STATISTICAL REPORTING AND ANALYSIS PLAN

A Clinical Study Investigating the Gingivitis Efficacy of a Stannous Fluoride Dentifrice in a Chinese Population

Protocol Number: 207014

Phase: NA

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Amendment 1	19-Jan 2018	Separate repeatability population into two, repeatability population for MGI and repeatability population for PI
Original Analysis Plan	24-Oct-2017	Not applicable (N/A)

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Glossary

AE	Adverse Event
ANCOVA	Analysis of covariance
BI	Bleeding Index
BDRM	Blind Data Review Meeting
CI	Confidence Interval
ITT	Intent-to-Treat
κ	Kappa coefficient
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Manufacture Formulation Code
MGI	Modified Gingival Index
MLSI	MacPherson modification of the Lobene stain index
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PI	Plaque Index
PP	Per Protocol
RAP	Statistical Reporting and Analysis Plan
RLR	Review Listing Requirement
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyzes and outputs to be included in the Clinical Study Report for Protocol 207014.

1 Summary of Key Protocol Information

This will be a single-centre, examiner-blind, randomized, stratified, two-treatment, parallel group clinical study in healthy adult volunteers with moderate gingivitis. Treatment effect will be determined by evaluating the efficacy, in a Chinese population, of a dentifrice containing 0.454% w/w stannous fluoride to control gingivitis and supra-gingival plaque following 6 and 12 weeks twice daily brushing, compared to a fluoride control dentifrice. During the 12 week treatment period, subjects will brush with their allocated study product twice daily.

General safety and tolerability will be assessed based on the frequency and severity of Adverse Events (AEs).

1.1 Study Design

This clinical study follows the study schedule below.

Procedure/Assessment	**Visit 1**	**1 – 28 days between Visit 1 and Visit 2[5]**	**Visit 2 Week 0 (Day 0)[1]**	**Visit 3 Week 6 (Day 42+/-3)[1]**	**Visit 4 Week 12 (Day 84+/-3)[1]**
	Screening		**Baseline[1]**	**Week 6**	**Week 12**
Informed consent	X				
Demographics	X				
Medical History[2]	X				
Current / Concomitant medication	X		X	X	X
Urine pregnancy test[6]			X	X	X
Oral soft and hard tissue (OST/OHT) examination[3]	X				
Gross gingival assessment	X				
Inclusion/ Exclusion Criteria	X		X		
Subject Eligibility/ Continuance	X		X	X	X
Full OST examination			X	X	X
Modified Gingival Index (MGI),			X	X	X

Bleeding Index (BI) & Plaque Index (PI; disclosing)					
Stratification/ randomization			X		
Sub- & supra-gingival prophylaxis and flossing (with second clinician check after disclosing & residual plaque removal, if applicable i.e. confirmed plaque score of zero)			X		
Dispense study dentifrice, toothbrush, study instructions, diary & timer[4]			X	X	
Oral hygiene instruction review/ compliance checks including diary completion review			X	X	X
Supervised subject brushing at site			X	X	
Collect study dentifrice, toothbrush & diary				X	X
Compliance checks including diary review				X	X
Optional dental prophylaxis					X
Adverse Events			X	X	X
Study Conclusion					X

[1.] Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, -2hr) immediately prior to the assessment visits (Visits 2, 3 & 4).

[2.] Including smoking status.

[3.] In relation to the general dentition exclusion criteria.

[4.] Timer only dispensed once, at visit 2 only.

[5.] Subjects will be instructed to brush using their normal toothpaste and following their normal routine between screening and baseline visits.

[6.] Female subjects of child bearing potential only.

1.2 Study Objectives

Objectives	**Endpoints**
Primary	
To compare gingivitis, as measured by BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12	Mean BI at 12 weeks.

weeks twice daily use.	
Secondary	
To compare gingivitis, as measured by the number of bleeding sites using BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Number of bleeding sites at 12 weeks.
To compare gingivitis, as measured by MGI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean MGI at 12 weeks.
To compare dental plaque scores (PI; overall and interproximal) following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice to a fluoride control dentifrice after 12 weeks twice daily use.	Mean PI (overall and interproximal) at 12 weeks.
Other	
To compare gingivitis, as measured by BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean BI at 6 weeks.
To compare gingivitis, as measured by the number of bleeding sites using BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Number of bleeding sites at 6 weeks.
To compare gingivitis, as measured by MGI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean MGI at 6 weeks.
To compare dental plaque scores (PI; overall and interproximal) following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice to a fluoride control dentifrice after 12 weeks twice daily use.	Mean PI (overall and interproximal) at 6 weeks.
To evaluate and compare MGI and BI in low (<2.00) and high (>2.00) MGI subgroups	Mean MGI & BI at 6 & 12 weeks (in subgroups).

following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice after 6 and 12 weeks twice daily use.	
To evaluate examiner MGI & PI measurement reproducibility for a random subset of the study population.	Kappa coefficient for MGI & PI

1.3 Treatments

	Test Product	Reference Product
Product Name	Experimental dentifrice containing 0.454% w/w stannous fluoride & 0.0721% w/w sodium fluoride (1450ppm fluoride in total)	Regular fluoride dentifrice containing 0.14% w/w sodium monofluorophosphate – Colgate® Triple Protection Dentifrice (1400ppm fluoride as sodium monofluorophosphate; SMFP)
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available (Chinese marketplace)
Dose	Full ribbon of dentifrice to cover the head of the study toothbrush provided	Full ribbon of dentifrice to cover the head of the study toothbrush provided

1.4 Sample Size Calculation

A sufficient number of subjects will be screened to randomize at least 120 subjects to ensure approximately 112 evaluable subjects complete the entire study (approximately 56 per treatment group).

With 56 subjects per treatment group, the study has at least 80% power to detect a treatment difference of 0.08 in bleeding index over a period of 12 weeks treatment. The standard deviation used in calculation is 0.14. The difference of 0.08 represents more than 15% improvement in the test dentifrice compared to the fluoride control dentifrice reference product. CCI [redacted]

2 Planned Analyzes

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyzes

The final planned primary analyzes will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for Data Analyzes and Data Handling Conventions

3.1 Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value.

3.2 Subgroups/Stratifications

There will be eight strata according to gender, smoking status and baseline mean whole mouth MGI score (Low≤2.0/High>2.0):

- Stratum 1: Male, Smoker, Baseline MGI <=2.00
- Stratum 2: Male, Smoker, Baseline MGI >2.00
- Stratum 3: Male, Non-smoker, Baseline MGI <=2.00
- Stratum 4: Male, Non-smoker, Baseline MGI >2.00
- Stratum 5: Female, Smoker, Baseline MGI <=2.00
- Stratum 6: Female, Smoker, Baseline MGI >2.00
- Stratum 7: Female, Non-smoker, Baseline MGI <=2.00
- Stratum 8: Female, Non-smoker, Baseline MGI >2.00.

3.3 Timepoints and Visit Windows

Deviations from the scheduled assessment times should be avoided or kept to a minimum as possible. Any deviation will be noted in blind data review meeting (BDRM) before database lock and subjects may be considered for exclusion from the per protocol population.

The following are the assessment time windows.

Visit	Time window
Visit 2	1-28 days after Visit 1. Visit 2 is baseline and counted as Day 0.
Visit 3	42 ± 3 Day
Visit 4	84 ± 3 Days

4 Data Analysis

Data analysis will be performed by Syneos Health. Prior to database closure a Blind Data Review Meeting (BDRM) will be conducted in which various aspects of the trial will be discussed and agreed. The statistical analysis software used will be SAS version 9.4 or higher.

Except as described below, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

Unless otherwise specified, Tables described in this section will be produced for all randomized subjects.

4.1.1 Subject Disposition

Screen failures will be defined as subjects who consent to participate in the study but are never subsequently randomized. A summary will be provided of the number of subjects screened and the number of screen failures.

Subject disposition will be summarised as the number and percentage of subjects (out of the number of randomized subjects) who complete the study, with the number who discontinue broken down by reason for discontinuation (Table 14.1.1). The table will also summarise the number and percent of subjects assigned to each analysis population (defined in Section 2.1.3). The summary will be presented by treatment and overall.

Subject disposition will be listed for randomized subjects (Listing 16.2.1.1) and non-randomized subjects (Listing 16.2.1.2) separately.

4.1.2 Protocol Deviations

Protocol violations will be tracked by the study team throughout the conduct of the study. All violations will be reviewed prior to unblinding and closure of the database to ensure all important violations are captured and categorized.

Major violations identified as liable to influence the efficacy outcome will include but not necessarily limited to those listed below:

- Major violation of inclusion/exclusion criteria
- Significant non-compliance with assigned product regimen (e.g., under- or over- use)
- Significant non-compliance with the visit schedule
- Use of prohibited treatment or medication before or during the study

Further violations liable to influence the efficacy outcome will be given in the "Review Listing Requirement (RLR)" document and major violations will be identified in blinded data review stage. The number and percentage of subjects with any major protocol deviations and with each type of major protocol deviations will be presented by treatment (Table 14.1.2) and listed (Listing 16.2.2.1). Any minor protocol deviations will be listed similarly (Listing 16.2.2.2).

4.1.3 Analysis Populations

Six analysis populations are defined.

Population	Definition / Criteria	Analyzes Evaluated
All Screened Subjects	All subjects who are screened	Disposition
Randomized	All subjects who are randomized and may or may not receive the application of the study products.	Protocol deviations
Safety	Safety population includes all subjects who are randomized, administered a study product at least once.	Safety analysis
Intent-to-Treat (ITT)	The 'Intent to treat' (ITT) population includes all subjects who are randomized, administered the study product at least once and provide at least one post-baseline assessment of efficacy.	Efficacy analysis
Per-Protocol (PP)	The Per Protocol (PP) population is a subset of the ITT population which excludes subjects with a protocol violation that is deemed to affect efficacy for all efficacy	Efficacy analyzes for BI score and number of bleeding sites and MGI score.

Population	Definition / Criteria	Analyzes Evaluated
	assessments. Subjects with a protocol violation that is deemed to affect efficacy for only some (but not all) of the efficacy assessments will be part of the PP population. PP analyzes will use only the data considered unaffected by protocol violations.	
Repeatability population for modified gingival index (MGI) assessment	All subjects who have an initial and a repeat assessment on MGI.	Repeatability analysis
Repeatability population for plaque index (PI) assessment	All subjects who have an initial and a repeat assessment on PI.	Repeatability analysis

The primary population for assessment of efficacy will be the ITT population. A PP analysis will be performed on the primary variable only if more than 10% of the subjects in the ITT population are excluded from the PP population.

The numbers of subjects excluded from each population broken down by the reason for exclusion will be presented (Table 14.1.2). Subjects excluded from any of the analysis populations will be listed (Listing 16.2.3.1).

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the ITT.

4.2.1 Demographic Characteristics

Categorical demographic variables include year of birth, gender and race. These variables will be summarised by the number and percentage of subjects with each relevant characteristic (Table 14.1.3.1 for the Safety population, Table 14.1.3.2 for the ITT population and Table 14.1.3.3 for the PP population if PP analysis is performed). Age will be summarised by the mean, standard deviation (SD), median, minimum and maximum values. Baseline stratification will also be summarised by the number and percentage of subjects in each stratum. All summaries will be presented by treatment, and overall. All demographic information will be listed for randomized subjects (Listing 16.2.4.1).

4.2.2 General Medical History

Medical history data will be listed in Listing 16.2.4.2 with start date and end date or ongoing at the start of study drug. A data listing will also be produced for evaluation of protocol violations at the blinded data review stage.

4.3 Treatments (Study Product, Rescue Medication, other Concomitant Therapies, Compliance)

4.3.1 Study Product Compliance and Exposure

Brushing compliance (using study products twice daily) will be listed and checked at the blinded data review stage for evaluation of protocol deviations.

4.3.2 Prior and Concomitant Medication

Prior and concomitant medication/non-drug treatments data will be listed (Listing 16.2.5.1 for prior medication, Listing 16.2.5.2 for concomitant medication/non-drug treatments). Prior medications are defined as those stopped before the first administration of the study products. Concomitant medications are defined as those ongoing or started on or after the first administration of the study products.

4.4 Analysis of Efficacy

Statistical testing of all endpoints in this study will be conducted at unadjusted two-sided significant level of 0.05. The null and alternative hypotheses are

- H_0: there is no difference between treatment groups;
- H_a: there is a difference between treatment groups.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The bleeding index (BI) will be assessed on the facial and lingual gingival surfaces of each scorable tooth (7-7 in each arch). Three scores (according to the scale below) should be recorded bucally/labially (distal, body, mesial sites) and three scores lingually/palatally. All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed. The BI scoring system will be as follows:

0 = no bleeding after 30 seconds

1 = bleeding upon probing after 30 seconds

2 = immediate bleeding observed.

The study examiner will assess and record BI for each tooth site. The BI score for each subject will be calculated as the mean BI over all tooth sites. The primary endpoint is the BI score at Week 12.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

Summary statistics including mean, SD, SE, median, minimum, maximum will be provided by visit and randomized treatment group (Table 14.2.1.2). ANCOVA model will be applied to Week 12 BI score with treatment group, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values (Table 14.2.1.1).

4.4.1.3 Supportive Analyzes

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated through residual plots. If violated, data transformation or a nonparametric method (van Elteren test, adjusting for gender, smoking status and baseline MGI stratification) will be used. If the violation is caused by extreme values, a sensitivity analysis will be conducted by removing the extreme values. Nonparametric analysis, if performed, will be on change from baseline (as nonparametric analysis cannot incorporate continuous covariate). If nonparametric van Elteren test is performed and the inferences on treatment comparisons are similar to that of ANCOVA, both sets of results will be reported and the emphasis will be made on the ANCOVA results. Otherwise, nonparametric results will be used to draw conclusions.

4.4.2 Secondary Efficacy Variables

Secondary efficacy variables of the study are listed below.

4.4.2.1 Number of bleeding sites at Week 12

Number of bleeding sites will be calculated as the number of sites with a BI of 1 or 2. Summary statistics for number of bleeding sites by visit and treatment will be provided (Table 14.2.2.2).

4.4.2.2 MGI score at Week 12

The modified gingival index (MGI) will be assessed on the facial and lingual surfaces of each scorable tooth (7-7 in each arch). Two scores will be recorded bucally/labially (papilla and margin) and two scores lingually/palatally (papilla and margin). The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity. The MGI scoring system will be as follows:

0 = absence of inflammation

1 = mild inflammation; slight change in color, little change in color; little change in texture of any portion of the marginal or papillary gingival unit.

2 = mild inflammation; criteria as above but involving the entire marginal or papillar gingival unit.

3 = moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit.

4 = severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

The study examiner will assess and record the modified MGI for each site. MGI score of a subject will be calculated as the mean MGI over all tooth sites. Summary statistics for MGI score by visit and treatment will be provided (Table 14.2.3.2).

4.4.2.3 Overall plaque score and interproximal plaque score at Week 12

The plaque index (PI) will be assessed on the facial and lingual surfaces of each scorable tooth (7-7 in each arch). Three scores should be recorded bucally/ labially (distal, body, mesial sites) and three scores lingually/ palatally (distal, body, mesial sites). Disclosed plaque will be scored as follows:
0 = No plaque
1 = Slight flecks of plaque at the cervical margin of the tooth
2 = A thin continuous band of plaque (1mm or smaller) at the cervical margin of the tooth
3 = A band of plaque wider than 1mm but covering less than 1/3 of the area
4 = Plaque covering at least 1/3 but less than 2/3 of the area
5 = Plaque covering 2/3 or more of the crown of the tooth.
The study examiner will assess and record the plaque index for each site. Overall plaque score and interproximal plaque score will be calculated as the mean PI over all tooth sites and mean PI over interproximal sites (distal and mesial) respectively. Summary statistics for overall and interproximal plaque score by visit and treatment will be provided (Table 14.2.4.2, Table 14.2.5.2).

4.4.3 Exploratory Efficacy Variables

Exploratory variables of the study are listed below.

4.4.3.1 BI score at Week 6

BI score will be calculated in the same way as stated in Section 4.4.1.1.

4.4.3.2 Number of bleeding sites at Week 6

Number of bleeding sites will be calculated in the same way as stated in Section 4.4.2.1.

4.4.3.3 MGI score at Week 6

MGI score will be calculated in the same way as stated in Section 4.4.2.2.

4.4.3.4 Overall plaque score and interproximal plaque score at Week 6

Overall plaque score and interproximal plaque score will be calculated in the same way as stated in Section 4.4.2.3.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

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

4.5 Analysis of Secondary Objectives

Number of bleeding sites will be analyzed using ANCOVA model with treatment, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95% CI and P-values (Table 14.2.2.1).

MGI score will be analyzed using ANCOVA model with treatment, gender, smoking status as factors and baseline score as covariate. As baseline MGI is included as covariate, baseline MGI stratification will not be included in the model. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values (Table 14.2.3.1).

Overall plaque score and interproximal plaque score will be analyzed using the same ANCOVA model with treatment, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment differences will be provided together with 95%CIs and P-values (Table 14.2.4.1, Table 14.2.5.1).

4.6 Analysis of Exploratory Objectives

All exploratory variables will be summarized by visit and treatment. The same ANCOVA models as in Section 4.4.1.2 and Section 4.5 will be applied to corresponding variables of Week 6.

4.7 Analysis of Safety

4.7.1 Adverse Events and Serious Adverse Events

All safety data will be reported for the Safety population as per actual treatment received. All subjects screened will be included in the list of AEs.

AE will be regarded as treatment emergent if they occur on or after the start date and time of the first treatment usage (as determined by start date and time from the EXPOSURE/dispensing panel; if this date is missing a suitable alternative will be used eg date and time of randomization). All other AEs prior to this will be considered non-treatment emergent.

All AEs will be reviewed by Clinical Research prior to database freeze 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.

The following summary tables and listings will be presented by treatment group.

- Table of treatment emergent AEs by SOC and Preferred Term (Table 14.3.1.1)
- Table of treatment emergent AEs by Oral/Non-Oral and Preferred Term (Table 14.3.1.2)
- Table of Treatment emergent treatment related AEs by Oral/Non-Oral and Preferred Term (Table 14.3.1.3)
- Listing of all AEs (including all subjects: Listing 16.2.7.1 for all randomized subjects; Listing 16.2.7.2 for non-randomized subjects)
- Listing of death (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of treatment emergent AEs leading to withdrawal (Listing 14.3.2.3)
- Listing of treatment emergent AEs classified as oral (Listing 14.3.2.4)

In the event that there is nothing to report a null listing will be produced.

4.7.2 Other Safety Variables

All incidents captured in the study will be listed (Listing 16.2.7.3). A null listing will be provided if there is no incident reported.

4.8 Analysis of Other Variables

A number of subjects will have repeated plaque index (PI) or gingivitis index (MGI) assessments conducted by the examiner. The repeat assessments will be compared to the original assessments separately for PI and MGI. The repeat assessments will not be used in any efficacy analysis. The first and second assessments on each tooth at a given visit will be cross-tabulated and a weighted Kappa coefficient (κ) will be calculated, along with the 95% confidence interval, to assess the intra-examiner repeatability (Table 14.2.6 and Table 14.2.7). Repeatability will be deemed

- Excellent, if $\kappa > 0.75$
- Fair to good, if $0.4 \leq \kappa \geq 0.75$
- Poor if $\kappa < 0.4$

All subjects who have repeatability data will be included in this analysis. SAS PROC FREQ will be used for this analysis with codes similar to the following:

```
PROC FREQ DATA = INTRA;
TABLES R1*R2/AGREE (wt = fc);
RUN;
```

Where R1 = first assessment score by an assessor, R2 = second (repeat) assessment score by an assessor.

5 Changes to the Protocol Defined Statistical Analysis Plan

There is no change to the planned statistical analysis specified in the protocol version 5.0 [(Dated: 05/Apr/2017)].

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Attachment 1: List of Data Displays

Study XXXX_List of Outputs.xlsx

Attachment 2: Template for Tables, Figures and Listings

This is a guideline which will give the guidance of treatment labels that will be used for the table header and in the figures, listings and in the footnotes.

The treatment labels for the column heading will be as follow:

- Test Dentifrice
- Reference Dentifrice

Add following footnote to all TLFs.
Test Dentifrice: Experimental dentifrice containing 0.454% w/w stannous fluoride & 0.0721% w/w sodium fluoride
Reference Dentifrice: Regular fluoride dentifrice containing 0.14% w/w sodium monofluorophosphate.

Protocol 207014 Program Run Date:xxxx

Table 14.1.1
Subject Disposition
All Screened Subjects

All Screened Subjects (N=xxx)

	Test Dentifrice N (%)	Reference Dentifrice N (%)	Overall N (%)
TOTAL SUBJECTS SCREENED			xxx
SUBJECTS NOT RANDOMIZED			xxx (xx.x)
DID NOT MEET STUDY CRITERIA			xxx (xx.x)
ADVERSE EVENT			Xxx (xx.x)
LOST TO FOLLOW UP			xxx (xx.x)
PROTOCOL VIOLATION			Xxx (xx.x)
WITHDRAWAL OF CONSENT			Xxx (xx.x)
OTHER			Xxx (xx.x)
SUBJECTS RANDOMIZED	xxx	xxx	xxx
COMPLETED STUDY	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DID NOT COMPLETE STUDY	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DID NOT MEET STUDY CRITERIA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ADVERSE EVENT	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
LOST TO FOLLOW-UP	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PROTOCOL VIOLATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WITHDRAWAL OF CONSENT	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

	Test Dentifrice N (%)	Reference Dentifrice N (%)	Overall N (%)
OTHER	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
SAFETY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ITT POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PP POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Percentages for non-randomized category are based on number of screened subjects; percentages for randomized category are based on number of randomized subjects

Protocol 207014 Program Run Date:xxxx

Table 14.1.2
Analysis Population
All Randomized Subjects

Randomized Population (N=xxx)

	Test Dentifrice N (%)	Reference Dentifrice N (%)	Overall N (%)
SUBJECTS EXCLUDED FROM SAFETY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			
SUBJECTS EXCLUDED FROM ITT POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			
SUBJECTS WITH AT LEAST ONE DATA POINT EXCLUDED FROM PP ANALYSIS	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
SUBJECTS COMPLETELY EXCLUDED FROM PP POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PROTOCOL DEVIAIONS LEADING TO EXCLUSION FROM PP			
ALL VISITS			

	Test Dentifrice N (%)	Reference Dentifrice N (%)	Overall N (%)
DEVIATION 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			
WEEK2			
DEVIATION 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			
WEEK4			
DEVIATION 5	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 6	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			

Protocol 207014 Program Run Date:xxxx

Table 14.1.3.1
Subject Demographics and Baseline Characteristics
Safety Population

Safety Population (N=XX)

	Test Dentifrice (N=XX)	Reference Dentifrice (N=XX)	Overall (N=XX)
SEX n (%)			
MALE	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEMALE	xx (xx.x)	xx (xx.x)	xx (xx.x)
RACE n (%)			
ASIAN	xx (xx.x)	xx (xx.x)	xx (xx.x)
BLACK or AFRICAN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AMERICAN INDIAN OR ALASKA NATIVE	xx (xx.x)	xx (xx.x)	xx (xx.x)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	xx (xx.x)	xx (xx.x)	xx (xx.x)
WHITE	xx (xx.x)	xx (xx.x)	xx (xx.x)
MULTIPLE	xx (xx.x)	xx (xx.x)	xx (xx.x)
AGE (YEARS)			
n	XX	XX	XX
MEAN	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX
MEDIAN	XX.X	XX.X	XX.X
MINIMUM	XX	XX	XX

	Test Dentifrice (N=XX)	Reference Dentifrice (N=XX)	Overall (N=XX)
MAXIMUM	XX	XX	XX
STRATIFICATION n, (%)			
MALE, SMOKER, BASELINE MGI ≤ 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
MALE, SMOKER, BASELINE MGI > 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
MALE, NON-SMOKER, BASELINE MGI ≤ 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
MALE, NON-SMOKER, BASELINE MGI > 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEMALE, SMOKER, BASELINE MGI ≤ 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEMALE, SMOKER, BASELINE MGI > 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEMALE, NON-SMOKER, BASELINE MGI ≤ 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEMALE, NON-SMOKER, BASELINE MGI > 2.0	xx (xx.x)	xx (xx.x)	xx (xx.x)

Protocol 207014 Program Run Date:xxxx

Table 14.2.1.1
Statistical Analysis of Bleeding Index Score
Intent-to-Treat Population

Intent-to-Treat Population (N=XX)

Visit		Test Dentifrice (N=XX)	Reference Dentifrice (N=XX)
Week 6	LSmean (SE) [1]	x.xx (x.xxx)	x.xx (x.xxx)

Comparison [1][2]	Difference	95% CI	P-value	%Diff[3]
Test Dentifrice vs Reference Dentifrice	x.xx	(x.xx, x.xx)	0.xxxx	xx.x

Week 12 Same as above

[1] From ANCOVA with treatment, gender, smoking status and baseline MGI stratification as factors and baseline as covariate.

[2] Difference is the first named treatment minus second named treatment such that a negative difference favors the first named treatment.

[3] Percentage difference calculated as (treatment difference/adjusted mean of reference treatment)*100%.

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Programming Note: For Table 14.2.3.2, please update footnote [1] as

[1] From ANCOVA with treatment, gender, smoking status as factors and baseline as covariate.

Protocol 207014 Program Run Date:xxxx

Table 14.2.1.2
Summary of Bleeding Index Score
Intent-to-Treat Population

Intent-to-Treat Population (N=XX)

Visit		Test Dentifrice (N=XX)	Reference Dentifrice (N=XX)	Overall (N=XXX)
Baseline	n	Xx	xx	xx
	MEAN	x.xx	x.xx	x.xx
	SD	x.xxx	x.xxx	x.xxx
	SE	x.xxx	x.xxx	x.xxx
	MEDIAN	x.xx	x.xx	x.xx
	MINIMUM	X.xx	x.xx	x.xx
	MaxIMUM	X.xx	x.xx	x.xx
Week 6	n	Xx	xx	
	MEAN	x.xx	x.xx	
	SD	x.xxx	x.xxx	
	SE	x.xxx	x.xxx	
	MEDIAN	x.x	x.x	
	MINIMUM	X.x	x.x	
	MAXIMUM	X.x	x.x	
Week 12	Same as above			

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Table 14.2.6
Repeatability for Modified Gingival Index
Repeatability Population

Repeatability Population (N=XX)

Initial	Repeated	Missing	0	1	2	3	4
Missing		**xx**	**xx**	**xx**	**xx**	**xx**	**xx**
0		xx	xx	xx	xx	xx	xx
1		xx	xx	xx	xx	xx	xx
2		xx	xx	xx	xx	xx	xx
3		xx	xx	xx	xx	xx	xx
4		xx	xx	xx	xx	xx	xx
Kappa	0.xx						
95% CI	(0.xx, 0.xx)						

MGI Score
0: Absence of inflammation; 1: Mild inflammation; slight change in color, little change in color, little change in texture of any portion of marginal or papillary gingival unit; 2: Mild inflammation; criteria as above but involving the entire marginal or papillar gingival unit; 3: Moderate inflammation; glazing,redness,edema and/or hypertrophy of marginal or papillary gingival unit; 4: Severe inflammation; marked redness,edema and/or hypertrophy of marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

PPD

Programming Note: For Table 14.2.5.2, use PI score descriptions in footnote.

Protocol 207014 Program Run Date:xxxx

Table 14.3.1.1
Treatment Emergent Adverse Event by System Organ Class and Preferred Term
Safety Population

Safety Population (N=xx)

System Organ Class Preferred Term	Test Dentifrice (N=XX)		Reference Dentifrice (N=xx)		Overall (N=xx)	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
NUMBER OF SUBJECTS WITH AT LEAST ONE TEAE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
NUMBER OF SUBJECTS WITH NO TEAE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ERYTHEMA	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DERMATITIS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
GASTROINTESTINAL SYSTEM	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ABDOMINAL PAIN	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DRY MOUTH	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
VOMITTING	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Etc.						

n (%) = Number (percent) of subjects
nAE = Number of adverse events.

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Note to Programmer: For Table 14.3.1.2, change 'System Organ Class' to 'Oral/Non-Oral'

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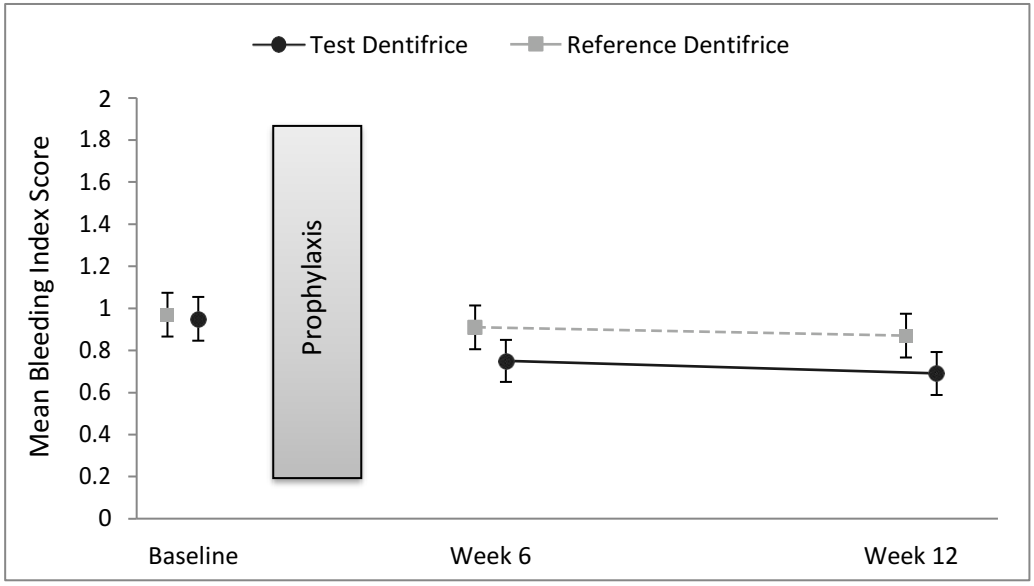
Figure 14.2.1
Mean Bleeding Index Score over Time
Intent-to-Treat Population

Intent-to-Treat Population (N=XX)



Mean and SE are plotted from summary statistics in T 14.2.1.2

PPD

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Listing 16.1.7
Randomization Information
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Stratum 1: MALE, Smoker, BASELINE MGI ≤ 2.0

Subject Number	Age/Sex/ Race [1]	Randomization Number	Treatment Randomized	Actual Treatment Received	Date of Randomization
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple

Protocol 207014 Program Run Date:xxxx

Listing 16.2.1.1
Subject Disposition
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject	Age/Sex/ Race [1]	Screening Date	Treatment Start Date and Time	Date of Completion or Withdrawal	Duration of Treatment (Days)	Completed	Primary Reason for Withdrawal	Further Details[2]
PPD								

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Further details of reasons for withdrawal.

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Listing 16.2.1.2
Subject Disposition
Non-Randomized Subjects

Study Population: Non-Randomized Subjects (N=XX)

Subject Number	Age/Sex/ Race [1]	Screening Date	Reason for Screen Failure	Further Details[2]
PPD				

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Further details of reasons for screen failure.

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Listing 16.2.2.1
Important and Major Protocol Deviations
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject	Sex/Age/ Race [1]	Week(s) Excluded from PP Population	Deviation Reason
PPD			

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

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Listing 16.2.2.2
Minor Protocol Deviations
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/Race[1]	Visit	Deviation Sequence	Protocol Deviation
PPD				

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

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Listing 16.2.3.1
Exclusion from Analysis Populations
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/Race[1]	Treatment Start Date and Time	Randomized Population	Safety Population	ITT Population	PP population
PPD						

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

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Programming Note for Listing 16.2.3: This listing is based on population definition document.

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Listing 16.2.4.1
Demographic Characteristics
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age (years)	Sex	Race	Stratification
PPD				

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Listing 16.2.4.2
Medical History and Current Medical Conditions
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject	Age/Sex/Race [1]	Any Medical History?	Medical Condition	Start Date	Ongoing?	End Date
PPD						

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

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Listing 16.2.5.2
Concomitant Medications and Significant Non-drug Therapies Taken During Treatment
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/Race[1]	Sequence Number	Treatment or Drug Synonym	Reason for Treatment	Frequency	Start Date (Study Day[2])	End Date/Ongoing
PPD							

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Study day relative to the date of Randomization

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Listing 16.2.6.1
Bleeding Index
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/Race[1]	Visit	Tooth Number (universal/FDI)	Surface	Site	Index
PPD						

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

PPD

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Listing 16.2.6.4
Efficacy Endpoints
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/Race[1]	Visit	BI Score[2]	Number of Bleeding Sites[3]	MGI Score[4]	Overall PI Score[5]	Interproximal PI Score[6]
PPD							

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] BI score is the average bleeding index over all tooth sites.
[3] Number of the bleeding sites is the number of sites with bleeding index of 1 or 2.
[4] MGI score is the average modified gingival index over all tooth sites.
[5] Overall PI score is the average plaque index over all tooth sites.
[6] Interproximal PI score is the average plaque index over all interproximal tooth sites.

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Listing 16.2.7.1
All Adverse Events
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/ Race[1]	Adverse Event (Preferred Term) [System Organ Class]	Start Date /Study Day[2]	Start Time	End Date	End Time	Frequency /Intensity [3]	Related to Study Product?	Action Taken re Study Product	Outcome	Serious?	Withdrew? [4]
PPD												

@@ Adverse Events with verbatim text ending in this are designated as Oral AEs.
[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H =Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Study day is the day relative to start of treatment, day 1 being the day of first treatment.
[3] INT = Intermittent and SGLE = Single.
[4] Did subject withdraw from study as a result of this adverse event?

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Programming Note for Listing 16.2.7.2:

- *Repeat the same layout for listing 16.2.7.2*

- *Population should be used 'Non randomized Subjects'*
- *The fourth column should be only 'Start Date'*
- *Add footnote 'Only SAEs are collected for non randomized subjects'*
- *Delete the footnote related to study day and adjust the numbers accordingly.*

Protocol 207014 Program Run Date:xxxx

Listing 16.2.7.3
All Incidents
All Randomized Subjects

Study Population: All Randomized Subjects (N=XX)
Treatment Group: Test Dentifrice

Subject Number	Age/Sex/Race[1]	Incident
PPD		

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H =Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.