STATISTICAL ANALYSIS PLAN

Sponsor: Haleon

Protocol No.: 300058

CCI Code: HLN-003

Title: A REAL-WORLD EVIDENCE STUDY EVALUATING ORAL HEALTH RELATED QUALITY OF LIFE WITH USE OF A STANNOUS FLUORIDE ANTI-SENSITIVITY TOOTHPASTE FOR DENTIN HYPERSENSITIVITY MANAGEMENT

Contents

Statistical Analysis Plan Signature Page

We, the undersigned, have reviewed and approve this Statistical Analysis Plan (SAP).

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1. Abbreviations

Abbreviation	Definition
ADS	Analysis Dataset
AE	Adverse Event
CSR	Clinical study report
DH	Dentin hypersensitivity
DHEQ	Dentin Hypersensitivity Experience Questionnaire
eIC	Electronic Informed Consent
ITT	Intent To Treat
LMS	Labelled Magnitude Scales
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat
MMRM	Mixed Model Repeated Measures
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
OHQ	Oral Hygiene Questionnaire
OHrQoL	Oral Health Related Quality Of Life
RCT	Randomized Controlled Trial
RWD	Real World Data
RWE	Real-World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SQ	Screening Questionnaire
VAS	Visual analogue scale

2. Scope

This document describes the analysis plan for the statistical analysis of the study **HLN-003,** 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.

3. Study Introduction

3.1 Study Rationale

Clinical data supporting the efficacy of anti-sensitivity toothpastes are typically generated in randomized controlled trials (RCTs), conducted in well-defined populations (self-reported and clinically confirmed DH), with the investigational products used and evaluated according to a strict set of study procedures. Such studies do not necessarily fully reflect the general DH population behavior. Real-world evidence (RWE) studies offer an opportunity to gather information on marketed products from real-world heterogeneous populations that can complement clinical evidence, consumer insight data, and post-marketing surveillance. Real world data (RWD) can be generated in a number of different study designs ranging from observational (prospective/retrospective) to interventional studies, with or without randomization, and help to address the accepted limitations of randomized controlled studies which can make it difficult to generalize findings to larger, more inclusive populations (Sherman et al, 2016).

Few published RWE studies focus on DH and most formed part of larger, observational dental practice-based studies investigating the range of methods used for diagnosing and treating DH (Cunha-Cruz et al, 2010; Heft et al, 2018; KopyckaKedzierawski et al, 2017a; Kopycka-Kedzierawski et al, 2017b; Litaker et al, 2019). The effectiveness of a variety of treatments used to manage DH in clinical practice has been investigated in a 'real-world' setting (Heft et al, 2018). Patients self-assessed the effectiveness of their dentist-selected method for DH management (e.g., dental treatment, anti-sensitivity product use, oral hygiene advice, dietary advice) using Visual Analogue Scales (VAS), Labelled Magnitude Scales (LMS), and patient satisfaction questionnaire. Patients who experienced a reduction in DH pain also reported a positive satisfaction rating for their treatment strategy. The RWD generated in such studies can be used to improve clinical practice for the management of DH (Heft et al, 2018). The sponsor of this study recently completed a RWE study evaluating the impact of a commercially available anti-sensitivity toothpaste containing 5% potassium nitrate (KNO3) on OHrQoL in a self-reported DH population (Haleon clinical study 216953). RWD supported the effectiveness of a 5% KNO3 toothpaste in improving OHrQoL in this population.

The aim of this study is to evaluate the impact of a commercially available desensitizing toothpaste containing 0.454% SnF2 on OHrQoL in a DH population in a real-world setting.

3.2 Study Background

Dentin hypersensitivity (DH) has been defined as 'pain derived from exposed dentin 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. The dentin occlusion approach uses tubule occluding agents which physically block the exposed end of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Dentin tubule occluding agents, such as strontium salts, stannous salts, bioglasses, arginine/calcium carbonate complex, or silicas serve to physically block or narrow the exposed ends of dentin tubules, reducing dentinal fluid movement, thereby decreasing the effect of external stimuli. Numerous clinical studies demonstrate the DH efficacy of SnF2-containing formulations [e.g., short term (typically 1-14 days treatment): longer term (typically 4-12 weeks treatment).

Recently, greater consideration has been given 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 present multiple responses, not always described as pain, affecting 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 increasingly used in dentistry to capture the impact of clinical interventions on OHrQoL; they typically cover a number of oral health conditions and so may not detect the nuances of a specific condition (Bekes et al, 2009). The Dentin 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 the sponsor in collaboration with Sheffield University through a robust theoretical framework, specific to 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 as both long- (DHEQ-48) and short- (DHEQ-15) 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 in clinical efficacy studies provide robust and positive support for the use of the sponsor's desensitizing toothpastes for the relief and management of DH, as measured by

clinical indices and the DHEQ. However, these results were generated under the highly controlled conditions of a RCT in response to controlled but contrived DH stimuli. These studies may not necessarily fully reflect the experience of the general DH population when challenged with real world stimuli for DH.

Based on these assumptions, this RWE study will include participants from the general population who suffer with DH (self-reported symptoms) and will evaluate the impact of daily use of an anti-sensitivity toothpaste containing 0.454% SnF2 on DH-related OHrQoL. Data generated will provide real world information on the impact of daily use of a desensitizing treatment for DH management.

3.3 Study Objective

This study will be considered successful if a trend of improvement in OHrQoL is observed over the 24-week treatment period; however, it is expected that statistically significant improvements from Baseline will be observed in DHEQ endpoints, particularly DHEQ Total Score.

Primary Objective

The primary objective of this study is:

- To describe changes in OHrQoL over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF2, as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48: Total Score and Domain Scores), in a DH population.

Secondary Objectives

The secondary objective of this study are:

- To describe changes in OHrQoL over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF2, as measured by the DHEQ-48 (other endpoints), in a DH population.
- To summarize the individual DHEQ domain items of concern in a DH population before and after 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF2.
- To describe changes in the intensity of self-reported DH pain over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF2, as measured by a Numeric Pain Rating Scale (NPRS), in a DH population.
- To describe participant satisfaction with the DH treatment (anti-sensitivity toothpaste containing 0.454% SnF2), as measured by a Satisfaction Numeric Rating Scale (NRS).
- To describe the oral hygiene habits of a DH population using an oral hygiene questionnaire (OHQ).

3.4 Study Design

This will be a decentralized, prospective, 24-week, monadic design, open label, study in a DH population. The study will evaluate changes in OHrQoL in participants with self-reported DH symptoms over 24 weeks of use of a DH treatment (anti-sensitivity toothpaste). OHrQoL will be measured using a validated questionnaire, the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48), completed by study participants at Baseline, and Weeks 4, 8, 12, 16, 20, 24.

3.4.1 Study Population

Sufficient participants will be screened (to allow for up to 50% screen failure rate) to ensure approximately 500 participants are enrolled and approximately 400 complete (to allow for up to 20% drop-out rate).

An enrolled participant is one who has agreed to participate in the RWE study following completion of the electronic informed consent (eIC) process and has successfully met the eligibility criteria to proceed beyond the screening procedures, as applicable for the protocol design.

Eligibility to participate in this RWE study will be reviewed and documented by an appropriate member of the CCI study team before a participant is included in the study.

3.4.2 Study Product/Treatment

The study product is Sensodyne Repair and Protect (US market), an anti-sensitivity toothpaste containing 0.454% SnF2.

3.4.3 Study Period

The duration of the study is defined for each participant as the date that the signed eIC is provided through the end of the study follow-up period 168 days (± 7days), participant death, early withdrawal from the study, lost to follow-up or overall study termination.

4. Statistical Analysis

4.1 Sample Size Calculation

Sufficient participants will be screened (to allow for up to 50% screen failure rate) to ensure approximately 500 participants are enrolled and approximately 400 complete (to allow for up to 20% drop-out rate).

A sample size of 400 participants would ensure at least 90% power to achieve a statistically significant (two-sided 5% significance level) reduction in Baseline in DHEQ Total Score when using a one-sample t-test, assuming a true population effect size (mean reduction/standard deviation [SD]) of 0.2. The planned primary analyses in this study will use a Mixed Model with Repeated Measures (MMRM) with time point as a fixed effect, Baseline DHEQ score as a covariate and participant as a repeated measure.

As well as providing adequate power to demonstrate statistically significant reductions from Baseline at each timepoint (4, 8, 12, 16, 20 & 24 weeks), 400 participants will ensure adequate precision of the corresponding 95% confidence intervals (CIs) for the mean reduction, and robust RWE relating to the magnitude of benefit from product use, at each timepoint. In a previous study (Haleon study 216953) assessing the same DHEQ-48 endpoints over 24 weeks in a RWE setting for an anti-sensitivity toothpaste containing 5% KNO3, the SD of the change from Baseline in DHEQ Total Score was shown to increase from around 30 units at Week 4 to 50 units at Week 24. An SD of 30 units and 50 units across 400 participants would equate to precision of the 95% CIs for the mean reduction within +/- 3 and 5 units, respectively.

4.2 Endpoints

4.2.1 Primary Endpoints

Change from Baseline in Section 2 DHEQ endpoints at Weeks 4, 8, 12, 16, 20 & 24.

- Total DHEQ score – (sum section 2 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

4.2.2 Secondary Endpoints

- Change from Baseline in additional DHEQ endpoints at Weeks 4, 8, 12, 16, 20 & 24.
  - Section 1:
    - Impact on Everyday Life (Q1-3, individually)
  - Section 2:
    - Global Oral Health Score (Q35)
    - Effect on Life Overall Score (Sum Q36-39)
- Percentage (%) of participants who 'agree' (score 5-7) with each item (statement) in the 5 DHEQ domains (DHEQ Section 2, Q1-34) at baseline and week 24.
- Change from Baseline in NPRS score at Weeks 1, 2, 4, 8, 12, 16, 20 & 24.
- Satisfaction Numerical Rating Scale (NRS) at Week 24.
- Oral Hygiene Questionnaire (OHQ) responses at Baseline.

4.2.3 Safety Endpoints

- Treatment Emergent Adverse Events reported over the study period.
- Treatment Emergent Oral Related Adverse Events.
- Treatment Emergent Serious Adverse Events.

4.3 Analysis

4.3.1 General Considerations

All statistical evaluations will be conducted using SAS® version 9.4 or higher (SAS® Institute, Cary, North Carolina) or R version 4.03 or higher (© The R Foundation). All tables, figures and listings will be produced in landscape format.

4.3.2 Data Display

In general, all data will be listed by subject and visit/time point where appropriate. The total number of subjects under the stated population (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, standard error, minimum, median, and maximum. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation and standard error will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. Descriptive summaries of categorical endpoints will include counts (missing and non-missing) and percentage (%) out of the participants with non-missing data.

P-values will be displayed with 4 decimals, e.g., p=0.0001 and p-values below 0.0001 will be displayed as p<0.0001.

In by-visit summary tables only scheduled visits/timepoints will be summarized. In listings, all visits and timepoints with any data collected will be included.

The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation.

All dates will be displayed in ISO 8601 date format (YYYY-MM-DD).

Residual analyses will be conducted for each MMRM applied.

4.3.3 Populations to be Analyzed

For the purposes of analysis, the following analysis sets are defined:

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

The Enrolled population will include all participants who meet the inclusion/exclusion criteria as identified by their responses to the screening questionnaire.

The Safety population will include all enrolled participants who complete at least one use of study product (at least one entry in Brushing Diary). Safety population will be used for the analysis of AEs.

The modified Intent-To-Treat (mITT) population will include all participants in the Safety population who have at least one post-baseline derived DHEQ Total Score. Efficacy data will be analyzed using the mITT population only.

4.3.4 Randomization

Not applicable.

4.3.5 Subject Disposition

Participant disposition will be summarized by study group and overall using Screened, Enrolled, mITT, and Safety populations. The number and percentage of participants will be presented for mITT and Safety populations. The denominator for percentages will be the number of participants enrolled.

Discontinued participants will be summarized by discontinued reasons.

A listing for disposition will include the participants who are enrolled and will cover the following information: informed consent date population assigned (mITT and/or Safety), study completion status and reason for discontinuation.

4.3.6 Demographics and Baseline Characteristics

Age (years) will be summarized as both a continuous and categorical (<=40 years, >40 years) variable. Gender, race, and ethnicity will be summarized for safety and mITT populations and listed for the safety population.

The following baseline characteristics will be derived and summarized for safety and mITT populations:

- DH diagnosis (from OHQ):
  - self-reported DH without previous diagnosis by a dentist
  - self-reported DH with previous diagnosis by a dentist
- Use of anti-sensitivity toothpaste (from OHQ):
  - 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
- Frequency of DH symptoms (from SQ):
  - 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

All categorical responses to the Screening Questionnaire and Oral hygiene Questionnaire will be summarized for the safety and mITT populations and listed for the safety population.

4.3.7 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 each study schedule and assessments (yes/no)
- Summary of product usage according to product instructions (more than 5 days/5 days or fewer)
- 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 for the safety population.

4.3.8 Prior and Concomitant Medications

All concomitant medications will be coded using WHO Drug dictionary.

Prior and concomitant medications taken during the study will be listed for the safety population. The listing will include reason for the medication as well as the start and stop date/time will be presented WHO Drug Class and Preferred term.

4.3.9 Medical History

All medical history will be coded using MedDRA dictionary.

Medical history will be listed for the safety population. The listing will include start and end date, ongoing status, and treatment status, and will be presented with System Organ Class, Preferred Term and Reported term.

4.3.10 Protocol Deviations

A listing for individual participants will be presented to describe the participant level protocol deviations for this study based on the safety population.

4.3.11 Primary Objective Analysis

Change from Baseline will be calculated at each post-Baseline time point (4, 8, 12, 16, 20 & 24 weeks) for the primary DHEQ endpoints:

- Section 2
  - DHEQ Total Score (sum of Q1-34)

- DHEQ Restrictions Domain score (sum of Q1-4)
- DHEQ Adaptation Domain score (sum of Q5-16)
- DHEQ Social Impact Domain score (sum of Q17-21)
- DHEQ Emotional Impact Domain score (sum of Q22-29)
- DHEQ Identity Domain score (sum of Q30-34),

Change from Baseline in each DHEQ endpoint listed above will be analyzed using a MMRM with time point fitted as a fixed effect, the respective Baseline DHEQ score as a covariate and participant fitted as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom will be applied. The estimates of the adjusted mean (standard error [SE]) change from Baseline will be presented along with 95% CIs.

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4.3.12 Secondary Objectives Analysis

4.3.12.1 DHEQ, Secondary Endpoints

Change from Baseline will be calculated at each post-Baseline time point (4, 8, 12, 16, 20 & 24 weeks) for the secondary DHEQ endpoints:

- **Section 1**
  - Change from Baseline in Impact on Everyday Life: Q1, Q2, & Q3 (separate scores)
- **Section 2**
  - Change from Baseline in DHEQ Global Oral Health (Q35)
  - Change from Baseline in DHEQ Effect on Life Overall (sum of Q36-Q39)

Each DHEQ endpoint listed above will be analyzed using a MMRM with time point fitted as a fixed effect, the respective Baseline score as a covariate and participant fitted as a repeated measure with unstructured covariance matrix. Kenward-Rogers degrees of freedom will be applied. The estimates of the adjusted mean (SE) change from Baseline at each post-Baseline timepoint will be presented along with 95% CIs.

For each DHEQ endpoint listed above (Sections 4.3.13 and 4.3.14), and each individual DHEQ question, the score at each timepoint (including Baseline) and the corresponding change from Baseline (at each post-Baseline timepoint) will be summarized descriptively.

Plots of mean score (SE) for each DHEQ endpoint listed above, and the individual DHEQ questions, over time will also be provided.

The number and percentage (%) of participants who 'agree' (score 5-7) with the 34 items (statements) in 5 domains of the DHEQ (Section 2, Q1-Q34) will be summarized at Baseline and Week 24. The percentage for each item will be summarized and presented in descending order of percentage at baseline.

4.3.12.2 Numeric Pain Rating Scale (NPRS)

Change from Baseline will be calculated at each post-Baseline time point (1, 2, 4, 8, 12, 16, 20 & 24 weeks) for the NPRS score. Change in NPRS score will be analyzed using identical methods to each of the DHEQ endpoints detailed above. Mean profile plots, descriptive summaries (including change from Baseline) and MMRMs will be presented.

An additional summary of the number of participants who achieve a reduction from Baseline in NPRS of > 30% will be presented at each post-Baseline time point (1, 2, 4, 8, 12, 16, 20 & 24 weeks).

$$Percent\ Change = \frac{Post\ Baseline\ Score - Baseline\ Score}{Baseline\ Score} * 100$$

4.3.12.3 Satisfaction Numeric Rating Scale (NRS)

Cross-tabulations of the number of participants reporting at each level of the NRS and the cumulative number of participants reporting at each level or higher at Week 24 will be presented. The NRS score at Week 24 will be summarized descriptively.

4.3.13 Safety Objective Analysis

Safety is measured by incidence of adverse events (AEs) and serious adverse events (SAEs).

AEs will be coded using MedDRA and categorized as either oral or non-oral by CCI prior to database lock. The number of AEs/SAEs and the number of participants with AEs/SAEs will be listed and tabulated overall and by System Organ Class (SOC) and Preferred Term (PT). This will be repeated including only Oral AEs.

AE summary tables will have system organ class listed in descending order of frequency and preferred terms are listed in descending order of frequency within system organ class.

4.3.14 Tabulation of Individual Participant Data

Individual participant data will be listed. The enrolled population data will include information on subject disposition, demographic and baseline characteristics, and protocol deviations. The safety population will include brushing diary, concomitant medications, medical history, adverse events, and serious adverse events. The modified intention-to-treat (mITT) population will include Dentin Hypersensitivity Experience Questionnaire (DHEQ),

Numeric Pain Rating Scale (NPRS), Numeric Rating Scale (NRS), and the Oral Hygiene Questionnaire (OHQ).

4.3.15 Missing Values

Missing data due to dropouts/withdrawals will be assessed on an ongoing basis during the study.

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

The MMRM approach will include all participants in the mITT population in the analysis. Any missing data from such participants will be treated as 'missing at random', i.e., their missing data at a particular time point will be assumed to behave in similar fashion to a participant with non-missing data at that time point who has similar data at other time points. This approach ensures an unbiased approach to handling missing data under the 'missing at random' assumption.

4.3.16 Multiplicity Control

No multiplicity adjustment will be made to secondary endpoints, nor sensitivity analyses.

4.3.17 Interim Analysis

No interim analysis is planned for this study.

5. Quality Control

5.1 Data and Output Quality Checks

Analysis related to the primary, secondary, and exploratory objectives will be validated by two biostatisticians or statistical programmers.

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

6. Reporting

6.1 Statistical Analysis Output

A Statistical Analysis Outputs will be developed and provided by CCI. 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.

6.2 Clinical Study Report

A Clinical Study Report will be developed and provided by CCI 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.

7. Revision History

VERSION	EFFECTIVE DATE	CHANGES
1.0	08Dec2023	Original Document