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

Name of Investigational Compound:	ST266
IND:	15,825
Investigational Phase:	Phase 2a
Study Number:	ST266-PERIO-201
Sponsor:	Stemnion, Inc. 100 Technology Drive, Suite 200 Pittsburgh, PA 15219

Date: 08 September 2017

Confidentiality Statement

APPROVAL SIGNATURE PAGE

Approved by Stemnion, Inc.

Jan Lessem, MD, PhD
Medical Monitor, Consultant

Sept 8, 2017
Date

INVESTIGATOR'S AGREEMENT

I have read the protocol ST266-PERIO-201 and agree to conduct the study as outlined and in accordance with Good Clinical Practice (GCP) Guidelines. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company:
Stemnion, Inc.

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

Name of Active Ingredient:
ST266 (ACCS) is a novel secretome derived from proprietary cells. ST266 is composed of a complex mixture of cytokines, growth factors, nucleic acids, and undefined cellular components produced by cultured amnion-derived multi-potent progenitor (AMP) Cells in Iscove's Modified Dulbecco's Medium (IMDM). It contains at least 75 cytokines and growth factors in physiological concentrations and 2 proteins (0.5% human serum albumin and epidermal growth factor) that are added to support the growth of the cells.

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 (approximately 5 to 7 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 (SRP).

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 9 months of treatment. Subjects will be followed for 9 months for safety and radiographic evaluations.

Subjects who meet inclusion 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 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 PD 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. Any dental condition that requires immediate treatment, such as carious lesions.
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 average change in each patient between the PD at baseline and the PD at 9 months (Day 270) for those pockets ≥6 mm at baseline.

Secondary efficacy endpoints of this study are: (1) change from baseline in CAL at 9 months (Day 270); (2) change from baseline in BOP at 9 months (Day 270); and (3) change from baseline in PD at 9 months (Day 270) using all tooth-sites.

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; (4) FMPI analyzed at Days 90, 180 and 270; and (5) change from baseline in PD, CAL and BOP will be analyzed on Days 90 and 180.

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 reject the null hypothesis for the primary efficacy endpoint.

The number of subjects was estimated based on 2 meta-analysis studies that reviewed 50 and 72 articles respectively (Bonito, 2005) to reach a significant difference in PD reduction at 9 months compared with placebo.

Using the normal approximation for sample size determination for 2 independent samples, t-tests, 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), and 85% power, a sample size of 44 per group will be required. The expected dropout rate is 20% based on previous experiments; hence 50 subjects will be enrolled per group. Generalized estimating equations (GEE) analyses will be performed and therefore, the actual power will be between 85 and 90%.

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 as a main effect 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. Results will be considered significant if $p<0.05$.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

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

5. INTRODUCTION

Periodontal disease is a problem affecting millions of Americans and one for which adequate therapy is lacking. In periodontitis, an acute inflammatory reaction occurs and, if unresolved with failure of return of tissue to homeostasis, there is neutrophil-mediated tissue destruction, and inflammation becomes chronic. Although infection by Gram-negative bacteria such as *Porphyromonas gingivalis* is considered to be the primary etiologic factor in periodontal disease, the cause-and-effect relationship between the pathogen and disease is not clear. What is clear, however, is that a biofilm develops and left unchecked, tissue and bone of the periodontium are destroyed. To reduce the inflammatory response in tissues, drugs such as non-steroidal anti-inflammatory agents have been used with limited long-term success. Antibiotic therapy may provide a short-term benefit without a long-term solution. ST266 offers a novel alternative mechanism for treatment of periodontal disease.

5.1. Trial Rationale

Resolution of inflammation may reduce injury, promote healing, and return tissue homeostasis. Rapid elimination of the invading leukocytes from a lesion is the desired outcome following an inflammatory event. This task becomes more formidable when the acute inflammatory response progresses to chronic inflammation with destruction of the cellular matrix, scarring, and fibrosis. Thus, an essential goal for intervention in inflammatory disease is the return of tissue homeostasis (Serhan, 2011). Interventions in the management of periodontitis such as root planing offer some benefit in removing etiologic agents associated with inflammation and thereby arrest to some degree the periodontal disease; however, such procedures do not resolve the inflammation and restore tissue homeostasis. Without restoration of tissue homeostasis, inflammatory cells having pro-inflammatory products, such as prostaglandin E2 (PGE2), persist causing swelling, irritation, pain, collagen destruction, and ultimately bone resorption (Kantarci, 2006). Agents that stimulate the resolution of inflammation may offer some therapeutic advantage in the treatment of periodontitis compared with more traditional pharmacologic interventions.

5.2. Experience with ST266

ST266, in some ways, may be ideally suited for treating periodontitis. ST266 has been shown in *in vitro* experiments to reduce the amount of inflammatory cytokines, specifically PGE2. In *in vivo* experimental models of periodontitis in rabbits, employed to evaluate the effect of ST266 on periodontal disease, there was a marked reduction in the inflammation with the use of ST266. Furthermore, there was restoration of lost bone with histological evidence of resolution of the inflammatory infiltrates.

In a phase 1 study of gingivitis, a related disease, 54 subjects (18 per arm) were treated. Subjects had a modified gingival index score of 2.0 or greater and >40% bleeding sites at initial presentation. Three (3) cohorts were tested: Two (2) different ST266 concentrations (1X and 0.3X ST266) were compared with the saline placebo control cohort. Subjects received daily 20 µL topical treatments per tooth for 10 days administered over 2 weeks (560 µL maximum dose). A follow-up visit was conducted at Day 42 for clinical measurements and safety analysis.

Efficacy results of the phase 1 study are summarized in Table 2. Statistically significant changes in clinical attachment level (CAL) and pocket depth (PD) were observed relative to placebo for both the 0.3X and 1X ST266 treatment groups at Day 42 ($p < 0.05$). Furthermore, pro-inflammatory cytokine biomarkers, interleukin (IL)-1ß and IL-6, were significantly decreased in both the 0.3X and 1X ST266 treatment groups relative to placebo at Day 12 ($p < 0.05$). These findings suggest that ST266 has a beneficial effect in subjects with gingivitis and supports prior studies demonstrating anti-inflammatory properties of ST266 mediated via modulation of pro-inflammatory cytokines.

Table 2: ST-04-13 Efficacy Outcomes

	Mean Difference	95% Confidence Interval		p-value
Probing Depth (mm) day 42				
0.3X ST266 minus placebo	-0.13	-0.23	-0.04	0.005*
1X ST266 minus placebo	-0.13	-0.23	-0.03	0.008*
Clinical Attachment Level (mm) day 42				
0.3X ST266 minus placebo	-0.17	-0.28	-0.06	0.002*
1X ST266 minus placebo	-0.20	-0.31	-0.08	0.001*
Crevicular Fluid IL-1ß day 12				
0.3X ST266 minus placebo	-0.24	-0.44	-0.04	0.021*
1X ST266 minus placebo	-0.25	-0.45	-0.05	0.015*
Crevicular Fluid IL-6 day 12				
0.3X ST266 minus placebo	-0.38	-0.65	-0.11	0.005*
1X ST266 minus placebo	-0.35	-0.57	-0.12	0.002*

* Significant difference p<0.05 using GEE analysis (adjusted for baseline)

No significant safety issues were identified in the phase 1 study. Safety parameters were compared for both ST266 treatment groups (1X and 0.3X) relative to placebo using appropriate statistical methods. This included adverse events (AEs), vital signs, and oral cavity examination results. One serious adverse event (SAE; assault-fractured cheek bone, laceration) occurred during this study that was clearly not related to the study protocol or study product. There were 125 AEs/oral cavity exam findings reported during the entire study, all of which were categorized as mild. Out of 125 events, 3 (2.5%) were categorized as related, 5 (4%) were categorized as possibly related, and 5 (4%) were categorized as unlikely related. All related and possibly related events were reported by the same two subjects, both of whom were assigned to placebo. These results suggest that ST266 was safe and was well tolerated by subjects with gingivitis when administered at the 0.3X and 1X concentrations for at least 10 days of treatment.

Periodontitis with severe bony destruction remains the primary cause of tooth loss. ST266 has been shown to be profoundly anti-inflammatory in both *in vitro* and *in vivo* preclinical experiments including an accepted rabbit model of periodontitis. These findings, coupled with the excellent safety profile for ST266 in both animal testing and a phase 1 clinical trial as well as use of ST266 in topical dermal and topical ocular trials in more than 90 subjects, support the proposed clinical investigation of ST266 in the treatment of periodontal disease.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

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

6.2. Secondary Objectives

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)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

The study is a 9-month, randomized, double-blind, placebo-controlled, parallel-design study of subjects with existing moderate to severe periodontal disease. The study design and duration is similar to the study design with previous compounds, e.g. Minocycline Microspheres, chlorhexidine chip, and others. Subjects will be recruited at multiple treatment sites. 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. 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 1 of 3 treatment groups indicated in Section 7.3. 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 effectiveness endpoint of this study is the average change in PD from baseline to 9 months (Day 270) in tooth-sites with baseline PD ≥ 6mm. This endpoint will be analyzed at the patient level similar to other studies.

Secondary Endpoints: Secondary efficacy endpoints of this study are: (1) change from baseline in CAL at 9 months (Day 270) with baseline PD ≥ 6mm; (2) change from baseline in BOP at 9 months (Day 270) using whole-mouth average, and (3) change from baseline in PD at 9 months (Day 270) using all tooth-sites.

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 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 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. Change from baseline in RBL will be measured at Days 90 and 270. All x-rays for RBL will be read at a central location using predefined criteria. PD, CAL and BOP will also be analyzed at Days 90 and 180. FMPI will also be analyzed at Days 90, 180 and 270.

7.2. Number of Subjects

One hundred and fifty (150) subjects will be enrolled. The sample size for the study is based on the sample size required to reject the null hypothesis for the primary efficacy endpoint which contains two comparisons. Using the normal approximation for sample size determination for two independent samples, t-tests, 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 (Bonferroni corrected, alpha 0.025 per comparison), and 85% power, a sample size of 44 per group will be required. The expected dropout rate is 20% based on previous experiments and current enrollment trends hence 50 subjects will be enrolled per group. GEE analyses will be performed and therefore, the actual power will be between 85 and 90%.

7.3. Treatment Assignment

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.

7.4. Rescue Therapy

If at Day 90 or later a subject experiences progression of periodontitis in any tooth, rescue therapy will be provided. Progression of periodontitis is defined as an increase of 2 mm or more in PD or CAL from the baseline measurement (Goodson, 1982). Rescue therapy will consist of

the standard of care therapy at the tooth site where progression of periodontal disease occurred. Rescue therapy at the tooth site may occur immediately at the scheduled visit, or as soon as the investigator determines is reasonable to ensure the subject receives standard of care therapy.

Subjects that receive rescue therapy will continue to participate in all remaining study visits through study completion.

7.5. Criteria for Study Termination

Safety assessments will be performed throughout the course of the study. Any potential safety issues that arise will be reviewed by the sponsor's Medical Monitor in consultation with the study investigators to identify the appropriate course of action. If the sponsor elects to terminate the study for any reason, the investigator will be responsible for notification of the institutional review board (IRB) and will withhold further treatment of study participants.

Table 3: Study Design and Schedule of Assessments

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.

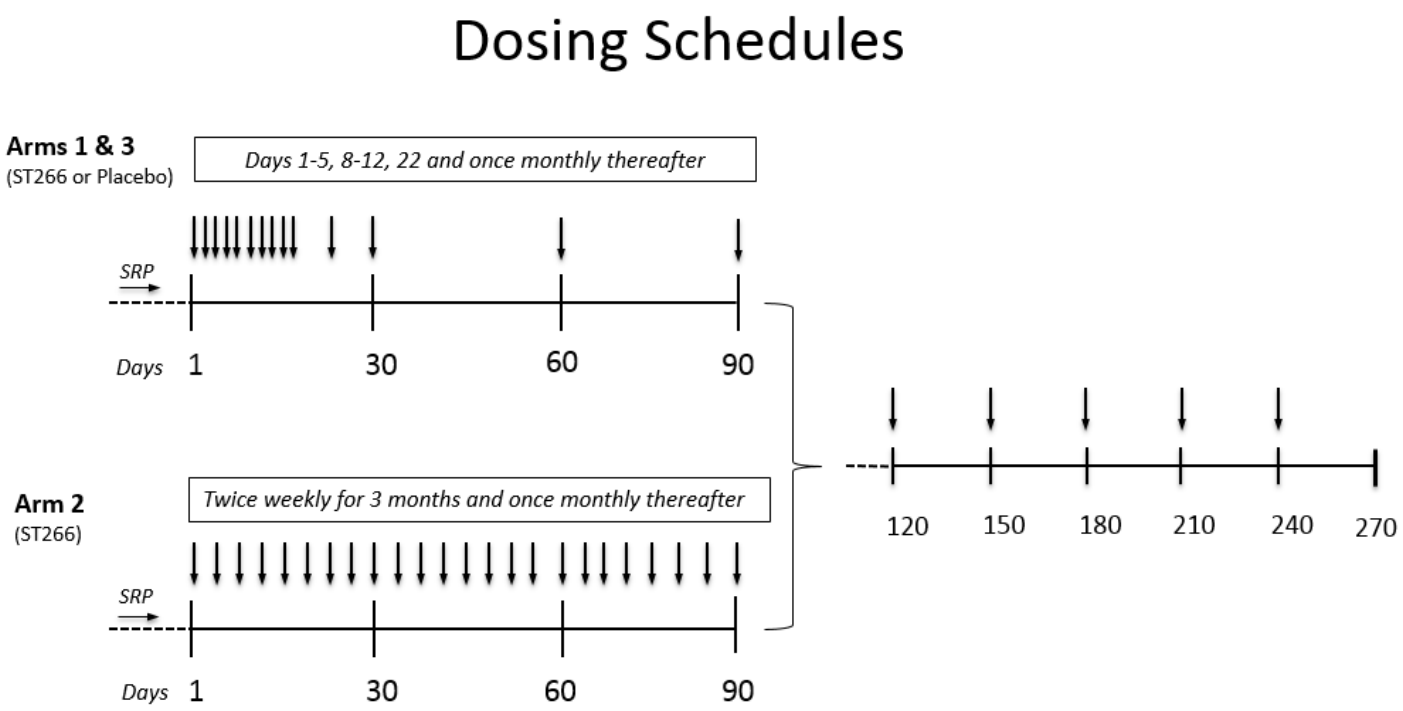
[d] SRP may be initiated on the same day as the Baseline visit and may require more than one visit. Subjects with moderate to heavy deposits will typically have no more than two quadrants treated in a single SRP visit. Local anesthesia must be used for SRP.

[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.

Figure 1: Dosing Schedules



Treatment Windows by Group (+/- Days)

	Visit Day									
Groups 1, 3	≤12	22	30	60	90	120	150	180	210	240
	N/A	3	3	3	5	7	7	7	7	7
Group 2	≤ 90					120	150	180	210	240
	N/A					7	7	7	7	7

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Provision of signed, written informed consent prior to participation in any study-related procedures.
2. Good general health as evidenced by the medical history.
3. Between 18 and 85 years of age at the 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 American Academy of Periodontists (AAP) definition (at least 6 teeth with ≥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 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).

8.2. Subject Exclusion Criteria

1. Presence of orthodontic appliances.
2. A soft or hard tissue tumor of the oral cavity.
3. Any dental condition that requires immediate treatment, such as carious lesions.
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[1], 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.

8.3. Re-screening of Subjects

Subjects may be re-screened provided that they do not fail inclusion criterion 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]).

8.4. Subject Withdrawal Criteria

Subjects may voluntarily withdraw from the study, or be removed from the study at the discretion of the investigator or sponsor at any time. If such withdrawal occurs, or if the subject fails to return for visits, the investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study records.

All subjects prematurely discontinuing from the trial, regardless of cause, should be scheduled as soon as possible for a follow-up safety visit, which will include all assessments planned for Day 270 (end of study).

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should document all steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

Subjects who are withdrawn from the study after beginning treatment will not be replaced.

[1] For the purposes of subject exclusion, *diabetes* is defined as any subject with (i) a history of type 1 or type 2 diabetes, (ii) prior or concomitant prescription of diabetes medications, or (iii) a laboratory test for glycated hemoglobin ≥6.5.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Table 4: Investigational Product

	Investigational Product
Product Name:	ST266 [Amnion-derived Cellular Cytokine Solution (ACCS)]
Dosage Form:	Liquid to be applied by pipette
Unit Dose	20 µL/tooth
Route of Administration	Topical application directly to the marginal gingiva
Physical Description	Clear to slightly yellow liquid that is free of particulates
Manufacturer	Stemnion, Inc.

9.2. Concomitant Medications

Use of concomitant treatment must be recorded in the subject's medical record and the electronic case report form (eCRF), including treatment/drug name, dose, indication, and start/stop dates. In addition, no homeopathic remedies (such as treatment with coconut oil) may be used during the study.

9.3. Treatment Compliance

Every treatment application of study drug will be performed in the dental clinic by the clinician/investigator (dental professional); therefore, non-compliance can be assessed easily by the investigator.

Treatments that are missed may be completed if done within the number of days indicated in Table 5 from the original scheduled date.

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

Table 5: Treatment Windows by Group (+/- Days)

	Visit Day									
Groups 1, 3	≤12	22	30	60	90	120	150	180	210	240
	N/A	3	3	3	5	7	7	7	7	7
Group 2	≤ 90					120	150	180	210	240
	N/A					7	7	7	7	7

9.4. Randomization and Blinding

A randomization scheme will be generated via interactive web response system (IWRS). Subjects will be randomized at the site after SRP is complete. 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). Any subjects that are discontinued after randomization and prior to treatment may be replaced. Examiners will be blinded to the treatment assignment.

A list of all subjects who have been treated will be maintained at the trial site, including each subject's identity, date of enrollment, and corresponding subject ID, so that any subject may be identified if required for any reason. The list is kept by the clinical site and must not be available to the sponsor. The electronic data collection system (EDC) will assign a screening ID number when a subject's data is entered at the screening visit. The subject will be identified only by that number until he/she is either randomized or withdrawn from the study. Upon randomization, the subject's screening ID number will be converted to a randomization ID number. Subjects will be identified only by either the screening ID number or the randomization number.

Treatment assignments will be blinded to the examiner, treatment administrator, and the subjects. Only in case of medical emergency or occurrence of AEs that warrant unblinding in the opinion of the Medical Monitor, will the treatment assignment be unblinded and made available to the investigator and the Medical Monitor. In the event of study unblinding, a non-study statistician will be assigned as the "unblinded statistician" to assist in unblinding and any safety review.

If the investigator feels it is necessary to unblind a subject's treatment assignment after an emergency situation, the investigator should contact the Medical Monitor or designee. Only after consultation with the Medical Monitor will a decision be made as to whether the treatment for the subject should be unblinded. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the blinding on the remaining subjects intact.

9.5. Treatment Visits

Treatment visits will consist of a review of the subject's medical and dental history, including recording concomitant medications. Additionally, the study medication will be applied to the buccal and lingual surfaces of the teeth. Following the application of the study medication an assessment of AEs will be performed. Subjects will be given oral hygiene instructions prior to the end of the visit.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

ST266 (ACCS) is a novel secretome derived from proprietary cells. ST266 is composed of a complex mixture of cytokines, growth factors, nucleic acids, and undefined cellular components produced by cultured amnion-derived multi-potent progenitor (AMP) Cells in Iscove's Modified Dulbecco's Medium (IMDM). It contains at least 75 cytokines and growth factors in very low or physiological concentrations and 2 proteins (0.5% human serum albumin and epidermal growth factor) that are added to support the growth of the cells.

10.2. Study Drug Packaging and Labeling

ST266 will be provided to the clinical site in two container types: frozen in sterile, single-use glass vials and in refrigerated liquid form provided in single-use plastic ampoules. Eppendorf pipettes and sterile pipette tips to be used for topical application of ST266 will also be provided to the site. The dispensing vials and pipette tips are single-use and will not be re-used.

10.3. Study Drug Storage

ST266 must be stored per container type.

- ST266 in single-use glass vials must be stored frozen (-20±5°C) until the day of use.
- ST266 in single-use plastic ampoules must be stored refrigerated (2-8°C) until the day of use.

10.4. Study Drug Preparation

The study staff assigned and trained for "product handling" will transfer ST266 to a 5 mL tube (RNase, DNase and pyrogen free) that is then provided to the dental clinic.

- ST266 in single-use glass vials must be thawed prior to dispensing 1.5 mL of ST266 to a 5 mL tube.
- ST266 contained in a single-use plastic ampoule is ready to use. Approximately, 1.3±0.2 mL of ST266 is transferred to a 5 mL tube.

10.5. Administration

In the dental clinic, the Eppendorf pipette with the sterile tip supplied by the sponsor will be filled with 1 mL of ST266. Twenty (20) microliters (10 µL to buccal surfaces and 10 µL to lingual surfaces) of ST266 will be applied directly to each tooth at the gingival margin by the study clinician at each treatment visit. The total daily dose will be less than 1 mL.

10.6. Study Drug Accountability

Used and unopened containers of study drug will be retained in the study pharmacy for drug reconciliation by study staff trained in product handling and accountability.

10.7. Study Drug Handling and Disposal

Study drug must be handled with protective gloves and mask. Opened containers of study drug from the clinic will be disposed of onsite using the standard handling protocol for the clinic after drug accountability has been performed by the sponsor or its agents. Unopened containers of study drug will be returned to Stemnion after accountability is performed at the end of the study for each site.

10.8. Placebo

Commercially available sterile saline (0.9% NaCl) will be supplied to the clinical site by the sponsor for use as the placebo (treatment for Group 3) for the study. Sterile saline is stored at room temperature as indicated by the packaging and is ready for use. Sterile saline will be applied in the same manner and in the same volume as the investigational product, ST266. Accountability, handling, and disposal procedures are the same as for the study drug.

11. ASSESSMENT OF EFFICACY

11.1. Criteria for Primary and Secondary Efficacy Endpoint Evaluations:

a. Pocket Depth (PD): Periodontal pocket depth will be determined with a UNC-15 periodontal probe at 6 sites per tooth, and rounded to the next lower whole millimeter.

b. Clinical Attachment Level (CAL): The measurement of the position of the soft tissue in relation to the cemento-enamel junction (CEJ) that is a fixed point, using probing depth and the distance from the gingival margin to the CEJ.

c. Bleeding On Probing (BOP): Dichotomous score of 0 or 1 indicating whether the site bleeds upon probing is performed independently of the gingival index measurement. Bleeding on probing will be measured from the 6 sites of the tooth as a secondary periodontitis variable:

   0 = No bleeding

   1 = Bleeding within 15 seconds following probing

11.2. Exploratory Evaluations

a. Cytokine/Chemokine Analysis: In order to detect the changes in local (GCF) and systemic (blood serum) levels of pro-inflammatory mediators, enzymes, and bone markers that are known to play a role in the tissue destruction and bone resorption/formation, analysis will be analyzed in the of GCF and serum specimens. For this purpose, pro-inflammatory mediators including, cytokines/chemokines (IL-1b, IL-6, IL-8, IL-17A), matrix metalloproteinases (MMPs) including MMP-1, MMP-8, and MMP-9, and bone markers (RANKL, Osteoprotegrin) will be analyzed. Crevicular fluid samples will be obtained from up to 4 teeth before the first dose of ST266, and before dosing on Days 15, 90, 180, and 270, if applicable. Cytokine analysis will also be obtained from serum samples collected at baseline and on Days 15, 90, 180, and 270.

b. Microbial Analysis: To detect subgingival microflora, subgingival plaque samples from the 2 teeth with the deepest PD will be collected at baseline and on Days 15, 90, 180, and 270, and analyzed using a DNA-DNA hybridization technique to provide a qualitative and semi-quantitative assessment of oral bacteria including: *Treponema denticola, Tannerella forsythia, Porphyromonas gingivalis, Centruroides gracilis, Campylobacter rectus, Campylobacter showae, Eubacterium nodatum, Fusobacterium periodonticum, Fusobacterium nucleatum polymorph, Fusobacterium nucleatum nucleatum, Fusobacterium nucleatum vincenti, Prevotella intermedia, Parvimonas micra, Prevotella nigrescens, Streptococcus constellatus, Streptococcus gordonii, Streptococcus intermedia, Streptococcus mitis, Streptococcus oralis, Streptococcus sanguinis, Aggregatibacter actinomycetemcomitans, Capnocytophaga gingivalis, Capnocytophaga ochracea, Capnocytophaga sputigena, Eikenella corrodens, Actinomyces odontolyticus, Veillonella parvula, Actinomyces gerencseriae, Actinomyces israelli, Actinomyces naeslundii, Actinomyces viscosus, Eubacterium saburreum, Gemella morbillorum, Leptotrichia bucallis, Neisseria*

mucosa, Propionibacterium acnes, Prevotella melaninogenica, Streptococcus anginosus, Selenomonas noxia, and Treponema socranskii. Results will be compared with known probe standards and scored on an ordinal scale of 0 to 5 as follows:

0 = No signal detected

1 = $<10^5$ bacteria

2 = $\sim10^5$ bacteria

3 = $>10^5$ bacteria

4 = $\sim10^6$ bacteria

5 = $>10^6$ bacteria

c. Radiographic Bone Level (RBL): Up to four vertical bitewing x-ray radiographs will be obtained at baseline and Days 90 and 270. For each time point, a total of two (2) radiographs will be taken from each side of the mouth. Crestal bone levels will be measured in mm relative to the CEJ, and changes in bone levels at Days 90 and 270 will be calculated relative to the baseline measurement. This procedure will be standardized for all sites, and radiographs will be interpreted by a central reading center.

d. Full-mouth Plaque Index (FMPI, Turesky modification of Quigley-Hein): Disclosing solution will be applied to the teeth and then plaque will be measured at 6 sites of each tooth.

0 = No plaque

1 = Separate flecks of plaque at the cervical margin of the tooth.

2 = A thin continuous band of plaque (up to 1 mm) at the cervical margin of the tooth.

3 = A band of plaque wider than 1 mm but covering less than one-third of the crown of the tooth.

4 = Plaque covering at least one-third but less than two-thirds of the crown of the tooth.

5 = Plaque covering two-thirds or more of the crown of the tooth.

11.3. Standardization and Calibration of Procedures

Clinical assessments of PD, CAL, and BOP will be used to assess the efficacy of the therapy. Radiographic procedures, GCF, FMPI, and microbial sampling will also be performed. All of these procedures are prone to technique-sensitive sources of variability and require standardization and/or calibration exercises to minimize measurement variability. Such training exercises at each site will occur prior to the start of screening at each respective site. A dedicated oral examiner at the primary clinical center will serve as the “gold standard” examiner for calibration sessions. Details of the training protocols are provided in the Clinical Procedures Manual.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The scope of safety monitoring is to assess the potential risks to the participants and ensure the safety of the participants during this trial. In order to monitor the data and safety, all necessary data including AE/SAE reports, safety reports (from Stemnion), subjects' medical/medication history, concomitant medication reports, review of subject conduct/compliance, soft and hard tissue evaluations at every visit, and dropout rates will be used and reviewed throughout the study. Serum chemistry including liver and kidney function, complete blood count, and urinalysis will be done at screening, Day 90, and Day 270. In women of child-bearing potential, a pregnancy test will be performed prior to enrollment and again at the last study visit (Day 270).

12.1.1. Demographic/Medical History

Complete medical history will be taken at screening. Interim history will be taken at each treatment and follow-up visit.

12.1.2. Vital Signs

Blood pressure, heart rate, temperature, and respiratory rate will be recorded at screening, baseline, and at each evaluation visit.

12.1.3. Weight and Height

Height and weight will be recorded at screening and weight will be recorded at Day 270.

12.1.4. General Assessments

A general assessment looking for allergic and potential toxic reactions will be made at each visit prior to treatment with study drug. The oral mucosa will be examined at each visit.

12.1.5. Laboratory Assessments

Blood (10 to 15 mL) and urine samples (3 to 5 mL) will be sent to a certified laboratory for hematology, blood chemistry, and urine tests at screening and at Days 90 and 270. If a subject has any laboratory value that was normal upon entry into the trial and becomes abnormal, the sponsor's Medical Monitor will review the data with the investigator to assess whether the laboratory value represents a safety concern.

12.1.6. Hematology

Complete blood count will be performed at screening and at Days 90 and 270. If a subject develops hemoglobin, hematocrit, or white blood cell count outside the normal range (as per the laboratory normal range values), that case will be reviewed by the sponsor's Medical Monitor. The Medical Monitor may determine that the subject will receive no further study drug treatment.

12.1.6.1. Blood Chemistry

Serum glucose, C-reactive protein, blood urea nitrogen, creatinine, electrolytes, HbA1c (at screening only), and liver function including bilirubin and hepatic enzymes will be measured at screening and at Days 90 and 270.

12.1.6.2. Urinalysis

Urinalysis will be performed at screening and at Days 90 and 270. If a subject develops hematuria or proteinuria after treatment is initiated, that case will be reviewed by the sponsor's Medical Monitor, who may determine that the subject will receive no further study drug treatment.

12.1.6.3. Pregnancy Screen

Urine pregnancy testing will be performed at screening and at the final visit (Day 270) on females of child-bearing potential using commercially available pregnancy tests.

12.2. Adverse and Serious Adverse Events

12.2.1. Introduction

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with Title 21 Code of Federal Regulations (CFR) Part 312, International Conference on Harmonisation (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and ICH Guideline E6: Good Clinical Practice: Consolidated Guidance.

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the sponsor or its designated representative.

12.2.2. Adverse Event (AE)

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

All AEs that occur after any subject signed consent, before treatment, during treatment, or within 30 days following the last final dose of treatment, whether or not they are related to the study, must be recorded.

12.2.3. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor whether it is considered treatment related or not.
- Is life-threatening: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the investigator or the sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- In-patient hospitalization or prolongation of existing hospitalization. Planned hospitalization or planned prolonged hospitalization do not fulfill the criteria for being an SAE, but should be documented in the subject's medical record. Additional details further defining hospitalization criteria can be found in the Clinical Procedures Manual.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect.

Or

- Is a medically important condition, i.e., events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

All SAEs that occur after any subject has signed consent, before treatment, during treatment, or within 30 days following the final dose of treatment, whether or not they are related to the study, must be recorded.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the sponsor as described in Section 12.5.1.

12.2.4. Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants according to the following criteria:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- Life-threatening

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 12.2.3 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate,

or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

12.3. Relationship to Study Drug and Expectedness

An investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (not related, possibly related, or definitely related). The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possibly" or "definitely," the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

The sponsor's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table 6. Additionally, in this study there are no suspected SAEs and all SAEs will be considered suspected unexpected serious adverse reactions (SUSARs).

Table 6: Attribution of Adverse Events

Not related	The AE is clearly not related.
Possibly related	The AE has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
Definitely related	The AE is clearly related.

12.4. Collection and Recording Adverse Events

12.4.1. Period of Collection

All AEs and SAEs will be collected from the time the informed consent is signed until the end of the study. All AEs and SAEs that occur after any subject has signed consent, before treatment, during treatment, or within 30 days following the final dose of treatment, whether or not they are related to the study, must be recorded.

12.4.1.1. Methods of Collection

Adverse events may be collected as follows:

- Observing the participant

- Questioning the participant in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the participant

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stable, establishing a new baseline and the participant's safety is not at risk.

An abnormal laboratory value recorded at screening is not considered an AE, but is treated as a preexisting condition and should be recorded in the subject's medical history.

12.4.2. Recording Method

12.4.2.1. Adverse Events

Throughout the study, the investigator will record AEs on the appropriate eCRF regardless of their severity or relation to the study product. The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

Once recorded, an AE will be followed until it either; resolves with or without sequelae, the subject ends study participation, 30 days after the final dose of study treatment, or 30 days after the subject prematurely withdraws (without withdrawing consent) or is withdrawn from the study, whichever occurs first.

12.4.2.2. Serious Adverse Events

Serious adverse events will be recorded on the AE eCRF and on the SAE eCRF, and health authorities will be notified as outlined in Section 12.5.2.

12.5. Recording and Reporting Adverse Events

After learning that a participant has experienced an AE, the investigator or designee is responsible for recording the AE in the eCRF, regardless of relationship or expectedness. If the AE is determined to be serious, expedited reporting is required per Section 12.5.1.

12.5.1. Reporting SAEs to the Sponsor

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE, regardless of relationship or expectedness, within 1 business day of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Reporter
- Subject ID
- Serious AE term
- Relationship to study medication(s)

- Reason why the event is serious

Supplemental eCRF pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, and death as applicable. If an SAE is related or possibly related, unblinding may occur per Section 9.4.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE eCRF should be updated and re-submitted via the EDC system. Every time the SAE eCRF is submitted, it should be signed by the investigator or sub-investigator.

For additional information regarding SAE reporting, contact Rho Product Safety:

Rho Product Safety
6330 Quadrangle Drive, Suite 500
Chapel Hill, NC 27517
Toll-free: 1-888-746-7231
SAE Fax Line: 1-888-746-3293

Email: rho_productsafety@rhoworld.com

12.5.2. Reporting SAEs to Health Authorities

The Sponsor will report Investigational New Drug (IND) Safety Reports to the Food and Drug Administration (FDA) and investigators in accordance with the FDA regulations detailed in 21 CFR 312.32.

The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic. The sponsor shall notify the FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected.

These events, which require unblinding, must be reported by the sponsor to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days.

12.5.3. Reporting SAEs to IRB(s) or Ethics Committee(s)

It is the responsibility of the investigators to promptly notify their respective IRB(s) or independent ethics committee(s) (IECs) of IND Safety reports or other matters involving risk to patients as mandated by the IRBs/IECs.

SUSARs are to be reported to the investigators and to the IRBs/IECs when the following conditions occur:

- The event must be an SAE.
- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say, not foreseen in the Investigator's Brochure.

12.5.4. Reporting Pregnancy

During the study, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information within 1 business day of becoming aware of the event. Study treatment must be discontinued immediately in the event of a pregnancy. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy should be reported as it becomes available even if the subject was discontinued from the study.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 12.4.2.2. Elective abortions for no medical reason and without complications should not be handled as AEs. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the investigator suspects is related to the *in utero* exposure to the study treatment should also be reported.

13. STATISTICS

Analysis of the clinical efficacy data will consist of modeling endpoints, including PD, CAL, BOP, and FMPI, with treatment group as the main effect and adjusted for baseline. Post-baseline treatment comparisons will be modeled through a generalized estimating equations (GEE) method (with a linear link and exchangeable covariance matrix), adjusting for the baseline value. Methods of analysis for periodontal microbial flora profiles, inflammatory cytokine levels in GCF and in serum and RBL will be described in separate statistical analyses plans. Results will be considered significant if $p < 0.05$.

13.1. 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 deviate from the protocol as per the statistical analysis plan.

Further details regarding the specific analyses associated with each study population are provided in the statistical analysis plan.

13.2. Prevention and Treatment of Missing Data

Efforts will be made by the sponsor and investigators to maximize subject compliance with the study protocol. Previous studies of adjunctive treatments for periodontitis reported subject completion rates >90% (Paquette, 2004). Because this study requires a significant number of in-office treatments, a more conservative estimate of a 20% dropout rate has been made, which is reflected in the sample size calculation (Section 7.2).

Missing data in this study will be treated according to standard practices based on published recommendations of the National Research Council Panel on Handling Missing Data in Clinical Trials (National Research Council, 2010). Methods for imputation of missing data are provided in the statistical analysis plan.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative for the sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Stemnion or its representatives. This will be documented in a Clinical Study Agreement between Stemnion and the investigator.

During the study, a monitor or representative for the sponsor will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the clinical site, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the sponsor.
- Confirm AEs and SAEs have been properly documented on case report forms, any SAEs have been forwarded to Stemnion and SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Quality control and quality assurance may be performed before, during, and after the study by the sponsor or authorized personnel. Regulatory authorities in certain countries reserve the right to audit study sites following submission of data in regulatory applications. The investigator may be given due notice of any intended audit by a regulatory body. By signing this protocol and the FDA Form 1572, the investigator acknowledges that these inspection procedures may take place and agrees to provide access to the required subject records and other study documentation. Furthermore, the investigator agrees to inform the sponsor immediately of any known or suspected inspection by authorities. If the investigator does not comply with the protocol, GCP, or regulations, Stemnion, Inc. reserves the right to disqualify the investigator and/or site from the current or future protocols.

14.3. Institutional Review Board (IRB)

This study is being conducted under a United States IND application. All clinical study sites involved in this study must follow FDA and ICH GCP guidelines. United States federal regulations require that all investigational drug studies be conducted under the auspices of an IRB/IEC, as defined in 21 CFR 56, and in accordance with the Declaration of Helsinki (1989). This committee, the makeup of which must conform to federal, state, and local guidelines regarding such, will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent, prior to study initiation. The investigator will provide the sponsor with a copy of the communication from the IRB/IEC to the investigator indicating approval of the protocol and consent form. All changes to the protocol or consent form must be reviewed and approved prior to implementation except where necessary to eliminate apparent immediate hazards to human subjects.

The investigator will be responsible for obtaining an annual IRB/IEC re-approval throughout the duration of the study. Copies of the investigator's annual report to the IRB/IEC and copies of the IRB/IEC's continuance of approval must be retained in the site study files and furnished to the sponsor.

14.4. Access to Protected Health Information (PHI)

Study personnel will have access to a subject's protected health information (PHI). This information may be obtained by the sponsor, which includes any persons or companies that are working with, working for, or owned by the sponsor. PHI may be given to the U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, other governmental agencies in the U.S., governmental agencies in other countries, and governmental agencies to which certain diseases (reportable diseases) must be reported.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Stemnion, Inc. may conduct a quality assurance audit. Refer to Section 14.2 for details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the sponsor before he or she can enroll any subject into the study.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Stemnion will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The investigator will ensure that this study is conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the individual. The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline or with local law if it affords greater protection to the subject.

16.3. Written Informed Consent

The investigator will be responsible for obtaining an Informed Consent signed by each subject or his/her legally authorized representative, prior to his/her participation in the study, in accordance with 21 CFR Part 50.20. Informed Consent will be obtained from a subject or his/her legally authorized representative after a full explanation of the purpose of the study, the risks and discomforts involved, potential benefits, etc., have been provided by the investigator or designee, both verbally and in writing. The original or a copy of the signed copy of the Informed Consent must be maintained in the institution’s records, and is subject to inspection by a representative of Stemnion, Inc. or regulatory agencies. The subject or his/her legally authorized representative will also be given a copy of the signed consent form.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Stemnion, Inc. will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. Regulatory agencies and other government agencies may inspect study records.

17.2. Retention of Records

It is the responsibility of the investigator and study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by the sponsor, its designees, and regulatory agencies. These should minimally include:

- Subject files including the completed eCRF, supporting source documentation, and the Informed Consent.
- Study files (Regulatory Binder) including the protocol with all amendments, the Investigators' Brochure, copies of all regulatory documentation and all correspondence with the IRB/IEC, regulatory authority (if applicable), and Stemnion, Inc.
- Pharmacy files including all drug shipment, receipt, dispensing, destruction and accountability records, and pharmacy-related correspondence.

The FDA requires that an investigator retain records for a period of 2 years following the date a New Drug Application (NDA) or Biologics License Application (BLA) is approved for the indication for which the drug is being investigated. If the application or license is not approved for such indication, the investigator will retain records until 2 years after the investigation is discontinued. In the event that storage of records becomes a problem or the investigator moves, the investigator will contact the sponsor immediately so provisions can be made.

Upon completion of the study, and at yearly intervals during the study, the investigator is required to submit a summary report to the IRB. These reports may be prepared by Stemnion, Inc. in collaboration with the investigator.

18. PUBLICATION POLICY

Information concerning ST266 and patent application processes, scientific data, or other pertinent information is confidential and remains the property of Stemnion, Inc. The investigator may use this information for the purposes of the study only. It is understood by the investigator that Stemnion, Inc. will use information developed in this clinical study in connection with the development of ST266 and, therefore, may disclose it as required to other participating clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the sponsor, Stemnion, Inc.

19. REFERENCES

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