar summaries will be presented for overall population and each of the subgroups.

4.3.7.7 Exploratory Objective 7

Oral hygiene habits of DH sufferers according to oral hygiene questionnaire

A summary of oral hygiene habits at baseline will be provided as part of this objective

4.3.8 Missing Values

The digital implementation of the PPD Application limits the possibility of missing values, as participants are unable to submit questionnaires if they are incomplete.

For the DHEQ data, for any timepoint if response is missing will be excluded from the primary analysis however the data available for each subject (even though some time points may be missing) will still be included in the analysis.

For secondary/exploratory analyses missing data will be imputed. Multiple imputation by fully conditional specification (FCS MI) will be utilized if the missing data meet the assumption of Missing At Random (MAR) or Missing Completely At Random (MCAR). Demographic data between subjects with missing and non-missing data will be compared to identify any statistically significant differences. If no differences, data will be assumed at least MAR.

Quality Control

5.1 Data and Output Quality Checks

Analysis related to the primary, secondary, and exploratory objectives will be validated by a second biostatistician.

All discrepancies identified during the output review will be corrected or documented until there are no findings, or findings could be explained. At the end of the study, all data sets used for analysis and final output will be archived.

Reporting

6.1 Clinical Study Report

A Clinical Study Report (CSR) will be developed and provided by PPD after database lock, delivery of the statistical analysis, and the TLF deliverable is approved by the client. The report will address study background, methodology, and all required results including tables, listings, and figures agreed upon in the SAP.

6.2 Statistical Analysis Outputs

A Statistical Analysis Outputs will be developed and provided by PPD The report will include all required results in tables, listings, and figures agreed upon in the TLF Shells document. The Statistical Analysis Outputs will be output as either one file compiling all tables, listings, and figures, or a zip folder that houses the output items in separate files.

Revision History

VERSION	EFFECTIVE DATE	CHANGES
1.0	17 March 2022	Original Document