**CONFIDENTIAL**

# AMENDMENT #1 TO STATISTICAL ANALYSIS PLAN FOR PROTOCOL 207212

A Clinical Study Investigating the Efficacy of an Occluding Dentifrice in Providing Relief from Dentinal Hypersensitivity

**BIOSTATISTICS DEPARTMENT**

**GLAXOSMITHKLINE CONSUMER HEALTHCARE**

**INVENTIV HEALTH CLINICAL**


PPD

PPD **INDIA**

PPD (Statistician)

Timing of Amendment: ☐ Before unblinding ☒ After unblinding

**Appendix 2 List of Tables, Figures & Listings**

**Reason for amendment:**

1) During the medical review it is decided to update placebo treatment label as "Control Dentifrice"

2) It is decided to drop AEs listing 9.4.5, since it is not required and produce listing 9.4.9 for Non randomized Subject

**Original text:**

'Treatment 2' to be displayed as 'Negative Control Dentifrice'

- Negative Control Dentifrice: Colgate Cavity Protection (USA Marketed Product)

| | | |
|---|---|---|
| 9.4.5 | Listing of Treatment Emergent Adverse Events - Safety Population | Oral HealthCare standard. |
| 9.4.6 | Listing of serious AEs | Oral HealthCare standard.<br>If there are no treatment emergent serious AEs a null listing will be produced, if there are more than 5 treatment emergent SAEs a table will be produced by SOC and PT. |
| 9.4.7 | Table of Non Serious treatment emergent AEs by SOC and Preferred Term | To be produced only if there are more than 5 SAEs. |
| 9.4.8 | Listing of Incidents | Standard |
| 9.4.9 | Listing of Adverse Events – All Subjects | Standard |

**Amendment:**

'Treatment 2' to be displayed as '~~Negative~~ Control Dentifrice'

- ~~Negative~~ Control Dentifrice: Colgate Cavity Protection (USA Marketed Product)

| | | |
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| ~~9.4.5~~ | ~~Listing of Treatment Emergent Adverse Events - Safety Population~~ | ~~Oral HealthCare standard.~~ |

| | | |
|---|---|---|
| 9.4.~~5~~6 | Listing of serious AEs | Oral HealthCare standard.<br>If there are no treatment emergent serious AEs a null listing will be produced, if there are more than 5 treatment emergent SAEs a table will be produced by SOC and PT. |
| 9.4.~~6~~7 | Table of Non Serious treatment emergent AEs by SOC and Preferred Term | To be produced only if there are more than 5 SAEs. |
| 9.4.~~7~~8 | Listing of Incidents | Standard |
| 9.4.~~8~~9 | Listing of Adverse Events – ~~All Subjects~~ Non Randomized Subject | Standard |

## Appendix 3 Templates for Tables, Figures & Listings

**Reason for amendment:**

1 During the medical review it is decided to update the placebo treatment label as "Control Dentifrice"

2 It is decided to drop AEs listing 9.4.5, since it is not required and produce listing 9.4.9 for Non - randomized Subject.

**Original text:**

Table 9.3.1.2

| Comparison Between Treatments<br>Test Dentifrice vs Negative Control Dentifrice |
|---|

Figure 9.1.1

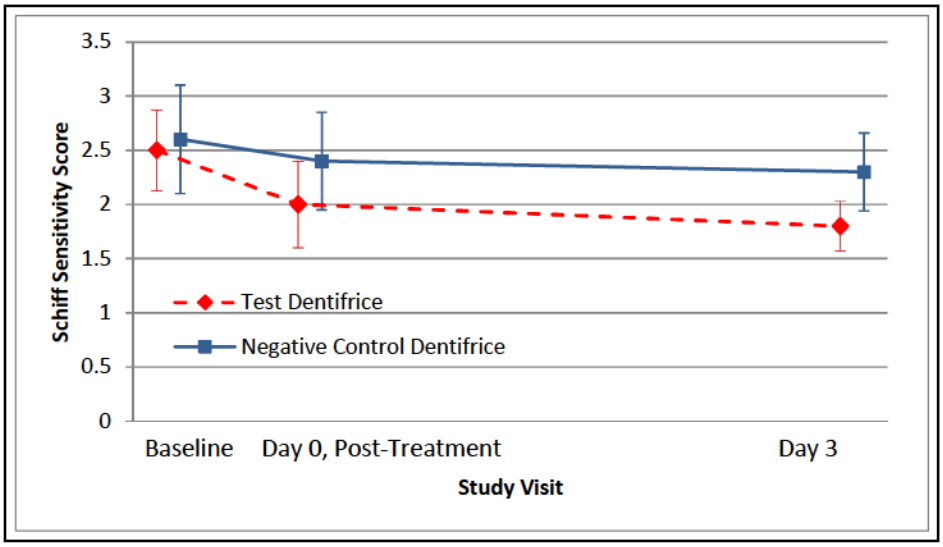
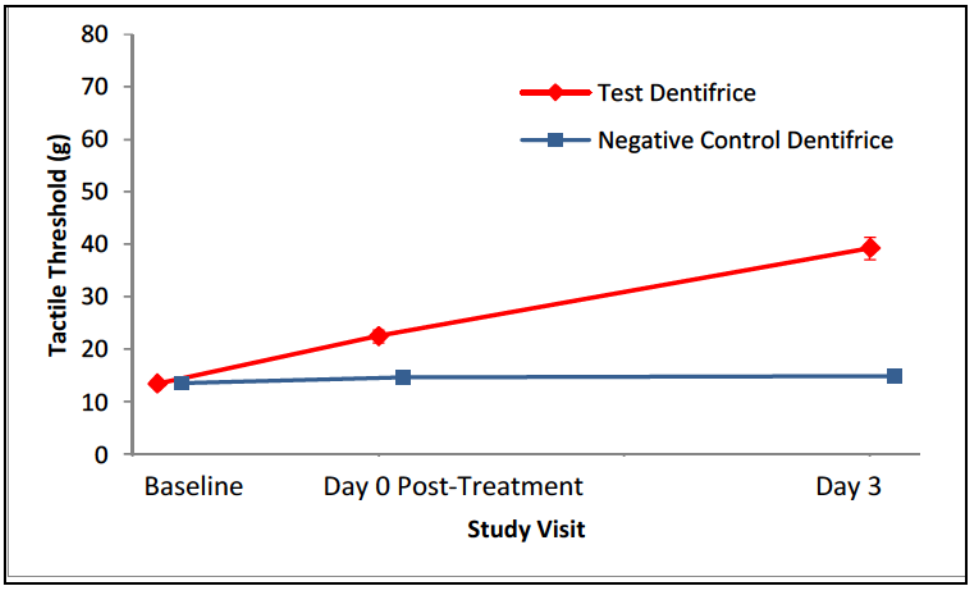



Figure 9.2.1




**Amendment:**

Table 9.3.1.2

| Comparison Between Treatments |
|---|
| Test Dentifrice vs ~~Negative~~ Control Dentifrice |

Figure 9.1.1

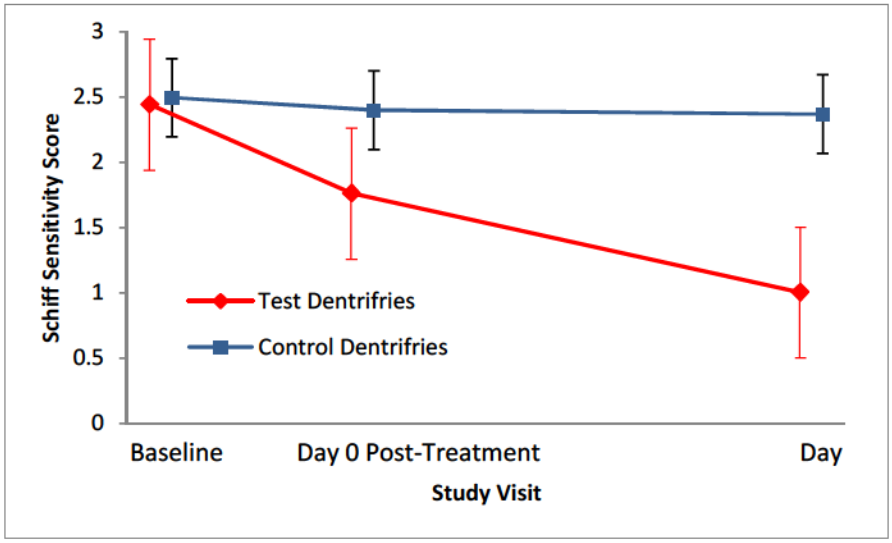
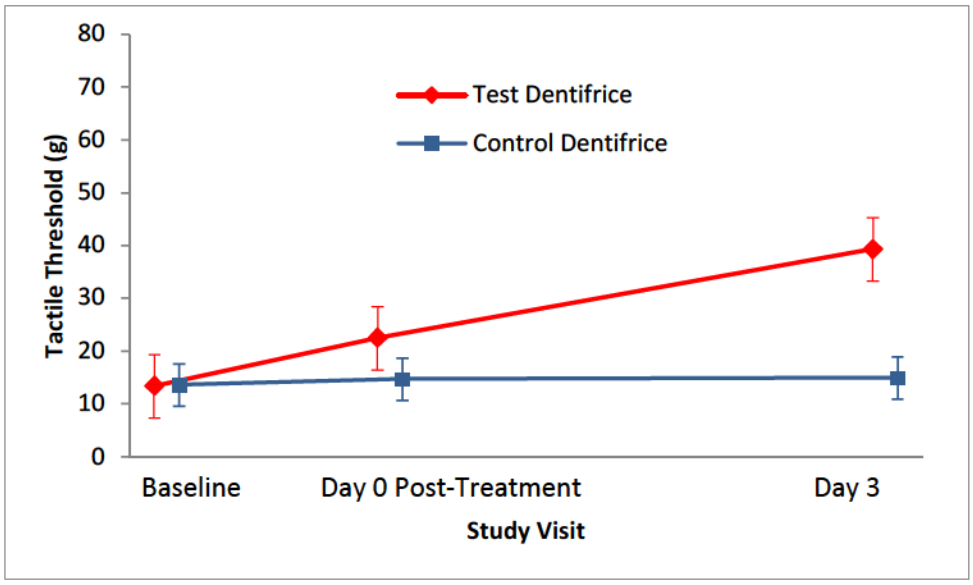



Figure 9.2.1



## Table of Contents

# Glossary

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CI | Confidence Interval |
| DH | Dentinal Hypersensitivity |
| EAR | Erosion, Abrasion, Recession |
| eCRF | Electronic Case Report Form |
| GSKCH | GlaxoSmithKline Consumer Healthcare |
| ITT | Intention to Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N | Number of Subjects |
| PP | Per Protocol |
| ppm | parts per million |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Of Organ |
| w/w | Weight/weight |

# 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 207212.

The statistical analysis plan (SAP) will be finalized and approved prior to database lock and study unblinding.

# 2 Objectives

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To investigate the ability of an experimental CCI stannous fluoride dentifrice to provide relief from DH, as elicited by an evaporative (air) stimulus (Schiff sensitivity scale) after 3 days use. | Change from baseline in Schiff sensitivity score after 3 days use. |
| **Secondary** | |
| To investigate the ability of an experimental CCI stannous fluoride dentifrice to provide relief from DH, as elicited by a tactile stimulus (Yeaple probe) after 3 days use. | Change from baseline in a tactile threshold after 3 days use. |
| To investigate the ability of a CCI stannous fluoride dentifrice to provide relief from DH, as elicited by an evaporative (air) stimulus (Schiff sensitivity scale) and a tactile stimulus (Yeaple probe) after a single use (60 second direct application on selected teeth). | Change from baseline in Schiff sensitivity score after a single 60 second direct application.<br><br>Change from baseline in tactile threshold after a single 60 second direct application. |

# 3 Study Design

| Overall Design |
|---|
| This will be a single center, three day, randomized, examiner blind, two treatment arm, parallel design, stratified (by maximum baseline Schiff sensitivity score of the two selected test teeth), controlled study, in subjects with at least two sensitive teeth that meet all the criteria at the screening and baseline (pre-treatment) visits. DH will be assessed at baseline (pre-treatment), post-treatment and after 3 days twice daily |

brushing.

At the Screening visit, subjects will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) and oral hard tissue (OHT) examination, dentition exclusions, assessment of erosion, abrasion, recession (EAR), gingival status, tooth mobility and subject response to a qualifying air sensitivity assessment (Y/N). Eligible subjects will be supplied with a standard fluoride dentifrice to use twice daily (morning and evening) during the acclimatisation period between the Screening and Baseline (pre-treatment). First use of the acclimatisation dentifrice will be carried out under supervision at the study site.

At the Baseline visit (pre-treatment), eligibility to continue will be assessed. Subjects will undergo an OST examination, followed by tooth sensitivity assessments (to a tactile stimulus [Yeaple probe, maximum 20g pressure], and an evaporative air stimulus [with Schiff Sensitivity Scale]), and a review of the inclusion/exclusion criteria. Eligible subjects will be stratified according to their maximum baseline Schiff sensitivity score of the two selected teeth (2 / 3) and then randomized to treatment.

At Visit 2, randomized subjects will directly apply assigned treatment to the two selected teeth (under supervision) as per the instructions provided. Following direct application of the assigned treatment (and within 5 minutes of it), tooth sensitivity of the two test teeth will be assessed to a tactile and evaporative air stimuli. Before leaving the site (after all the clinical assessments have been completed), subjects will brush their whole mouth for at least one minute under supervision. Subjects will brush at least once on the day of baseline (first brushing will be supervised at site). Subjects will return to the study site on day 3 (Visit 3) after six brushings. Every effort will be made to ensure similar appointment times are kept for subjects at Visit 3 as per Visit 2. Subjects will undergo an OST examination, followed by tooth sensitivity assessments (to a tactile stimulus [Yeaple probe, maximum 80g pressure], and an evaporative air stimulus [with Schiff Sensitivity Scale]). Following review of AEs and incidents subjects will be exited from the study.

| Visit 1 - Screening Visit |
|---|
| The following assessments will be conducted:<br>• Written informed consent.<br>• Inclusion/exclusion criteria<br>• Review of the oral care products the subject is currently using to confirm they do not contain any ingredients intended for treating sensitive teeth.<br>• Demographics, current/concomitant medications and medical history.<br>• Oral examination including an oral soft tissue (OST) and oral hard tissue (OHT) examinations, including eligible teeth assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility).<br>• Qualifying evaporative air sensitivity.<br>• Confirmation of subject eligibility.<br>• Dispensation of acclimatisation toothpaste, toothbrush, and timer.<br>• Supervised brushing with acclimatisation toothpaste.<br>• Adverse Events (AEs) and incidents will be documented from completion of the supervised brushing with acclimatisation toothpaste. |
| **Visit 2 - Baseline (Pre-treatment)** |
| The following assessments will be conducted:<br>• Review of current/concomitant medications, AEs.<br>• Return of acclimatisation toothpaste and toothbrush.<br>• Compliance check of acclimatisation product usage during acclimatisation period.<br>• OST examination.<br>• Tactile sensitivity assessment of eligible teeth.<br>• Evaporative air sensitivity assessment of eligible teeth which meet the tactile sensitivity entry criterion.<br>• Inclusion criteria 5d.<br>• Selection of two test teeth.<br>• Stratification and Randomization.<br>• Dispensation of study toothpaste with usage instructions and diary.<br>• Supervised direct application using finger with allocated study treatment (test teeth only).<br>• Adverse events and Incidents. |

| **Visit 2 – Post-treatment** |
|---|
| The following assessments will be conducted:<br>• Review of AEs and incidents.<br>• OST examination.<br>• Tactile sensitivity assessment of the two selected test teeth.<br>• Evaporative air sensitivity assessment of the two selected test teeth.<br>• Supervised brushing with allocated study treatment. |
| **Visit 3 – Day 3** |
| The following procedures will be conducted:<br>• Review of current/concomitant medications, AEs and incidents.<br>• Subject adherence<br>• Return of study supplies (toothpaste, toothbrush) and diary.<br>• Review of completed diary to determine usage compliance.<br>• OST examination.<br>• Tactile sensitivity assessment of the two selected test teeth.<br>• Evaporative air sensitivity assessment of the two selected test teeth.<br>• Subjects will be reminded to report AEs and incidents for 5 days after last treatment.<br>• Study conclusion. |

Qualifying subjects will be randomized to one of the two treatments:

| | Test dentifrice | Control dentifrice |
|---|---|---|
| **Treatment Description** | Experimental dentifrice containing [redacted] stannous fluoride ([redacted] fluoride) | Dentifrice containing [redacted] sodium monofluorophosphate ([redacted] fluoride) |
| **MFC or Commercial product** | [redacted] | Colgate Cavity Protection (USA Marketed Product) |
| **Route of administration** | Topical oral use | |
| **Supervised direct application time (Test Teeth only)** | 60 seconds | 60 seconds |
| **Supervised direct application (Test Teeth only) dosing instructions** | Subjects will directly apply (under supervision) a pea-sized dose to each of the two qualifying teeth using their washed, clean finger by direct application and gently rubbing into the tooth's cervical margin for the allocated time.<br>No rinsing will be permitted. | |
| **Supervised brushing (Visit 2)** | Before leaving the site (after all the clinical assessments have been completed), subjects will dose a dry toothbrush with a full strip of toothpaste.<br><br>Subjects will then brush each of the two selected sensitive test teeth first, followed by the whole mouth thoroughly for at least 1 minute.<br><br>Subjects will be permitted to rinse with 5 ml tap water (kept at room temperature) for a maximum 5 timed seconds. | Before leaving the site (after all the clinical assessments have been completed), subjects will dose a dry toothbrush with a full strip of toothpaste<br><br>Subjects will brush their whole mouth thoroughly for at least 1 minute under.<br><br>Subjects will be permitted to rinse with 5 ml tap water (kept at room temperature) for a maximum 5 timed seconds. |

| | | |
|---|---|---|
| **Home use instructions**<br><br>**Twice daily (morning/ evening)** | Subjects will be instructed to dose a dry toothbrush with a full strip of toothpaste.<br><br>Subjects will then brush each of the two selected sensitive test teeth first, followed by the whole mouth thoroughly for at least 1 minute.<br><br>Subjects will be permitted to rinse with tap water. | Subjects will be instructed to dose a dry toothbrush with a full strip of toothpaste.<br><br>Subjects will then brush the whole mouth thoroughly for at least 1 minute.<br><br>Subjects will be permitted to rinse with tap water. |

# 4 Sample Size Determination

Change from baseline in Schiff Sensitive Score will be used to evaluate treatment effects with regard to the primary objective. A sufficient number of subjects will be screened in order to ensure that 92 evaluable subjects per group complete the study.

With 92 evaluable subjects per group, it will be possible to detect a mean difference of 0.25 (SD=0.5198) in change from baseline in Schiff sensitive score after day 3 use between treatments 90% power. The estimate of SD was obtained from a review of GSKCH studies [GSKCH Study 205710; GSKCH Study205697 & GSKCH Study 205084]. The sample size is based on carrying out two-tailed two sample t-test at a 5% significance level and assumes that the group variances are equal.

Therefore, allowing for dropouts approximately 190 subjects will be randomized to ensure approximately 184 subjects (approximately 92 per arm) complete the study.

# 5 Data Considerations

## 5.1 Analysis Populations

The population of All Subjects includes all subjects that are screened for entry into the study

All assessments of safety will be based on the safety population, defined as all subjects who are randomized and receive at least one dose of study treatment during the study. Safety population summaries will be presented by treatment received.

The primary population for efficacy assessment will be the intent-to-treat (ITT) population, defined as all subjects who are randomized, receive the study treatment at least once and provide at least one post-baseline (post treatment) assessment of efficacy. All ITT population summaries and analyses will be presented by treatment randomized.

The per protocol (PP) population is defined as all subjects in the ITT population who have at least one assessment of efficacy considered unaffected by protocol violations.

PP analysis will be performed only on those data considered unaffected by protocol violations.

Efficacy analysis on the PP population will be performed on the clinical sensitivity measures (tactile threshold and Schiff sensitivity score) only if there is more than 10% difference in the number of subjects between PP and ITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding.

The following listings, but not limited to those below, will be reviewed with the purpose to identify protocol deviations that may lead to the exclusion of subjects from the PP population or the exclusion of affected data from PP analyses:

- Violation of inclusion or exclusion criteria that are deemed to affect efficacy.
- Medical history which is deemed to affect efficacy.
- Use of prohibited treatment or medication before or during the study, which is felt to affect the assessment of efficacy.
- Treatment non-compliance.
- Protocol deviations captured in case report form (CRF).
- Visit schedule non-compliance:
    - Day 0 (Pre-Treatment)
    - Day 0 (Post-Treatment)
    - Day 3
- Any other reason identified likely to affect efficacy.

Protocol violations which warrant exclusion from efficacy analysis will be identified between the statistician and clinical director or designee ahead of database lock and breaking the study blind.

## 5.2 Subgroups/Stratification

Subjects will be stratified by maximum baseline Schiff sensitivity score of the two selected test teeth. This will give rise to two strata:

- Schiff Maximum Score = 2
- Schiff Maximum Score = 3

No subgroup or stratified analyses are planned for this study.

## 5.3 Time Windows

The study schedule should be followed as per protocol. Deviations from the study schedule with respect to visit timings will be reviewed as outlined in Section 5.1 with significant deviations in timings classified as protocol violations potentially affecting efficacy assessments.

# 6 Demographics and Baseline Characteristics

## 6.1 Subject Disposition

The subject disposition summary will include the number of screened subjects and screen failures overall and the number of subjects randomised per treatment group and overall.

The number and percentage of subjects, in the Safety, ITT and PP populations will be presented per treatment group and overall. The percentages will be based upon the total number of subjects randomised.

The number and percentage of subjects completing the study and not completing the study, including a breakdown of the reasons for not completing the study, will be presented per treatment group and overall. The percentages will be based upon the total number of subjects randomised.

A separate summary table of protocol violations leading to exclusion of subjects/data from PP analyses will be produced indicating the number and percentage of subjects within each violation per treatment group and overall. The table will distinguish between violations leading to exclusion of the subject from the PP population and those leading to exclusion of specific data from PP analyses (not leading to full subject exclusion). Percentages will be based on the ITT population.

## 6.2 Demographics

Summary statistics of number of subjects, mean, standard deviation, median, minimum and maximum will be presented for age and counts and percentages will be presented for gender and race. The summaries will be split by treatment group. An overall column will be included into the table.

Summary tables will be produced for the Safety and ITT populations. In case the PP analysis is performed another demography table will be provided for the PP population.

## 6.3 Baseline Characteristics

Number and percentage of subjects in each stratum (stratified by maximum baseline Schiff Sensitivity Score of the two selected test teeth) will be summarised by treatment group for safety and ITT populations. If the criterion for a PP analysis is met then descriptive statistics will be provided for the PP population also.

# 7 Treatment Compliance and Concomitant Medications

## 7.1 Treatment Compliance

Treatment compliance will be assessed during blinded data review and a listing will be produced for evaluation of protocol violations only. This will be based on the product and brushing compliance questions and any protocol deviations noted on the electronic case report form (eCRF). Non-compliance will be assessed on a subject by subject basis. Those subjects with treatment and brushing non-compliance deemed to potentially affect efficacy, will have associated efficacy data excluded from the PP analysis. Any subject and/or time point excluded from PP analysis will be clearly documented in the population definition document.

## 7.2 Concomitant Medications

Concomitant medications and concomitant non-drug treatments used during the study, including any prohibited medications will be databased but no formal listing of these data will be produced for the study report. These data will be used to determine eligibility of efficacy data for PP analyses only.

# 8 Efficacy Analysis

*Criteria for assessing efficacy*

The success criterion for this study is to observe a statistically significant greater reduction in evaporative air sensitivity (Schiff Sensitivity Scale) for subjects using the experimental CCI stannous fluoride dentifrice, compared to use of a dentifrice containing CCI sodium monofluorophosphate, after 3 days use. The observed treatment mean difference & observed estimate of variability will be compared against the planned treatment mean difference (0.25) & planned estimate of variability (0.5198) respectively in the study report.

The primary population for assessment of efficacy is the ITT population. All efficacy endpoints will be analysed using the ITT population. Further PP analyses will be performed on the clinical sensitivity measures (tactile threshold and Schiff sensitivity score) only if there is more than 10% difference in the number of subjects between PP and ITT populations. ITT analysis will be based on planned treatment allocation; any mis-randomisations will exclude subjects from the PP population.

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for the efficacy variables.

Treatment differences in the study variables will be tested with the null hypothesis:

H0: there is no treatment difference versus the alternate hypothesis

H1: there is a treatment difference.

Treatment differences, p-values (for the null hypothesis) and 95% confidence intervals will be presented. Adjusted mean change from baseline (day 0 pre-treatment) in each treatment will also be provided and tested against the null hypothesis of no change from baseline.

All significance tests will be conducted at the two-sided 5% significance level with no adjustments for multiple testing as the criteria for assessing efficacy is based only on one primary variable.

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. No data will be imputed in the case of dropouts or missing data.

Raw means with standard error bars for each treatment group will be plotted over time for measures of Schiff sensitivity score and tactile threshold.

For all analysis of covariance (ANCOVA) models, the OBSMARGIN / OM option will be specified within the LSMEANS statement in order to weight the computations of least-squares means using coefficients that are proportional to the observed marginal distributions across any specified classification effects (strata) rather than using equal coefficients per stratum, as per default. Due to random sampling, the observed distribution across strata is assumed to reflect that of the target population and so the use of the OBSMARGIN option is considered to provide more accurate least-squares estimates. All statistical analysis will be conducted using SAS version 9.2.

## 8.1 Primary Efficacy Analysis

*Schiff Sensitivity Score (Day 3)*

The change from baseline (day 0, pre-treatment) in Schiff sensitivity score after 3 days use will be the primary efficacy variable. For each subject, this variable is calculated as the mean change from baseline of the two selected teeth.

Raw Schiff sensitivity scores (raw values averaged over the two test teeth) at day 3 together with changes from baseline (day 0, pre-treatment application) will be summarized by treatment at each study time point. The summary table will display the 'Overall' summary statistics for the baseline (day 0, pre-treatment application) data only. To visually inspect the treatment effect on Schiff sensitivity scores, a plot across time, with the raw means together with standard error bars (SEs) will be produced. The plot will display a different symbol line for each treatment group.

The change from baseline in Schiff sensitivity score will be analyzed using analysis of covariance (ANCOVA) with treatment as factor and baseline Schiff sensitivity score as a covariate. Note that since the baseline Schiff sensitivity score will be included as a covariate, the baseline Schiff stratification value will not be included in the model.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. In case of violation of these assumptions the van Elteren test, adjusting for the maximum baseline Schiff Sensitivity scores will be performed and results will be compared with the ANCOVA results. If the inferences from the two analyses are similar then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between p-values of ANCOVA and van Elteren analysis, inferences will be drawn on the non-parametric analysis.

## 8.2 Secondary Efficacy Analysis

*Schiff Sensitivity Score (Day 0, Post-Treatment)*

The change from baseline (day 0, pre-treatment application) in Schiff sensitivity score to post-treatment application (day 0, post-treatment application) will be summarised and analysed as detailed for the primary endpoint. Analysis assumptions will be investigated as detailed for the primary efficacy analysis.

*Tactile Threshold (Day 0, Post-Treatment and Day 3)*

The change from baseline in tactile threshold to day 3 will be calculated as the mean change from baseline of the two selected test teeth.

Tactile threshold scores (raw values averaged across the two test teeth) together with changes from baseline will be summarized at each time point as described for the Schiff sensitivity score. A plot with raw means and standard error bars for each treatment group across time will be produced to visually inspect the treatment effect on tactile threshold score. The plot will display a different symbol line for each treatment group.

The change from baseline (day 0, pre-treatment) in tactile threshold to day 3 will be analyzed using ANCOVA with treatment and baseline Schiff stratification included as factors and baseline tactile threshold included as a covariate.

The assumption of normality and homogeneity of variance in ANCOVA model will be assessed as described for the primary efficacy analysis.

The change from baseline (day 0, pre-treatment) in tactile threshold to day 0 post-treatment application will be summarised and analysed as described for the changes from baseline in tactile threshold to day 3.

## 8.3 Other Efficacy Analysis

Not applicable.

# 9 Safety Analysis

Safety population will be used for safety assessments. Safety analyses will be performed according to the treatment that the subject received (using variable ATRT).

No inferential analysis will be performed to compare treatments with respect to safety.

All adverse events (AEs) will be reviewed by the Clinical Research Scientist or Designee prior to database lock and unblinding and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorized as oral or non-oral. AEs will be listed and summarized by treatment received. Serious AEs will also be listed. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the baseline visit.

The following AEs tables split by treatment will be produced:

- Listing of all AEs (including Non-treatment emergent AEs from all subjects)
- Listing of all AEs for screened subjects
- Treatment emergent AEs by Oral/Non-Oral Preferred Term (PT)
- Treatment emergent AEs by System Organ Class (SOC) and PT
- Treatment emergent treatment related AEs by Oral/Non-Oral
- Listing of serious AEs (if there are none a null listing will be produced; if there are more than 5 treatment emergent serious AEs (SAEs) a table will be produced instead by SOC and PT)
- Non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 SAEs).
- Listing of incidents (if there is none a null listing will be produced).

Oral soft tissue (OST) abnormalities will be listed only.

# 10 Interim Analysis

No interim analyses are planned for this study.

# 11 Topline Summary

## 11.1 Variables for topline

***Efficacy***

Efficacy variable 1 (Change from baseline in Schiff sensitivity score after a single 60 second direct application and 3 days use)
Efficacy variable 2 (Change from baseline in Tactile score after a single 60 second direct application and 3 days use)

***Safety***

Adverse events
Incidents

## 11.2 Outputs for topline

| Datasets/Tables | Description |
|---|---|
| Datasets | PONNFL, POPNEXCL, RANDOM<br><br>ADSL, ADAE, ADXXXX, ADXXXX, INCIDENT, S_DH_W and S_DH_B |
| Tables Safety | 9.4.1 – Listing of Adverse Events — Safety Population<br><br>9.4.2 – Treatment Emergent Adverse Events, Oral and Non-Oral by Preferred Term - Safety Population |
| Tables Efficacy (In-text table) | Statistical Analysis of Change from Baseline in Evaporative (Air) Sensitivity – Schiff Sensitivity Score.<br><br>Statistical Analysis of Change from Baseline in Tactile Sensitivity – Tactile Threshold (g) - Intent to Treat Population. |
| Figures (Excel plot) | 9.3.1 – Evaporative (Air) Sensitivity - Schiff Sensitivity Score by Time and Treatment Group - |

| Datasets/Tables | Description |
|---|---|
| | Intent to Treat Population<br><br>9.3.2 – Tactile Sensitivity - Tactile Threshold (g) by Time and Treatment Group - Intent to Treat Population |
| Other output | Table 9.1.1 – Subject Disposition - All Screened Subjects |

### In-text table format for efficacy

Statistical Analysis of Change from Baseline in Evaporative (Air) Sensitivity - Schiff Sensitivity Score
Intent to Treat Population

| Time point | Adjusted Mean Change (95% Confidence Interval), p-value | | |
|---|---|---|---|
| | Test Dentifrice (N=XX) [1] | Control Dentifrice (N=XX) [1] | Treatment Comparison: Test Dentifrice vs. Control Dentifrice [2] |
| Baseline | x.xx (SE= x.xx) | x.xx (SE= x.xx) | |
| Day 0 (Post treatment) | x.xx (x.xx, x.xx)<br>p= x.xxxx | x.xx (x.xx, x.xx)<br>p= x.xxxx | x.xx (x.xx, x.xx)<br>p= x.xxxx |
| Day 3 | x.xx (x.xx, x.xx)<br>p= x.xxxx | x.xx (x.xx, x.xx)<br>p= x.xxxx | x.xx (x.xx, x.xx)<br>p= x.xxxx |

Note: Baseline values are Raw Means with SE included in brackets.
[1] Adjusted mean change, CI and p-value from ANCOVA model with treatment as factor and baseline Schiff score as covariate.
[2] Negative difference favours Test dentifrice.

Note to programmer: 1) Please create these tables in docs. Format
2) For tactile analysis footnote 1 & 2 will be changed to

[1] Adjusted mean change, CI and p-value from ANCOVA model with treatment and Schiff strata as factors and baseline Tactile score as covariate.
[2] Positive difference favours Test dentifrice.

3) If Non parametric methods used for analysis in-text table format and footnote will be changed and these will be provided by the statistician.

# 12 Changes to Planned Analysis

There are no planned changes from the analyses planned in the protocol.

# 13 References


GSK Study 205084: A Clinical Study Investigating the Efficacy of an Occluding Dentifrice in Providing Relief from Dentinal Hypersensitivity.

GSK Study 205710: A Clinical Study Investigating the Efficacy of an Occluding Dentifrice in Providing Relief from Dentinal Hypersensitivity.

GSK Study 205697: A Clinical Study Investigating the Efficacy of an Occluding Dentifrice in Providing Relief from Dentinal Hypersensitivity.

# Appendix 1 Study Schedule

| Procedure/ Assessment | Visit 1 | Acclimatisation Period (minimum 4 weeks – maximum 8 weeks) | Visit 2 | | Visit 3 |
|---|---|---|---|---|---|
| | Screening | | Day 0 Baseline (Pre-Treatment) | Day 0 Post-Treatment | Day 3 |
| Informed consent | X | | | | |
| Demographics and Medical History | X | | | | |
| Current / Concomitant medication | X | | X | | X |
| Inclusion / Exclusion Criteria | X | | X[1] | | |
| Subject Eligibility | X | | X | | X |
| Continuation Criteria | | | X | | X |
| Oral Soft Tissue (OST) Examination | X | | X | X | X |
| Oral Hard Tissue Examination including Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility) | X | | | | |
| Qualifying Evaporative Air Sensitivity Assessment (Y/N) | X | | | | |
| Dispense Acclimatisation Toothpaste, Toothbrush, Timer | X | | | | |
| Supervised Brushing with Acclimatisation Toothpaste | X | | | | |
| Return Acclimatisation Toothpaste, Toothbrush | | | X | | |
| Compliance Check | | | X[2] | | X[7] |
| Tactile Sensitivity Assessment (Yeaple Probe) | | | X[3] | | |
| Evaporative Air Sensitivity Assessments (Schiff sensitivity score) | | | X[4] | | |
| Selection of two 'Test Teeth' | | | X[5] | | |
| Stratification/Randomisation | | | X | | |
| Dispense Study Supplies | | | X[6] | | |
| Supervised direct application of allocated dentifrice (Test Teeth Only) | | | X[8] | | |
| Tactile and Evaporative Air Assessments[9] (Test Teeth only) | | | | X | X |
| Supervised Brushing | | | | X[10] | |
| Return Study Supplies | | | | | X |
| Adverse Events / Incidents [11] | X | | X | X | X |

| Study Conclusion | | | | | X |
|---|---|---|---|---|---|

1. Inclusion criteria 5d
2. Subject asked to confirm that they have brushed with the acclimatisation product as directed during the acclimatisation period.
3. To be performed pre treatment on all teeth that meet the dentition exclusions, EAR, MGI and tooth mobility criteria at Screening until the examiner selects 2 teeth meet the study criteria, at which point no further teeth will be tested. Maximum force to be tested will be 20g.
4. To be performed pre-treatment on teeth that meet tactile threshold inclusion criterion (<=20g) at Baseline and should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.
5. Tactile assessment to be performed, on the two selected test teeth only. Maximum force to be tested will be 80g. Evaporative air assessment should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.
6. Experimental dentifrice, control dentifrice, toothbrush, product usage instructions, and diary. Timer dispensed in Visit 1 will be kept and re used.
7. Based on subject completed diary card
8. To be performed after stratification and randomisation
9. Tactile assessment to be performed, on the two selected test teeth only. Maximum force to be tested will be 80g. Evaporative air assessment should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.
10. Supervised whole mouth brushing before leaving the site (after all clinical assessments have been performed)
11. Incidents captured from Visit 2.

# Appendix 2 List of Tables, Figures & Listings

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

'Treatment 1' to be displayed as 'Test Dentifrice'
'Treatment 2' to be displayed as '~~Negative~~ Control Dentifrice'

All tables and listings which make use of the above treatment labels will, in addition, include the following footnotes:

- Test Dentifrice: Dentifrice containing [redacted] stannous fluoride ([redacted] fluoride) ([redacted])
- ~~Negative~~ Control Dentifrice: Colgate Cavity Protection (USA Marketed Product)

| Table No. | Title | Standard / Template / Changes to Footnotes / Comments |
|---|---|---|
| 9.1.1 | Subject Disposition - All Screened Subjects | Appendix 3 |
| 9.1.2 | Protocol Violations Leading to Exclusion from Per Protocol Analyses - Intent to Treat Population | Appendix 3 |
| 9.2.1.1 | Demographic Characteristics - Safety Population | Standard |
| 9.2.1.2 | Demographic Characteristics -Intent to Treat Population | Standard |
| 9.2.1.3 | Demographic Characteristics - Per Protocol Population | Standard |
| 9.2.2.1 | Baseline Characteristics - Stratification Factors - Safety Population | Appendix 3 |
| 9.2.2.2 | Baseline Characteristics - Stratification Factors - Intent to Treat Population | 9.2.2.1 |
| 9.2.2.3 | Baseline Characteristics - Stratification Factors - Per Protocol Population | 9.2.2.1 |
| 9.3.1.1 | Summary of Evaporative (Air) Sensitivity – Schiff Sensitivity Score - Intent to Treat Population | Appendix 3<br>Create using: PARCAT1=98 and ITTFL=1 |
| 9.3.1.2 | Statistical Analysis of Change from Baseline in Evaporative (Air) Sensitivity – Schiff Sensitivity Score - Intent to Treat Population | Appendix 3<br>Create using: PARCAT1=98 and ITTFL=1 |
| 9.3.1.3 | Summary of Evaporative (Air) Sensitivity – Schiff Sensitivity Score - Per Protocol Population | 9.3.1.1<br>Create using: PARCAT1=99 and PPROTFL=1 |

| Table No. | Title | Standard / Template / Changes to Footnotes / Comments |
|---|---|---|
| 9.3.1.4 | Statistical Analysis of Change from Baseline in Evaporative (Air) Sensitivity – Schiff Sensitivity Score - Per Protocol Population | 9.3.1.2<br>Create using: PARCAT1=99 and PPROTFL=1 |
| 9.3.2.1 | Summary of Tactile Sensitivity – Tactile Threshold (g) - Intent to Treat Population | 9.3.1.1<br>Create using: PARCAT1=98 and ITTFL=1 |
| 9.3.2.2 | Statistical Analysis of Change from Baseline in Tactile Sensitivity – Tactile Threshold (g) - Intent to Treat Population | 9.3.1.2.<br>Create using: PARCAT1=98 and ITTFL=1<br>Change footnotes to:<br>[2] From ANCOVA model with change from baseline in Tactile threshold as response and treatment and baseline Schiff strata as factors and baseline Tactile threshold as covariate.<br>[4] Difference is first named dentifrice minus second named dentifrice such that a positive difference favours first named dentifrice. |
| 9.3.2.3 | Summary of Tactile Sensitivity – Tactile Threshold (g) - Per Protocol Population | 9.3.1.1<br>Create using: PARCAT1=99 and PPROTFL=1 |
| 9.3.2.4 | Statistical Analysis of Change from Baseline in Tactile Sensitivity – Tactile Threshold (g) - Per Protocol Population | 9.3.1.2<br>Create using: PARCAT1=99 and PPROTFL=1<br>Change footnotes to:<br>[2] From ANCOVA model with change from baseline in Tactile threshold as response and treatment and baseline Schiff strata as factors and baseline Tactile threshold as covariate.<br>[4] Difference is first named dentifrice minus second named dentifrice such that a positive difference favours first named dentifrice. |
| 9.4.1 | Listing of Adverse Events – Safety Population | Oral HealthCare standard. |
| 9.4.2 | Treatment Emergent Adverse Events, oral and non-oral by Preferred Term - Safety Population | Oral HealthCare standard. Include 'Overall' column.<br>Do not present p-values. |
| 9.4.3 | Table of treatment emergent AEs by SOC and Preferred Term - Safety Population | |
| 9.4.4 | Treatment Emergent Treatment Related Adverse Events, oral and non-oral by Preferred Term - Safety Population | Oral HealthCare standard.<br>Include 'Overall' column.<br>Do not present p-values. |
| ~~9.4.5~~ | ~~Listing of Treatment Emergent Adverse Events - Safety Population~~ | ~~Oral HealthCare standard.~~ |

| Table No. | Title | Standard / Template / Changes to Footnotes / Comments |
|---|---|---|
| 9.4.~~5~~6 | Listing of serious AEs | Oral HealthCare standard.<br>If there are no treatment emergent serious AEs a null listing will be produced, if there are more than 5 treatment emergent SAEs a table will be produced by SOC and PT. |
| 9.4.~~6~~7 | Table of Non Serious treatment emergent AEs by SOC and Preferred Term | To be produced only if there are more than 5 SAEs. |
| 9.4.~~7~~8 | Listing of Incidents | Standard |
| 9.4.~~8~~9 | Listing of Adverse Events – ~~All Subjects~~ Non Randomized Subject | Standard |

Per Protocol population tables will be produced only if a Per Protocol analysis will be performed

| Figure No. | Title | Standard / Template / Changes to Footnotes / Comments |
|---|---|---|
| 9.1.1 | Evaporative (Air) Sensitivity - Schiff Sensitivity Score by Time and Treatment Group - Intent to Treat Population | **NOTE TO PROGRAMMERS:** These figures should be produced in SAS – Appendix 3 |
| 9.1.2 | Evaporative (Air) Sensitivity - Schiff Sensitivity Score by Time and Treatment Group – Per Protocol Population | 9.1.1 |
| 9.2.1 | Tactile Sensitivity - Tactile Threshold (g) by Time and Treatment Group - Intent to Treat Population | **NOTE TO PROGRAMMERS**: These figures should be produced in SAS. – Appendix 3 |
| 9.2.2 | Tactile Sensitivity - Tactile Threshold (g) by Time and Treatment Group – Per Protocol Population | 9.2.1 |

| Listing No. | Title | Standard / Template / Changes to Footnotes / Comments |
|---|---|---|
| 2.1 | Listing of Randomisation Details | Appendix 3 |
| 2.2 | Listing of Oral Soft Tissue Abnormalities | Standard |

# Appendix 3 Templates for Tables, Figures & Listings

## Table Templates

Protocol: 207212 Program Run Date: DDMMMYYY

Table 9.1.1

Subject Disposition

All Screened Subjects (N=xx)

| | Treatment 1<br>N (%) | Treatment 2<br>N (%) | Overall<br>N (%) |
|---|---|---|---|
| Total Subjects Screened | | | xx |
| Subjects Not Randomised | | | xx |
| Did Not Meet Study Criteria | | | xx (xx.x) |
| Adverse Events | | | xx (xx.x) |
| Etc. | | | |
| | | | |
| Subjects Randomised | xx | xx | xx |
| Completed Study | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Did Not Complete Study | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Did Not Meet Study Criteria | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Subjects Not Randomised | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Adverse Events | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Etc. | | | |
| | | | |
| Safety Population | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| ITT Population | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| PP Population | xx (xx.x) | xx (xx.x) | xx (xx.x) |

(Page X of Y)

Program: PPD Source: filename.xpt

**Programming note:** For categories under 'Subjects Not Randomised' percentages will be calculated using the number of 'All Screened Subjects' as the denominator. Percentages under the 'Subjects Randomised' categories will be computed using number of subjects randomised as the denominator.

Protocol: 207212 Program Run Date: DDMMMYYY

Table 9.1.2

Protocol Violations Leading to Exclusion from Per Protocol Analyses

Intent to Treat Population

Study Population: ITT (N=xx)

| | Statistics | Treatment 1 (N = xx) | Treatment 2 (N = xx) | Overall (N = xx) |
|---|---|---|---|---|
| Number of Subjects with at Least One Protocol Violation Affecting Efficacy | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Number of Subjects Excluded from Per Protocol Population | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Protocol Violations Leading to Subject Exclusion*: | | | | |
| Reason 1 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Reason 2 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Etc. | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Protocol Violations Leading to Data Exclusion*: | | | | |
| Day 0 Pre-Treatment | | | | |
| Reason 1 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Reason 2 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Etc. | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Day 0 Post-Treatment | | | | |
| Reason 1 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Reason 2 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Etc. | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |

(Page X of Y)

*Subjects may have more than one associated violation.

Program: PPD Source: filename.xpt

Protocol: 207212

Program Run Date: DDMMMYYY

Table 9.2.2.1

Baseline Characteristics - Stratification Factors

Safety Population

Study Population: Safety (N=xx)

| | Statistics | Treatment 1 (N = xx) | Treatment 2 (N = xx) | Overall (N = xx) |
|---|---|---|---|---|
| Maximum Baseline Schiff Sensitivity Score | | | | |
| 2 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 3 | n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |



Program:PPD

Source: filename.xpt

Protocol: 207212 Program Run Date: DDMMMYYY

Table 9.3.1.1
Summary of Evaporative (Air) Sensitivity - Schiff Sensitivity Score
Intent to Treat Population

Study Population: ITT (N=xx)

| | Statistics | Treatment 1 (N = xx) | Treatment 2 (N = xx) | Overall (N = xx) |
|---|---|---|---|---|
| Baseline (Day 0, Pre-treatment) | n | xx | xx | xx |
| | Missing | xx | xx | xx |
| | Mean | xx.x | xx.x | xx.x |
| | SD | xx.xx | xx.xx | xx.xx |
| | SE | xx.xx | xx.xx | xx.xx |
| | Median | xx.x | xx.x | xx.x |
| | Minimum | xx | xx | xx |
| | Maximum | xx | xx | xx |
| Day 0, Post-Treatment | n | xx | xx | |
| | Missing | xx | xx | |
| | Mean | xx.x | xx.x | |
| | SD | xx.xx | xx.xx | |
| | SE | xx.xx | xx.xx | |
| | Median | xx.x | xx.x | |
| | Minimum | xx | xx | |
| | Maximum | xx | xx | |
| Day 3 | n | xx | xx | |
| | Missing | xx | xx | |
| | Mean | xx.x | xx.x | |
| | SD | xx.xx | xx.xx | |
| | SE | xx.xx | xx.xx | |
| | Median | xx.x | xx.x | |
| | Minimum | xx | xx | |
| | Maximum | xx | xx | |



Baseline = Day 0 Pre-Treatment.
Program: PPD Source: filename.xpt
**Programming Note**: Summaries for the Overall column are displayed only for the baseline data.

Protocol: 207212 Program Run Date: DDMMMYYY

Table 9.3.1.2

Statistical Analysis of Change from Baseline in Evaporative (Air) Sensitivity - Schiff Sensitivity Score

Intent to Treat Population

Study Population: ITT (N=xx)

| | Treatment 1 (N = xx) | | Treatment 2 (N = xx) | |
|---|---|---|---|---|
| | Baseline [1] | Change | Baseline [1] | Change |
| Day 0, Post-Treatment | | | | |
| n | xx | xx | xx | xx |
| Missing | xx | xx | xx | xx |
| Mean | xx.x | xx.x | xx.x | xx.x |
| SD | xx.xx | xx.xx | xx.xx | xx.xx |
| SE | xx.xx | xx.xx | xx.xx | xx.xx |
| Median | xx.x | xx.x | xx.x | xx.x |
| Minimum | xx | xx | xx | xx |
| Maximum | xx | xx | xx | xx |
| Adjusted Mean (SE) [2] | | xx.x (xx.xx) | | xx.x (xx.xx) |
| 95% CI [2] | | (xx.x, xx.x) | | (xx.x, xx.x) |
| P-value [2] | | 0.xxxx | | 0.xxxx |

| Comparison Between Treatments | Difference [2,3] | 95% CI | P-value |
|---|---|---|---|
| Test Dentifrice vs ~~Negative~~ Control Dentifrice | xx.x | (xx.x, xx.x) | 0.xxxx |
| **Supportive Non-Parametric Analysis [4]** | | | 0.xxxx |

Day 3



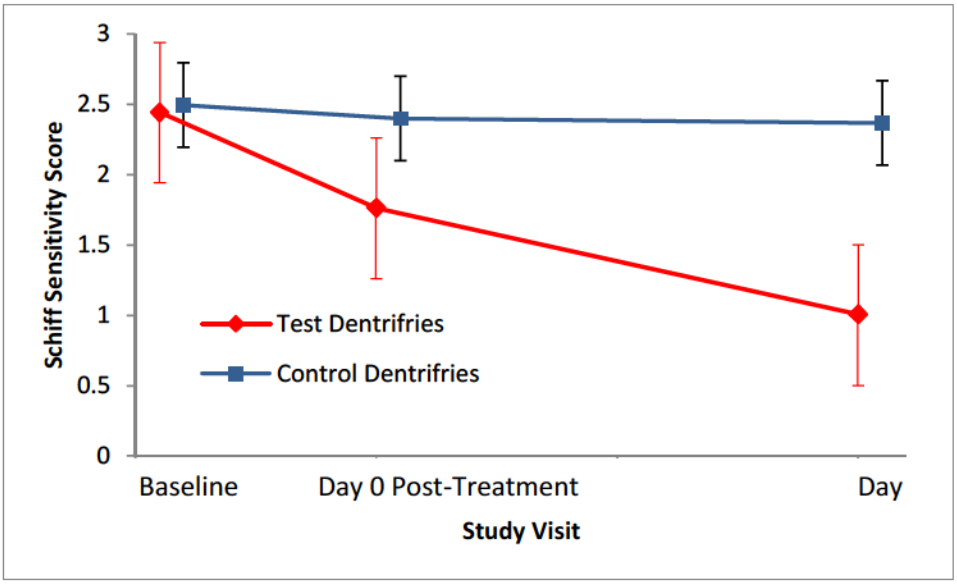
[1] Baseline only includes those subjects who have a corresponding post-baseline assessment. Baseline = Day 0 Pre-Treatment.
[2] From ANCOVA model with change from baseline in Schiff Sensitivity Score as response and treatment as a factor and baseline Schiff sensitivity score as a covariate.
[3] Difference is first named dentifrice minus second named dentifrice such that a negative difference favours first named dentifrice.
**[4] P-value from van Elteren test.**
Program: PPD Source: filename.xpt
**Programming Note:** Table will display statistical results for Day 3 also. The supportive non-parametric results will be included the table only if the ANCOVA assumptions are violated and the non-parametric analysis is carried out. Footnote [4] will be removed if the non-parametric analysis is not being performed.
For Table 9.3.2.2 (and 9.3.2.4) please use the following footnotes:

- [2] From ANCOVA model with change from baseline in Tactile threshold (g) as response and treatment and baseline Schiff strata as factors and baseline Tactile threshold as a covariate.
- [3] Difference is first named dentifrice minus second named dentifrice such that a positive difference favours the first named dentifrice.

# Figure Templates

Protocol: 207212 Program Run Date: DDMMMYYY

Figure 9.1.1
Evaporative (Air) Sensitivity - Schiff Sensitivity Score by Time and Treatment Group
Intent to Treat Population

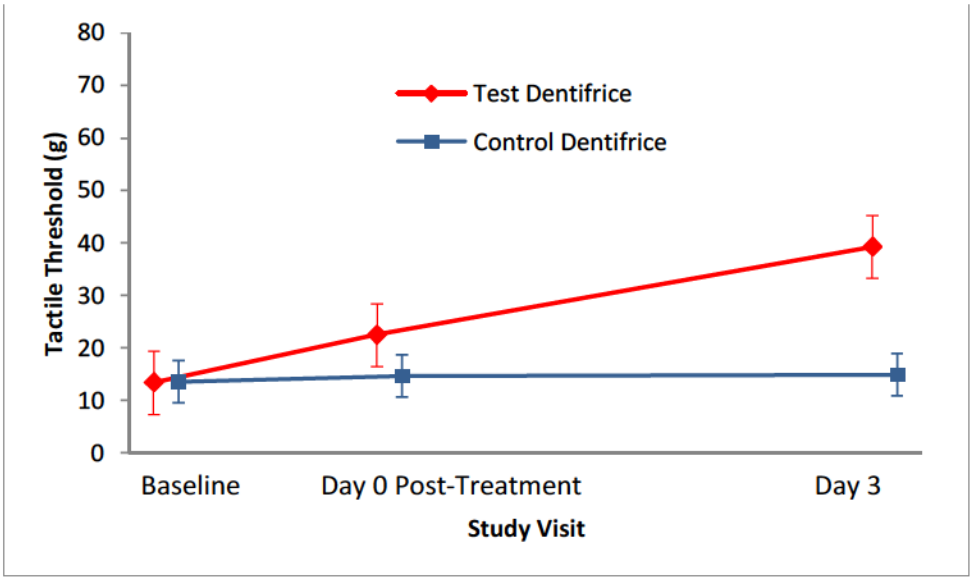



Raw Means ± SEs.
Baseline = Day 0, Pre-Treatment.

Programming note 1) Please make sure that Y-axis scale should be 0-3

Protocol: 207212 Program Run Date: DDMMMYYY

Figure 9.2.1
Tactile Sensitivity - Tactile Threshold (g) by Time and Treatment Group
Intent to Treat Population




Raw Means ± SEs
Baseline = Day 0, Pre-Treatment.

Programming note 1) Please make sure that Y-axis scale should be 0-80 g

# Listing Templates

Protocol: 207212 Program Run Date: DDMMMYYY

Listing 2.1
Listing of Randomisation Details
All Randomised Subjects

| Subject Number | Randomisation Number | Randomised Treatment | Received Treatment |
|---|---|---|---|
| 01Sxxxx | 10xx | Treatment x | Treatment x |
| Etc. | | | |

(Page X of Y)

Program: PPD Source: filename.xpt

**Programming Note**: Please add treatment footnotes.

# SIGNATURE PAGE

## SAP 207212

| Date | Signed By |
|---|---|
| 25-Apr-2017 02:50:14 | PPD |
| **Justification** | Biostatistics Approval |

| Date | Signed By |
|---|---|
| 26-Apr-2017 05:42:16 | PPD |
| **Justification** | Approved |

| Date | Signed By |
|---|---|
| | |
| **Justification** | |

| Date | Signed By |
|---|---|
| | |
| **Justification** | |

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