ST266-PERIO-201

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TREATMENT REGIMEN OF ST266 IN SUBJECTS WITH MODERATE TO SEVERE PERIODONTITIS

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STATISTICAL ANALYSIS PLAN
02 October 2017
VERSION 4.0

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TREATMENT REGIMEN OF ST266 IN SUBJECTS WITH MODERATE TO SEVERE PERIODONTITIS

PROTOCOL NUMBER ST266-PERIO-201

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
0.1	08 August 2016	Original Version
0.2	08 November 2016	Updated per sponsor comments
0.3	26 December 2016	Updated per sponsor comments
0.4	09 January 2016	Updated per sponsor comments. Includes options for managing the analysis of rescue therapy.
0.5	31 January 2017	Updated per teleconference with team on 26Jan17
0.6	10 February 2017	Updated per teleconference with team on 03Feb17 and continuing discussion among statisticians from Forsyth and Rho and the team at Stemnion/Noveome
1.0	20 March 2017	Finalize per phone call on 2/28/2017
2.0	05 April 2017	Updated primary endpoint analysis to be only on tooth-sites with baseline PD >=6mm. Re-organization of endpoints into secondary versus exploratory analyses
3.0	10 April 2017	Updated missing data imputation section for clarity and method
3.1	14 September 2017	Updated the SAP to fully characterize the statistical model. Added site and smoker status as covariates in the primary analysis. Changed the Primary Endpoint from change from baseline PD at 90 days to the change from baseline PD at 270 days. Removed Amended Per Protocol (APP) population
3.2	29 September 2017	Added smoking status and treatment group in model as an interaction term. Added exploratory endpoints % of patients

		with pockets a) < 5mm, b) decreasing by 2 mm or more that at baseline were ≥5mm, and c) 75% of pockets < 5 mm that at baseline were ≥5mm
4.0	02 October 2017	Final

APPROVALS

Approved: _____ Date: Oct 9, 2017

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On behalf of Noveome

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AAP	American Academy of Periodontists
AE	Adverse event
AMP	Amnion-derived multi-potent progenitor cells
BOP	Bleeding on probing
CAL	Clinical attachment level
CEJ	Cemento-enamel junction
eCRF	Electronic case report form
FDA	Food and Drug Administration
FMPI	Full-mouth plaque index
GCF	Gingival crevicular fluid
GCP	Good Clinical Practice
GEE	Generalized estimating equation
HbA1c	Glycated hemoglobin
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IL	Interleukin
IMDM	Iscove's Modified Dulbecco's Medium
IND	Investigational New Drug Application
IRB	Institutional review board
IWRS	Interactive web response system
MMP	Matrix metalloproteinase
PD	Pocket depth
PGE2	Prostaglandin E2
RBL	Radiographic bone level
SAE	Serious adverse event
SAR	Suspected adverse reaction
SRP	Scaling and root planing
ST266	Study drug: amnion-derived cellular cytokine solution

LIST OF IN-TEXT TABLES

1. PURPOSE OF THE ANALYSES

This study is a randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and treatment regimen of ST266 in subjects with moderate to severe periodontitis. The purpose of the analysis is to estimate both the safety and efficacy of two regimens of ST266 at 270 days following scaling and root planing. Analysis of the primary and secondary endpoints will be conducted after all subjects have completed the Day 270 visit ("Primary Completion Date").

The statistical analysis plan (SAP) for protocol ST266-PERIO-201 is being developed before database lock and any analyses of the primary endpoint. The SAP contains detailed information of the planned statistical analyses and reporting of the study data for use in the final clinical study report (CSR). It is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials [1] and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports [2].

Separate statistical analysis plans are being developed for exploratory endpoints: cytokines in gingival crevicular fluid (GCF) and serum, periodontal microbial flora as determined from microbial analyses, and radiographic bone level (RBL). These analyses will be appended to this SAP upon completion.

The SAP describes the populations that will be analyzed and the efficacy and safety assessments that will be evaluated. It also provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post-hoc analyses in the CSR.

2. PROTOCOL SUMMARY

Name of Sponsor/Company:
Stemnion, Inc.

Name of Investigational Product:
ST266 [Amnion-derived Cellular Cytokine Solution (ACCS)]

Title of Study:
A randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and treatment regimen of ST266 in subjects with moderate to severe periodontitis.

Study Center(s): Multi-center (6 clinical sites in the United States)

Phase of Development: Phase 2a

Objectives:

Primary:

To determine the efficacy of ST266 to reduce pocket depth (PD) adjunctive to scaling and root planing 270 days after initiation of treatment.

Secondary:

To determine safety and changes in:

- Clinical attachment level (CAL)
- Bleeding on probing (BOP)

Study Design:

The study is a 9-month, randomized, double-blind, parallel-design study of subjects with existing moderate to severe periodontal disease randomly assigned to one of three groups. The primary endpoint of PD change will be evaluated following 270 days on study. Subjects will be followed for 9 months for safety and radiographic evaluations.

Subjects who meet inclusion and exclusion criteria will be randomized to one of three treatment groups. Randomization will be stratified by site and smoker status (never smoked or quit smoking more than two years ago vs. has smoked within the last two years). Randomization will be blocked such that assignment to treatment groups both within sites and within smoker status will be approximately even (1:1:1). Treatment will be initiated after scaling and root planing (SRP).

All subjects will be evaluated at baseline and Days 1, 15, 30, 60, 90, 180, and 270.

Number of Subjects (Planned): A total of 150 subjects will be enrolled in the study, 50 per group.

Study Duration per Subject: Each subject will be enrolled in the study for 9 months.

Diagnosis and main criteria for inclusion:

Moderate to severe periodontal disease according to American Academy of Periodontists (AAP) definition (at least 6 teeth with 6mm or greater pocket depth and 3 mm or greater CAL at baseline).

Inclusion Criteria:

1. Provision of signed, written informed consent prior to participation in any study-related

procedures.

2. Good general health as evidenced by medical history.
3. Between 18 and 85 years of age at time of informed consent signature.
4. Male or female.
5. Minimum of 18 teeth, excluding third molars.
6. Having moderate to severe periodontal disease according to AAP definition (at least 6 teeth ≥6 mm PD and ≥3 mm CAL at baseline).
7. Having >30 percent bleeding sites upon probing.
8. Willing to abstain from chewing gums and other mouth rinses for the study duration.
9. Ability and willingness to attend all study visits and comply with all study visits and comply with all study procedures and requirements.
10. Willingness to abstain from routine dental care.
11. For women with reproductive potential, willingness to use highly effective contraception (e.g. licensed hormonal contraception, intrauterine device, abstinence, or vasectomy in partner).

Exclusion Criteria:

1. Presence of orthodontic appliances.
2. A soft or hard tissue tumor of the oral cavity.
3. Carious lesions requiring immediate treatment.
4. Participation in any other clinical study within 30 days of screening or during the study.
5. Pregnancy or lactation. If a subject meets this criterion, she may be rescreened for study participation when she no longer meets this criterion.
6. Antibiotic therapy within the last 30 days.
7. Chronic use (≥3 times/week) of anti-inflammatory medications (e.g., non-steroidal anti-inflammatory drugs, steroids). Low-dose aspirin (less than 325 mg daily) is allowed.
8. Immunocompromised subjects.
9. Subjects with cancer or a history of cancer within the last 5 years of screening.
10. Any medical history or any concomitant medication that might affect the assessment of the study treatment or periodontal tissues, such as diabetes, nifedipine, phenytoin (Dilantin), or anticoagulant medications (e.g., warfarin [Coumadin] etc.).
11. Involvement in the planning or conduct of the study.
12. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or interfere with interpretation of the subject's study results.
13. Previous randomization for treatment in the present study.

Investigational product, dosage and mode of administration: 1X ST266 applied in a dose of 20 microliters per tooth. Total daily dose will be less than 1 milliliter. ST266 will be applied directly to the marginal gingiva around each tooth (buccal and lingual) using sterile packaged pipette tips compatible with the Eppendorf Repeater M4 device.

Duration of Treatment:

Group 1: ST266 dosed daily on Days 1-5, 8-12, 22, and 30, and then monthly for 7 months (Days 60, 90, 120, 150, 180, 210, and 240).

Group 2: ST266 dosed 2x/week (with at least one day between treatments) for the first 3 months and monthly for 5 months thereafter (Days 120, 150, 180, 210, and 240).

Group 3: Placebo dosed at the same frequency as Group 1.

Placebo, Dosage, and Mode of Administration: Sterile saline (0.9% NaCl) will be applied in the same manner and in the same volume as the investigational product, ST266.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint of this study is the change from baseline in the PD for each patient at 9 months (Day 270) for those pockets ≥6mm at baseline.

Secondary efficacy endpoints of this study are:

(1) Change from baseline in CAL at 9 months and (2) change from baseline in BOP at 9 months for those pockets ≥6mm at baseline.

Exploratory endpoints of this study are:

(1) Pro-inflammatory mediators, enzymes and bone markers will be measured in gingival crevicular fluid (GCF) and serum at the baseline, Days 15, 90, 180, and 270;

(2) Microbial analysis of periodontal flora will be performed at baseline and at Days 15, 90, 180, and 270; and

(3) Change from baseline in radiographic bone levels (RBL) at Days 90 and 270. PD, CAL, BOP, and FMPI will also be summarized at Days 90, 180 and 270.

(4) Smoker/treatment interaction will be summarized for PD and CAL at Days 90, 180, and 270.

(5) Percent of patients with all pockets < 5mm will be summarized at Days 90, 180 and 270.

(6) Percent of patients with pockets decreasing by 2mm or more that at baseline were ≥5mm will be summarized at Days 90, 180 and 270.

(7) Percent of patients with 75% of pockets < 5mm that at baseline were ≥5mm will be summarized at Days 90, 180 and 270.

Safety: The safety endpoints are frequency and pattern of adverse events (AEs) and serious adverse events (SAEs).

Planned Sample Size:

The sample size for the study is based on the sample size required to compare treatment with ST266 versus placebo for the primary efficacy endpoint.

The number of subjects was estimated based on two meta-analysis studies that reviewed 50 and 72 articles respectively (Bonito, 2005).

Using the normal approximation for sample size determination for an independent sample t-test, and assuming a PD reduction of 0.5 mm on average (difference in means) with a standard deviation of 0.7 mm, alpha=0.05 (0.025 per comparison, Bonferroni correction), and 85% power, a sample size of 44 per group will be required. The expected dropout rate is approximately 10% based on previous experiments; hence 50 subjects will be enrolled per group.

Statistical methods:

Analysis of the clinical efficacy data will consist of modeling endpoints, including change from

baseline in PD, CAL, BOP, and FMPI, with treatment group, smoking status, and investigational site as main effects and the interaction of smoking status and treatment group. Post-baseline treatment comparisons will be modeled through a GEE method (with a linear link and within-patient exchangeable covariance matrix), adjusting for the baseline value. Methods of analysis for periodontal flora, inflammatory cytokine levels in GCF and in serum, and RBL will be described in separate statistical analysis plans.

2.1 Study Objectives

The primary objective is to estimate the efficacy of ST266 to reduce pocket depth (PD) as an adjunctive to scaling and root planing (SRP).

The secondary objectives of this study are to determine: (1) safety as established by assessment of AEs and SAEs, and (2) changes in the following clinical parameters:

- Clinical attachment level (CAL)
- Bleeding on probing (BOP)

Additional exploratory objectives are to compare the effects of the treatments and dosing schedules in the following:

- Proinflammatory mediators, enzymes, and bone markers in gingival crevicular fluid (GCF) and serum
- Periodontal flora as determined from microbial analyses
- Radiographic bone level (RBL)
- Full-mouth plaque index (FMPI)
- Percent of patients with all pockets < 5mm
- Percent of patients with pockets decreasing by 2mm or more that at baseline were ≥5mm
- Percent of patients with 75% of pockets < 5mm that at baseline were ≥5mm

2.2 Overall Study Design and Plan

The study is a 9-month, randomized, double-blind, placebo controlled, parallel design study of subjects with existing moderate to severe periodontal disease. All subjects will be treated by a dental professional at the study site. The dental professional will be a qualified and trained licensed periodontist, dentist, or dental hygienist skilled in periodontal clinical research. All investigators will be trained in grading clinical parameters in the same manner for consistency. Subjects will be recruited at multiple treatment sites. After signing informed consent, subjects will be screened with a medical and dental history and full mouth dental examination. Clinical parameters will be recorded including PD, CAL, and BOP. Subjects will have urinalysis in addition to blood

tests including hematology and chemistry (liver and kidney function) panels. Women of child-bearing potential will be administered a pregnancy test.

If inclusion/exclusion criteria are met, subjects will undergo a baseline visit with measurements of FMPI, collection of gingival crevicular fluid (GCF) and blood samples. Subgingival plaque samples will be collected for microbial analysis. Vertical bitewing X-rays will be collected to assess RBL. Subjects will undergo SRP procedure(s) prior to being randomly assigned to one of three treatment groups as described in section 2.5. Local anesthesia must be used for SRP. All treatments of ST266 or placebo will be administered in office by a dental professional.

All subjects will be evaluated at screening, baseline, and Days 1, 15, 30, 60, 90, 180, and 270. Evaluations will be performed by a blinded dental professional to mask the group as all groups do not have the same study schedule. The blinded examiners will be independent from the dental professionals who apply the study drug to the subjects, thereby ensuring that the treatment assignment cannot be inferred based on the treatment schedule.

At each evaluation, medical and dental history will be updated, an oral exam will be performed, and AEs and SAEs will be assessed and recorded. PD, CAL, and BOP will be evaluated at screening and on Days 15, 30, 60, 90, 180, and 270. Subjects will have urinalysis in addition to blood tests including hematology and chemistry (liver and kidney function) panels done at screening and repeated at Days 90 and 270. FMPI will be recorded at baseline and on Days 15, 30, 60, 90, 180, and 270. Inflammatory cytokines in serum will be measured at baseline and on Days 15, 90, 180, and 270. GCF will be collected and analyzed at baseline and on Days 15, 90, 180, and 270. Microbial analysis of periodontal flora will be performed at baseline and on Days 15, 90, 180, and 270.

At each treatment visit, in addition to administration of ST266 or placebo, medical and dental history will be updated, AEs and SAEs will be assessed and recorded, concomitant medications will be recorded, and oral hygiene instruction will be provided.

Randomization will be stratified by site and smoker status (never smoked or quit smoking more than two years ago vs. has smoked within the last two years). Randomization will be blocked such that assignment to treatment groups both within sites and within smoker status will be approximately even (1:1:1). ST266 will be supplied to the study site and prepared for use by trained clinical staff, who will not be the same as the dental professionals evaluating the subjects.

Primary Endpoint: The primary endpoint of this study is the average change from baseline in tooth site PD for each patient at 9 months (Day 270) in tooth sites with baseline PD $\geq$ 6mm. The change in pocket depth at each tooth site will be the dependent variable with the average over all tooth-sites for each patient being estimated by the statistical model.

Secondary Endpoints: The secondary endpoints of this study are:

- change from baseline in CAL at 270 days in tooth sites with baseline PD ≥ 6mm
- change from baseline in BOP for each patient at 270 days. BOP for each patient is calculated as the percent of tooth sites in the whole mouth with bleeding on probing.

Baseline refers to the initial measurement of the endpoint, which may occur at the screening or baseline visit according to the schedule of assessments.

Safety Endpoints: The safety endpoints are the frequency and pattern of AEs and SAEs.

Exploratory Endpoints: Pro-inflammatory mediators, enzymes, and bone markers will be measured in GCF and serum at baseline and Days 15, 90, 180, and 270. Microbial analysis of periodontal flora will be performed at baseline and at Days 15, 90, 180, and 270. Change from baseline in RBL will be measured at Days 90 and 270. PD, CAL, BOP, will also be analyzed at Days 180 and 270. FMPI will also be analyzed at Days 90, 180 and 270. Percent of patients with all pockets < 5mm, percent of patients with pockets decreasing by 2mm or more that at baseline were ≥5mm, and percent of patients with 75% of pockets < 5mm that at baseline were ≥5mm will be shown at Days 90, 180 and 270.

2.3 Study Population

The population of this study comprises adults with moderate to severe periodontitis who meet the inclusion/exclusion criteria as described in the protocol synopsis in Section 2 of the SAP. Approximately 150 subjects will be enrolled with 50 subjects per treatment group. Subjects may be re-screened if they do not fail inclusion criteria #6 (having moderate to severe periodontal disease according to the AAP definition [at least 6 teeth with ≥6 mm PD and ≥3 mm CAL at baseline).

2.4 Treatment Regimens

Group 1: ST266 dosed daily on Days 1-5, 8-12, 22, and 30 and then monthly for 7 months (Days 60, 90, 120, 150, 180, 210, and 240).

Group 2: ST266 dosed 2x/week (with at least one day between treatments) for the first 3 months and monthly for 5 months thereafter (Days 120, 150, 180, 210, and 240).

Group 3: Placebo dosed at the same frequency as Group 1.

2.5 Treatment Group Assignments or Randomization

Randomization will be stratified by site and smoker status (never smoked or quit smoking more than two years ago versus has smoked within the last two years). Randomization will be blocked such that assignment to treatment groups both within sites and within

smoker status will be approximately even (1:1:1). ST266 will be supplied to the study site and prepared for use by trained clinical staff, who will not be the same as the dental professionals evaluating the subjects.

At the 90-Day analysis, one statistician and one programmer will be unblinded in order to generate the unblinded 90-day analysis. Another team of statisticians and programmers will remain blinded until the 270-day analysis at the end of the study.

2.6 Sample Size Determination

One hundred and fifty (150) subjects will be enrolled. The sample size for the study is based on the sample size required to compare treatment with ST266 versus placebo for the primary efficacy endpoint.

The number of subjects was estimated based on two meta-analysis studies that reviewed 50 and 72 articles respectively (Bonito, 2005).

Using the normal approximation for sample size determination for an independent sample t-test, and assuming a PD reduction of 0.5 mm on average (difference in means) with a standard deviation of 0.7 mm, alpha=0.05 (0.025 per comparison, Bonferroni correction), and 85% power, a sample size of 44 per group will be required. The expected dropout rate is approximately 10% based on previous experiments; hence 50 subjects will be enrolled per group.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

For continuous endpoints, the summary statistics will generally include number of subjects with data (n), mean, standard deviation, median, minimum and maximum. No preliminary rounding will be performed; rounding will only occur after analysis. To round, the digit to right of last significant digit will be considered: if < 5 then round down, if ≥ 5 then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. Minimums and maximums will be presented with the same precision as the original data.

For categorical endpoints, the summary statistics will generally include: number of subjects randomized and/or dosed, number of subjects with data, and the percentage of those with data in each category. Frequency distributions will be presented as appropriate.

Analysis of the clinical efficacy data will consist of modeling endpoints, including change from baseline in PD, CAL, BOP, and FMPI, with treatment group, patients, smoking status, and investigational site as main effects and adjusting for baseline values of a given endpoint. Post-baseline treatment comparisons will be modeled through a GEE method (with a linear link and exchangeable covariance matrix), adjusting for the baseline value. Methods of analysis for periodontal flora, inflammatory cytokine levels in GCF and in serum, and RBL will be described in separate statistical analysis plans.

Hypothesis testing, unless otherwise indicated, will be two-sided. When confidence intervals are presented, they will be two-sided with a confidence coefficient of 95%. Actual P-values will be reported to 3 decimal places if greater than 0.001. If less than 0.001, the value '<0.001' will be reported.

The statistical software, SAS® version 9.3 or above, will be used for all summaries and statistical analyses.

4. ANALYSIS POPULATIONS

Statistical analyses will be based on the analysis populations as defined below:

- Safety population: All randomized subjects who use at least one dose of study drug, regardless of whether or not they undergo any study assessments.
- Intention-to-Treat (ITT) population: All randomized subjects.
- Per Protocol (PP) population: All subjects who use at least one dose of study drug and do not have major protocol deviations as defined in § 5.2.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Subject disposition will be summarized in tables and listings: overall, by treatment, by smoking status at baseline, and by site.

- The number of subjects screened (overall)
- The number of subjects enrolled and randomized
- The number of subjects treated
- The number of subjects who have completed each visit
- The number of subjects who discontinued study treatment; overall and by discontinuation reason:
  - Adverse Event
  - Death
  - Lack of Efficacy
  - Lost to Follow-up
  - Non-Compliance with Study Duration
  - Physician Decision
  - Pregnancy
  - Progressive Disease
  - Protocol Violation
  - Recovery
  - Screen Failure
  - Study Terminated by Sponsor
  - Technical Problems
  - Withdrawal by Subject
  - Other

5.2 Protocol Deviations

Major protocol deviation information will be maintained separately from the electronic CRF, and exports of these data will be delivered separately from the clinical datasets. A major deviation is one that may affect the outcome, analysis, or interpretation of the study. These deviations may include, but are not limited to, the following: Inclusion/exclusion criteria deviations, randomization deviations, and terminations for lack of compliance. Major protocol deviations will be identified by an expert committee prior to unblinding the study. Protocol deviations can be self-reported, recorded following interim monitoring visits, or following remote monitoring. For the per protocol analysis all subjects with minor deviations will be included. All subjects with major deviations will be reviewed as described above and will not be included in the per protocol analysis.

Subjects who miss 20% or more of their prescribed treatments will be considered non-compliant and will be excluded from the per-protocol statistical analysis.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline data (demography, medical history, dental history, and baseline disease characteristics) will be summarized.

Demography includes age, sex, race, and ethnicity. Sex, race, and ethnicity will be tabulated in frequencies and continuous summary statistics will be presented for age at screening. Data will also be presented in a listing.

The number and percentage of subjects with each medical history event will be presented by body system and event term. A listing will also be created which will include the body system, event term, whether the medical history event is ongoing and controlled, as well as the start and end dates of the event and any associated comments.

The number and percentage of subjects who have been diagnosed with periodontitis, abscesses, or who have had any oral surgeries or root canals, or are currently experiencing dental pain will be presented. A listing will also be created which will include the above events as well as their associated dates, the date the subject last visited a dentist or hygienist, frequency of flossing and mouth rinse, and interdental irrigation devices.

Results of the baseline oral exam will be listing by area examined and will denote an abnormal or normal result; and, if abnormal, the associated description of the abnormality will be listed. The presence of periodontal abscess or endodontic abscess will also be presented.

Tooth status at baseline will be presented in a listing by subject and tooth, and will denote whether the tooth is missing, sound, decayed, filled, fractured, has a crown, and/or is an implanted tooth.

Quadrants completed during the scaling the root planing procedure at visit 3 will be presented in a listing.

Demographic and baseline disease characteristics will be presented for the safety population.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

Every treatment application of study drug will be performed in the dental clinic by the clinician/investigator (dental professional); therefore, the investigator can assess non-compliance based on subject attendance of scheduled treatments.

Missed treatments may be completed if done within the treatment windows described in the protocol.

Subjects who miss 20% or more of their prescribed treatments will be considered non-compliant and excluded from the per-protocol statistical analysis.

Treatment compliance will be calculated as:

[(# doses completed within X days (with "X" as defined above) **from original scheduled dose date)/ (# planned doses)]*100**

Treatment compliance will be presented by group at each visit and overall using both continuous summary statistics and the following frequency cut-offs: <50%, 50 - 80%, >80% for the ITT population.

Treatment compliance will also be presented in a listing presenting subject, dosing schedule/treatment group, planned dosing day, whether the subject was dosed within "X" days (with "X" as defined above"), actual dosing day, and treatment compliance.

8. EFFICACY EVALUATION

8.1 Overview of Efficacy Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

All reasonable efforts will be made to minimize missing data. However, there are two possibilities for data being missing. In one case, the measurement associated with an individual pocket may be missing at an evaluation. In this case, the worst previous value for this variable will be imputed for that tooth/pocket. Furthermore, the data from an entire patient may be missing because they withdrew before completing the study. For this imputation, an approach similar to that for each site will be employed. For visits that would follow a patient's premature discontinuation from the study, the worst observation associated with each individual pocket will be imputed for all subsequent visits for that patient and will thus also be carried forward for the 270-day evaluation. Subjects who drop out of the study will not be replaced.

8.1.2 Rescue Therapy

The need for rescue therapy including the site requiring therapy, the date and study day, the pocket depth (PD), whether SRP was performed, the protocol version under which the subject was enrolled, and any associated comments will be presented in a listing.

Additionally, a table will be created to summarize and compare the need for and timing of rescue therapy across the three treatment groups.

Further ad-hoc exploratory analyses to examine the characteristics of subjects receiving rescue therapy and the circumstances surrounding the need for rescue therapy may be conducted.

8.1.2.1 Amendment to Protocol Rescue Criteria

In this study, rescue therapy was intended to occur only after the Day 90 evaluation. However, under early versions of the protocol, the timing of rescue therapy was not explicitly stated, and rescue therapy was permitted at any time after the initial SRP treatment if indicated by clinical parameters (PD or CAL). A subsequent amendment to the protocol (Amendment 2) was made to correct this issue, but some subjects enrolled under the earlier versions of the protocol received "premature" rescue therapy prior to Day 90.

Pockets/teeth that are "rescued" should be considered treatment failures after rescue. For this reason, rescued teeth/pockets will be assigned a value equal to the worst score observed at any previous visit for that pocket/tooth in the primary and secondary analyses..

8.1.3 Multicenter Studies

This is a multi-center study and randomization has been stratified by site.

8.1.4 Assessment Time Windows

See Section 15.2 for the Schedule of Assessments. Assessments within the stated visit windows will be considered for analysis of the given time point. If multiple assessments occur within a visit window, the assessment occurring closest to the target day for the assessment will be used in the analysis. In the case of a tie, the worst record will be used.

8.2 Efficacy Variables

Table 8-1 Efficacy Variables and Analysis Methods

Efficacy Variables	Method 1 [a]
Primary	
Pocket Depth	Δ from baseline at Day 270 in tooth-sites with baseline PD ≥6mm [a]
Secondary	
Clinical Attachment Level	Δ from baseline at Day 270 in tooth-sites with baseline PD ≥6mm [a]
Bleeding on Probing	Δ from baseline at Day 270 using whole mouth average percentage of site with bleeding on probing [b]

[a] Generalized Estimating Equations will be used as the primary analytical method. The dependent variable will be change from baseline to Day 270 and the model will include treatment group, patients, smoking status, and investigational site for a given endpoint. A linear link and exchangeable covariance matrix will be employed. Only treatment comparisons at Day 270 will report a p-value. Comparisons at other time points will only present the point estimate and 95% confidence interval. The analyses will incorporate all data from individual tooth sites within each subject.

[b] ANCOVA will be used for the analysis of this variable. The dependent variable will be change from baseline to Day 270 and the model will include treatment group, patients, smoking status, and investigational site for this endpoint. Only treatment comparisons at Day 270 will report a p-value. Comparisons at other time points will only present the point estimate and 95% confidence interval.

8.3 Analysis Methods

The Day 270 analyses will be independent of the Day 90 analyses. All primary and secondary efficacy analyses unless otherwise stated will be performed on the ITT population. Unblinding will be performed for the Primary and secondary analyses at Day 270.

8.3.1 Primary Efficacy Analyses

The generalized estimating equations (GEE) method with a linear link and exchangeable covariance matrix (within subject correlation structure) will be used to estimate the treatment group effects with respect to change from baseline PD at 270 days, adjusted for baseline PD in tooth-sites with baseline PD ≥6 mm. The two primary hypotheses to be tested are:

1) The change in PD from baseline (PD ≥6 mm) (Screening Visit) at the 270 Day Visit differs between the Group 1 (see section 2.4) and Group 3 (placebo) treatments. Point estimates and 95% confidence intervals will be presented for the

treatment group differences in PD change from baseline at Day 270 by baseline smoker status.;

2) The change in PD from baseline (PD ≥6 mm) (Screening Visit) at the 270 Day Visit differs between the Group 2 (see section 2.4) and Group 3 (placebo) treatments. Point estimates and 95% confidence intervals will be presented for the treatment group differences in PD change from baseline at Day 270 by baseline smoker status.

SAS code for the GEE model is as follows:

```
proc gee data=Day270dataset
  where (base>=6 and ITT Set='Y'  and paramcd='PDEPTH');
  class subjid trt01a site smoker_status;
  model chg = trt01a base site smoker_status smoker_status*trt01a;
  repeated  sub=subjid /type=exch;
  lsmeans trt01a/pdiff;
run;
```

Where:

1) The Day270dataset only includes records for Day 270visit)
2) chg = change from baseline of each individual toot site
3) (base>=6 and ittfl='Y' and paramcd='PDEPTH'): subsets the dataset to include only PD outcomes, the ITT population, and tooth sites with baseline PD greater or equal to 6mm.
4) chg= change in PD from baseline
5) trt01a = treatment group
6) site=investigator institution rather than tooth site
7) base = baseline PD

The 15-, 30-, and 60-Day visits were not included in the primary statistical model since the tooth-sites at the earlier visits may still be healing from the effects of the SRP procedure with possible SRP-related gingival swelling affecting the PD measures.

Since there are two primary hypotheses, Bonferroni corrections will control for multiplicity with $p<0.025$ considered significant. Point estimates and 95% confidence intervals will be presented for the treatment group differences in change from baseline at each assessment time point. These analyses will be performed once all the subjects (excluding those withdrawn) have been unblinded and completed their 270-Day Visit.

8.3.2 Secondary Efficacy Analyses

Additional secondary efficacy analyses will be performed to test the effects of treatment group and their interactions on the secondary endpoints of the change from baseline in CAL and BOP at Day 270. For the CAL analysis, the GEE analyses will be performed with the same statistical model as described in the primary PD efficacy analysis but with the change from baseline in CAL of tooth-sites with baseline PD ≥6 mm as the dependent

variable. Separate hypotheses will be performed for testing the treatment effects of group 1 versus group 3 (placebo) and group 2 versus group 3 (placebo). As described above, this model will include the baseline smoker status (smoker or non-smoker) by treatment group interaction. For the secondary efficacy analyses of the BOP change from baseline, ANCOVA will be performed with treatment group as the main effect, and covariates for baseline PD, site, patients, smoker status, and the baseline smoker status (smoker or non-smoker) by treatment group interaction . Point estimates and 95% confidence intervals will be presented for the treatment group differences in CAL and BOP change from baseline at Day 270 and by baseline smoker status.

The CAL and BOP secondary analyses described above will be tested hierarchically in the order of: CAL change from baseline at Day 270, and BOP (presented as a whole mouth average percentage) change from baseline at Day 270. The treatment effects for the CAL or BOP change from baseline at the Day 270 Visit will be compared between Treatment Group 1 and Placebo, and between Treatment Group 2 and Placebo. The alpha will be set at 0.025 to allow for the Bonferroni correction for 2 multiple comparisons for secondary endpoints. Since the smoker status by treatment group interaction is acting as a gatekeeper for further inference testing by smoker status, no additional corrections will be made for multiplicity for any additional analyses of the effects of treatment on CAL and BOP by smoker status. These analyses will be performed once all the subjects (excluding those withdrawn) completed their 270-Day Visit.

All primary and secondary analyses performed on the ITT population will be repeated using the per protocol population.

8.3.3 Efficacy Analyses at Other Time Points

The same technique used for the primary and secondary endpoints will be used for the other assessed time points. Point estimates and 95% confidence intervals will be presented for change from baseline at each assessment time point. The p-values will not be presented for these analyses. Actual value and change from baseline will be presented for each scheduled collection visit for the summarized endpoint. Please refer to Section 15.2 for the schedule of assessments.

8.3.4 Exploratory Efficacy Analyses

FMPI will be analyzed using the GEE method described in section 8.3.1 at days 90, 180, and 270. Additionally, CAL change from baseline at days 180 and 270 using all tooth-sites will be analyzed using GEE. PD change from baseline at days 90, 180, and 270 using a whole-mouth average will be analyzed using ANCOVA with the model described previously.

Analysis methods for the exploratory efficacy outcomes, (1) inflammatory cytokines in GCF and serum, (2) microbial periodontal flora and (3) RBL will be described in a separate statistical analysis plan.

8.4 Examination of Subgroups

To explore the potential effect of age and gender on response, and to further explore the effect of smoking, PD and CAL in tooth-sites with baseline PD ≥ 6mm will also investigated with exploratory analyses using the following categories:

- Age (< median age; ≥ median age)
- Gender (male, female)
- Current disease smoking status (smoker – has smoked within the past two years, non-smoker – has never smoked or quit > 2 years ago).

The model used for the original analyses of these variables will form the basis for separate analyses for each of these factors. However, in addition to the factors in the original model, an additional main effect (e.g. gender) and interaction term (e.g. gender by treatment) will be included in the model.

8.5 Exploratory Categorical Analysis of PD

In addition to analyzing PD as continuous variable, it is often useful to analyze PD categorically. The following may also be summarized descriptively:

- Percent of subjects in each group with a mean PD change from baseline <-4mm, <-3mm, <-2mm, <-1mm, -1mm to 1mm, >1mm, >2mm, >3mm, >4mm at 90, 180 and 270 days
- Percent of subjects with pockets decreasing by 2mm or more that at baseline were < 5mm at 90, 180, and 270 days.
- Percent of tooth sites in each group with a mean PD change from baseline <-4mm, <-3mm, <-2mm, <-1mm, -1mm to 1mm, >1mm, >2mm, >3mm, >4mm at 90, 180 and 270 days
- Percent of subjects in each group with a mean PD <5mm, <6mm and < 7mm at 90, 180 and 270 days
- Percent of subjects in each group with all PD <5mm, <6mm and < 7mm at 90, 180 and 270 days
- Percent of subjects with 75% of pockets < 5mm that at baseline were < 5mm at 90, 180, and 270 days.
- Percent of tooth sites in each group with a mean PD <5mm, <6mm and < 7mm at 90, 180 and 270 days
- Percent of subjects in each group with PD <5mm at day 90 by baseline PD

8.6 Pooled comparisons

In addition to the above analyses that compare results between each active treatment group (N=50/group) and the placebo group (N=50), "pooled" analyses will be performed that combine the data from both active treatment groups (N=100) for comparison to the placebo group (N=50). Point estimates and 95% confidence intervals will be presented for change from baseline at each assessment time point. The p-values will not be presented for these analyses.

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

Safety analyses will be presented descriptively on the safety population. No statistical testing will be performed.

9.2 Extent of Exposure

Treatment compliance will be presented at each visit and overall by group using both continuous summary statistics and the following frequency cut-offs: <50%, 50 - 80%, 80 - 90%%, >90%.

Treatment compliance will be calculated as:

[(# doses completed within X days (within 3 days in the first 60 days; within 5 days at Day 90; within 7 days at Day 180) **from original scheduled dose date)/(# planned doses)]*100**

Duration of therapy will be summarized by treatment group using continuous summary statistics. Duration of therapy in months will be calculated as:

(last dose date – first dose date + 1)/30.4375.

Number of doses received will be summarized by treatment group using continuous summary statistics.

Information regarding the extent of exposure will also be presented in a listing presenting subject, dosing schedule/treatment group, planned dosing day, whether the subject was dose within X days **(**within 3 days in the first 60 days; within 5 days at Day 90; within 7 days at Day 180), actual dosing day, treatment compliance, duration of therapy, and number of doses received.

9.3 Adverse Events

The most recently available MedDRA dictionary version will be used for the classification of adverse events.

On-study AEs are those with a start date on or after the first treatment dose date and prior to the last treatment dose date + 30 Days.

On-study adverse events will be summarized overall by treatment group and by worst severity. Drug-related adverse events will also be tabulated.

All adverse events will be presented in a listing which includes first treatment dose date, onset and resolution date/day (or whether it is ongoing), system organ class and preferred term, investigator term, whether the event is serious, whether the adverse event involves

hematuria or proteinuria, severity grade, relationship to study drug, action taken, sequelae, and outcome.

9.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The number of deaths will be presented along with the corresponding reason for death.

On study serious adverse events will be classified by system organ class and preferred term. They will be presented overall by treatment group and by worst severity. Drug-related serious adverse events will also be tabulated.

On study adverse events leading to discontinuation will be classified by system organ class and preferred term. They will be presented overall by treatment group and by worst severity. Drug-related adverse events leading to discontinuation will also be tabulated.

9.5 Clinical Laboratory Evaluation

Blood is to be drawn and urine collected for laboratory analysis at Screening, and on Days 90 and 270. The following clinical laboratory parameters are to be assessed:

- Hematology: Complete blood count
- Blood chemistry: serum glucose, C-reactive protein, blood urea nitrogen, creatinine, electrolytes, HbA1c (at screening only), and liver function including bilirubin and hepatic enzymes
- Urinalysis: hematuria, proteinuria, pregnancy test (at screening and final visit only)

Tables will present continuous summary statistics for each lab parameter collected by visit and treatment group.

Laboratory values outside the normal range will be flagged as “high” or “low”. Percentage of subjects with values falling in high, normal, and low ranges will be summarized by lab parameter and visit, by treatment group.

9.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.6.1 Vital Signs

Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature will be collected at screening, baseline, SRP visit, day 1, day 15, day 30, day 60, Day 90, Day 180 and Day 270 (or end of study). Height and weight will be collected at screening and Day 270 (or end of study).

Summaries of actual values and change from baseline at each visit will be presented in a table. A listing will also be provided with vital sign value at each visit as well as an indicator of the clinical significance of the finding, if any.

9.6.2 Physical Examinations

An oral exam will also take place at each visit. Results will be presented in a listing similar to that described in Section 6 of the SAP but will also include the visit associated with the exam results.

9.6.3 Other Safety Measures

Medical and dental history will be updated at each visit. Medical history events and dental history events since baseline will be presented in a listing similar to that described in Section 6 of the SAP but will also include the visit associated with the exam results.

10. TIMING OF DATA COLLECTION AND ANALYSES

In this study, subjects will be followed for a total duration of 9 months. After all subjects have completed their Day 270 visit, the database will be locked and Day 270 analysis will be performed. Results will be presented as described above with the additional data from Days 180 and 270.

11. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

2. US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

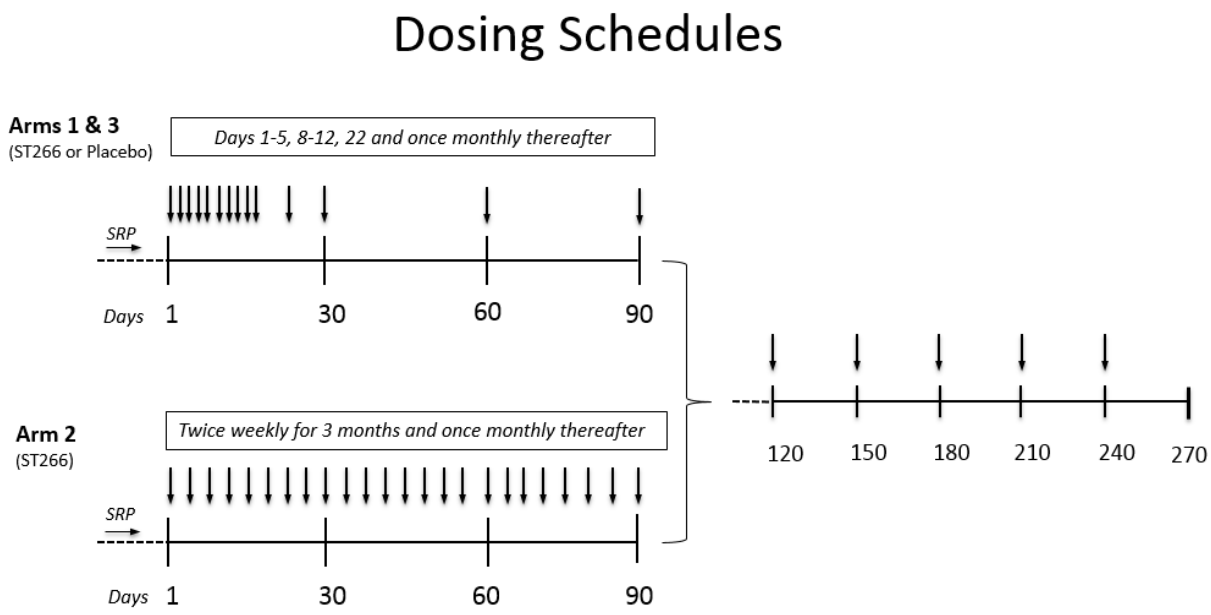
3. Yuan YC. Multiple imputation for missing data: Concepts and new development. SAS Institute, Inc. 2000.

4. Rubin DB. Inference and missing data. Biometrika 1976;63(3):581–90.

5. Schafer JL. Analysis of incomplete multivariate data. London: Chapman & Hall; 1997.

12. APPENDICES

12.1 Study Flow Chart



12.2 Schedule of Events

Evaluation					Treatment and Follow-up Period					
	Visit 1	Visit 2	Visit 3/3b	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10/EOS
	Screening	Baseline (≤30 days from screening)	SRP (≤10 days from baseline)	Day 1[a] (≤3 days from SRP)	Day 15 (±1 day)	Day 30 (±3 days)	Day 60 (±3 days)	Day 90 (±5 days)	Day 180 (±7 days)	Day 270 (±7 days)
Informed Consent	X									
Pregnancy Test (female subjects)	X									X
Demographics	X									
Inclusion/Exclusion	X	X								
Dental History	X									
Medical History	X									
Vital Signs	X	X	X	X	X	X	X	X	X	X
Height and Weight	X[b]									X
Medical/Dental History Update[g]		X	X	X	X	X	X	X	X	X
Oral Exam	X	X	X	X	X	X	X	X	X	X
Randomization			X[c]							
SRP[d]			X							
Full Mouth Plaque Index (FMPI)		X			X	X	X	X	X	X
Clinical Measurements (PD, CAL, BOP)	X				X	X	X	X	X	X
GCF Sampling		X			X			X[e]	X[e]	X
Serum Sampling		X			X			X	X	X
Microbial Sampling		X			X			X	X	X
Radiographs		X						X		X
General Labs	X[f]							X		X
Administration of Test Article				*In-office treatments as scheduled in Figure 1*						
Oral Hygiene Instruction[g]	X	X	X	X	X	X	X	X	X	X
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X
Concomitant Medication[g]	X	X	X	X	X	X	X	X	X	X

BOP=bleeding on probing; CAL=clinical attachment level; EOS=end of study; FMPI=full-mouth plaque index; GCF=gingival crevicular fluid; HbA1c=glycated hemoglobin; IWRS=interactive web response system; PD=pocket depth; SRP=scaling and root planing.

[a] The first in-office treatment may be performed on the same day as the last SRP visit. The last SRP may occur on Visit 3/3b, or as an Unscheduled Visit. The Unscheduled Visit may be combined with Visit 4. Product administration must occur within 3 days of the last SRP visit.

[b] Height is measured only at screening.

[c] Randomization occurs by IWRS after SRP has been completed.

[d] SRP may be initiated on the same day as the Baseline visit and may require more than one visit. Subjects with moderate to heavy deposits will typically have no more than two quadrants treated in a single SRP visit. Local anesthesia must be used for SRP.

[e] Sample is collected before treatment is applied.

[f] HbA1c is measured at screening only.

[g] Performed at each treatment visit, as well as at each evaluation visit.

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