PROTOCOL

A Randomized, Double-Blind, Controlled, Multicenter Dose Verification Clinical Trial to Evaluate the Safety and Effectiveness of [redacted] Growth Factor Enhanced Bone Graft Substitute for the Treatment of Periodontal Defects 6-months Post-Surgery

(NCT01728844)

Sponsor: Sunstar Americas, Inc.
1300 Abbott Drive
Elgin, IL 60123

Study Number: CLP-2011-10-31-1

IDE Number: [redacted]

Device: [redacted] Growth Factor Enhanced Bone Graft Substitute

Date: Feb 20, 2013

Protocol Revision:

Effective Date	Version	Description of Change
Oct. 31, 2011	1	New
Jul. 24, 2012	2	Amendment
Feb. 20, 2013	3	Amendment

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1.0 STUDY SUMMARY

Name of Sponsor: Sunstar Americas, Inc.	**Device:** [redacted] Growth Factor Enhanced Bone Graft Substitute
Title of Protocol: A Randomized, Double-Blind, Controlled, Multicenter Dose Verification Clinical Trial to Evaluate the Safety and Effectiveness of [redacted] Growth Factor Enhanced Bone Graft Substitute for the Treatment of Periodontal Defects 6-months Post-Surgery	**IDE No.:** Pending
Study Number: CLP- 2011-10-31-1	**Study Start:** After IDE and site IRB approval
Enrollment Completion Planned: TBD	
Study Design: This will be a prospective, randomized, double-blinded, controlled, multi-center, dose-verification clinical study in subjects who require surgical intervention to treat a qualifying periodontal defect. Treatment randomization will be stratified by smoking status. The parallel arms will be: Treatment I: β-TCP alone (active control) Treatment II: [redacted] GFeBGS: consisting of β-TCP and 0.1% rh-bFGF Treatment III: [redacted] GFeBGS: consisting of β-TCP and 0.3% rh-bFGF Treatment IV: [redacted] GFeBGS: consisting of β-TCP and 0.4% rh-bFGF After signing an informed consent for screening, being screened, having pre-surgical treatment and baseline measurements, signing an informed consent for study enrollment, subjects meeting inclusion criteria and not meeting any exclusion criteria will be randomized to one of four groups so that treatment is balanced within each investigational site and according to smoking status. Enrollment will be defined as randomization to one of the above-mentioned study arms. Investigators who perform evaluations will remain blinded to the investigational device implantation of all subjects for the 6-months post-surgery. The roles of Investigator will be determined at the start of the study and will remain until completion of the study. The study will be conducted in accordance with the Declaration of Helsinki (1996) and Good Clinical Practices (GCPs). The study will receive IRB approval at each investigational site prior to commencement of the study. Investigators will administer treatments to subjects following pre-surgical procedures, and subjects will receive surgical implantation of the investigational device or the active control in the intrabony periodontal defect located at the target tooth having pocket depths (PD) ≥ 7 mm and vertical bone defect ≥ 4 mm with at least 1 defect wall. Wound-healing (WH) scale of the surgical site will be examined at 2 and 4 weeks post-surgery. Clinical examinations, clinical attachment level (CAL), probing depth (PD), gingival recession (GR) and bleeding on probing (BOP), of the treated tooth will be performed at 3 and 6 months. Radiographic examination will also be performed at baseline, 3 and 6 months. After all subjects complete the 6-month follow-up post-surgery, the data will be assessed to select the optimal therapeutic rh-bFGF dose.	
Primary Objective: To obtain dosing data on [redacted] Growth Factor enhanced Bone Graft Substitute (GFeBGS) for the	

treatment of periodontal intrabony defects and to help guide the selection of dosing for future study.

Subject Population: Subjects 25 years and older with advanced periodontal disease in at least one site requiring surgical treatment to correct a bone defect. A total of 94 subjects will be randomized to obtain a minimum of 80 evaluable subjects for this multicenter trial.

Number of Subjects:	**Number of investigational sites:**
80 evaluable subjects	6 sites

Main Criteria for Inclusion:

Inclusion criteria include:

1. Male or female, age of 25 and older
2. Must have read, understood, and signed a consent form
3. Must be able and willing to follow study procedures and instructions
4. Must have undergone thorough scaling and root planing of the test site and be expected to demonstrate good plaque control after instruction in oral hygiene
5. The treated site must exhibit the following:
   - A pocket depth of 7 mm or greater
   - After surgical debridement, 4 mm or greater intrabony defect with at least 1 bony wall
   - Sufficient keratinized tissue to allow complete tissue coverage of the defect
   - Radiographic base of defect at least 3 mm coronal to the apex of the tooth

Main Criteria for Exclusion:

Significant exclusionary criteria are:

1. Failure to maintain adequate oral hygiene during the screening phase
2. Women of child-bearing potential
3. A history within the last 6 months of HIV, Type IV heart disease, or end-stage renal disease
4. A history of oral cancer or any other cancer (except for end of treatment for skin cancers such as squamous and basal carcinoma with end of treatment at least 6 months ago and/or prostate cancer with end of treatment at least 5 years ago)
5. A history within 12 months of previous open flap periodontal surgery on the study tooth
6. A diagnosis of pre-malignant oral lesion(s)
7. A traumatic occlusion of the target tooth
8. Target "study" tooth exhibiting Grade III mobility
9. Maxillary molars or maxillary first premolar with a prominent mesial concavity
10. Study tooth exhibiting a Class II or greater furcation defect
11. Clinical or radiographic signs of untreated acute or chronic periapical infection at the surgical site, apical pathology, root fracture, severe root irregularities, cemental pearls, cervical enamel projections not easily removed by odontoplasty, untreated carious lesions at the cemento-enamel junction (CEJ) or on the root surface, or restorations with open or otherwise defective margins at or below the CEJ
12. A history within the last 6 months of the daily use of any tobacco products besides cigarettes (smokeless chewing tobacco, pipe or cigar smoking), or of smoking more than 10 cigarettes per day
13. Subjects participating in other clinical trials within 30 days of enrollment
14. Subjects having uncontrolled endocrine-induced diseases (e.g. uncontrolled diabetes mellitus and

hyperparathyroidism)

15. Subjects undergoing current therapy with systemic steroids or other drugs that significantly alter bone metabolism

16. Subjects with Localized, Juvenile Periodontitis (LJP) sites in the oral cavity

Investigational Device Administration:

The investigational device, [redacted] GFeBGS as a "kit" product, consists of the synthetic bone graft substitute (β-TCP) granule saturated with reconstituted recombinant human basic fibroblast growth factor (rh-bFGF). The β-TCP is supplied in a sterile particulate form in one container. The active device kits contain a vial with a sterile lyophilized cake that contains rh-bFGF. The active control device kits contain a vial with a sterile lyophilized cake that does not contain rh-bFGF. The kits also contains a solvent, 1% hydroxypropyl cellulose (HPC) solution supplied in a sterile prefilled syringe for reconstituting lyophilized cake. The β-TCP is saturated with the reconstituted solution during the periodontal surgical procedures and placed into the periodontal defect.

Main Criteria for Evaluation and Analyses:

The primary effectiveness endpoint is a composite endpoint that considers radiographic and clinical measurements at six months post-implantation: the amount of linear bone growth (LBG), which is assessed with the use of radiographs, and the regain from baseline of clinical attachment level (ΔCAL), which is calculated from clinical assessments. The success criteria are a minimum of 1.5 mm for ΔCAL and a minimum of 1 mm for LBG. Both the ΔCAL and LBG must meet the success criteria for a subject to be considered a success.

The secondary endpoints will include the mean ΔCAL from baseline at three and six months and the mean ΔCAL between study treatments at three and six months post-implantation; the LBG at six months; percent bone fill (%BF) in a vertical and horizontal direction compared to baseline and six months post-implantation, a composite endpoint combining ΔCAL and %BF; Probing Depth Reduction (PDR) from baseline at three and six months post-implantation, Change in Gingival Recession (ΔGR) from baseline at three and six months post-implantation; Wound-Healing (WH) scale and gingival wound evaluation during the first four weeks, and bleeding on probing (BOP) at three months.

Dose Selection Overview:

The goal of the feasibility study is to identify either the 0.1%, 0.3% or 0.4% active dose to be compared vs. the β-TCP control in a pivotal study, based on the observed safety and effectiveness together with past study results. No formal interim analyses are planned.

This study will not be used for labeling purposes, but will be used to plan the subsequent pivotal study. The Sponsor retains the right to pick any of the three active doses moving forward to the pivotal study.

Statistical Considerations:

The primary effectiveness endpoint is a composite endpoint that considers radiographic and clinical measurements at six months post-implantation: the amount of linear bone growth (LBG), which is assessed with the use of radiographs, and the change from baseline of clinical attachment level (ΔCAL), which is calculated from clinical assessments. To be a success, ΔCAL ($CAL_{6\ mo} - CAL_{Baseline}$) must be at least -1.5 mm and a minimum measurement of 1 mm is required for linear bone growth (LBG) measured from baseline; both must be met at 6 months to define a primary effectiveness success for the tooth (Lynch S, Lavin P *et al. J Periodontal* 2006;77:1314). The number of teeth that meet the success criteria for the primary endpoint will be compared between the study treatments. The components of the primary effectiveness outcome, including LBG in particular, are also of interest.

2.0 STUDY REFERENCE INFORMATION

2.1 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified below. The identified vendors will perform these activities in full or in partnership with the Sponsor.

Issue	Organization
Site Management and Monitoring	[redacted]
Serious Adverse Event and Pregnancy Reporting	[redacted]
Dental Director	Robert J. Genco, DDS, PhD State University of NY at Buffalo Periodontal Disease Research Center 3435 Main Street Buffalo, NY 14214-3092 [redacted]
Lead Principal Investigator	David L. Cochran, DDS, PhD University of Texas Health Sciences Center at San Antonio Department of Periodontics 7703 Floyd Curl Drive San Antonio, TX 78284 [redacted]
Radiographic Analysis	Nicolaas C. Geurs, DDS University of Alabama at Birmingham School of Dentistry 1919 7th Avenue South Birmingham, AL 35294 [redacted]

Central Laboratory	[redacted]
Data Management	[redacted]
Statistical Analysis	[redacted]
Clinical Supply Packaging	[redacted]

2.2 Lead Principal Investigator

David L. Cochran, DDS, PhD
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Department of Periodontics
7703 Floyd Curl Drive
San Antonio, TX 78284

2.3 List of Abbreviations

AE	Adverse event
Rh-bFGF	Human recombinant basic fibroblast growth factor
BD	Bone defect depth
β-TCP	Beta-tricalcium phosphate
BOP	Bleeding on probing
BGS	Bone graft substitute
CAL	Clinical attachment level
CEJ	Cemento-Enamel junction
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good clinical practices
GLP	Good laboratory practice
GR	Gingival recession
GTR	Guided Tissue Regeneration
ICF	Informed consent form
IRB	Institutional review board
ITT	Intention-to-treat
LBG	Linear bone growth
mITT	Modified intention-to-treat
%BF	Percent bone fill
PD	Pocket depth
PDR	Probing depth reduction
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedure
SRP	Scaling and root planing
UADE	Unanticipated Adverse Device Effect
WH	Wound healing

3.0 INTRODUCTION

3.1 Background

3.1.1 Investigational Device

The investigational device, [redacted] Growth Factor Enhanced Bone Graft Substitute (GFeBGS) as a "kit" product, consists of the synthetic bone graft substitute, β-tricalcium phosphate (β-TCP), saturated with reconstituted recombinant human basic fibroblast growth factor (rh-bFGF) in 1% hydroxylpropyl cellulose (HPC) solution. The β-TCP is supplied in a sterile particulate form in one container. All kits contain a sterile lyophilized cake in a vial. The kits with investigational products have rh-bFGF added to the lyophilized cake and the kits for the control product do not. The kits also contain a solvent, 1% HPC sterile solution, supplied in a sterilized prefilled syringe for reconstituting the lyophilized cake. The β-TCP is saturated with the reconstituted rh-bFGF/HPC or control solution immediately prior to application to the periodontal defect site during the periodontal surgical procedure. The investigational device would be appropriately regulated under 21 CFR §872.3930, "Bone Grafting Material, Dental, With Biologic Component", Class III, Procode NPZ.

The investigational device was assessed for biocompatibility through pre-clinical studies. The studies have been conducted in a GLP compliant contract laboratory in the U.S.

3.1.2 β-TCP

β-TCP is a well-known synthetic bone graft substitute with a formula of $Ca_3(PO_4)_2$ (molecular weight: 310.18). Extensive animal and human clinical studies over the past 25 years have demonstrated biocompatibility of the β-TCP with no reports of any adverse reactions. The β-TCP used in this trial is OSferion D manufactured by Olympus Terumo Biomaterial Corporation. OSferion D was cleared by FDA for commercial distribution via the 510(k) Premarket Notification System (K081561, SE Date: 07/08/2008) and is intended to fill, augment, or reconstructive periodontal or bony defects of the oral and maxillofacial region including augmentation or reconstructive treatment of the alveolar ridge and filling of infrabony periodontal defects. OSferion D is a highly purified β-TCP particle approximately 100% with a 150-800 μm diameter. β-TCP is already known as an effective synthetic bone substitute to serve as a biocompatible scaffold to bone cells for osteoconduction shown in a variety of orthopedic and dental applications. β-TCP is absorbed and replaced gradually by new bone after implantation. This has been demonstrated in a defect for 6 months in orthopedic cases [(1)].

3.1.3 Rh-bFGF

Rh-bFGF (generic name: trafermin) was approved in April 2001 by the Japanese Ministry of Health, Labor and Welfare as an active agent in a drug for dermal ulcers named "Fiblast® Spray". The drug has been developed and marketed since then by Kaken Pharmaceutical Ltd. Co., a Japanese pharmaceutical company. Kaken has also been developing a product for periodontal

regeneration containing rh-bFGF in gel form in Japan. Kaken has completed a phase III clinical pivotal trial for periodontal application in Japan based on the clinical safety and effectiveness demonstrated through the prior phase II studies [(2)(3)]. However, the data analysis for this trial is not yet completed.

Rh-bFGF is a protein consisting of 154 amino acid residues ($C_{764}H_{1201}N_{217}O_{219}S_6$; molecular weight: 17,122.67) and 153 amino acid residues ($C_{761}H_{1196}N_{216}O_{218}S_6$; molecular weight: 17,051.59), produced in recombinant cells by expression of a human bFGF gene (N-terminal; Ala-Ala: more than 65%, Ala: not more than 35%). It is a single strand polypeptide molecule which has no sugar chain. It will be supplied as a lyophilized product in the [redacted] Growth Factor Enhanced Bone Graft Substitute combination product. Sodium edentate, sucrose and citric acid are contained in the lyophilized product as inactive ingredients with rh-bFGF protein.

Rh-bFGF is a biological stimulant which has been reported to promote proliferation and migration of certain kinds of cells, including osteoblasts, endothelial cells and periodontal ligament cells. Rh-bFGF is also unique in that it prohibits proliferation of epithelial cells. The primary characteristic of rh-bFGF is to help cells in wound surfaces grow and migrate toward the surface and inside a bone graft substitute. Furthermore, rh-bFGF is well known as a potent angiogenic factor to generate new blood vessels, which are important for accelerating the wound healing process.

Two recent pilot beagle studies in a one-wall periodontal defect model conducted at the State University of New York at Buffalo showed that the test group (β-TCP plus rh-bFGF) significantly promoted newly formed cementum on the root adjacent to the defect compared with the active control group (β-TCP alone) and sham group (non-graft) [(4)]. The result suggested that the addition of rh-bFGF could promote both new formation of periodontal ligament and cementum in the human. Regarding alveolar bone regeneration in the beagle study, bone height seemed to be promoted in the test group compared to the active control group, however, the osteoconductivity of the β-TCP component resulted in substantial bone regeneration also in the active control group. Even though some bone repair was found in the Sham group it was limited compared with the other two groups and the relapse of the connective tissue and downgrowth of the gingival epithelium into the wound was conspicuous. The pilot studies suggested that this beagle model was effective and predictive of the effectiveness and safety in human clinical use. Hence, the definitive study was implemented utilizing the same beagle model in a GLP compliant animal laboratory and the results verified the results of the pilot study [(5)].

3.2 Proposed Intended Use

The intended use of the investigational device is for the treatment of periodontal intrabony defects.

3.3 Scientific Rationale for the Proposed Study

Periodontitis is the primary reason for tooth loss in the United States among the adult population. The loss of teeth affects both systemic health and quality of life. Ten biocompatibility studies based on the requirements of ISO 10993-1 guidelines have demonstrated acceptable safety of the

investigational device. A pilot dog study employing a critical defect model, followed by another study using the same model and protocol that was conducted in a GLP compliant laboratory, have demonstrated the product effectiveness.

β-TCP, one of components of the investigational device, has been used as a dental bone filler material in the U.S. The other component, rh-bFGF has been developed in Japan for periodontal regeneration in a different application. The preliminary safety and effectiveness of rh-bFGF gel was shown in two phase II clinical studies. An early phase II feasibility study of 80 subjects randomized equally to one of four groups (placebo, 0.03% rh-bFGF, 0.1% rh-bFGF and 0.3% rh-bFGF) demonstrated a significant increase of alveolar bone height in the 0.3% group compared to the placebo group at 36 weeks. Reported complications were similar between the placebo and test groups. A late phase II dose finding study of 240 subjects randomized equally to one of four groups (placebo, 0.2% rh-bFGF, 0.3% rh-bFGF and 0.4% rh-bFGF) demonstrated a significant increase of alveolar bone height in the 0.3% and 0.4% groups compared to the placebo group at 24 weeks and in all three test groups compared to the placebo group at 36 weeks. Reported complications were similar between the placebo and test groups. A phase III clinical study has been completed to support a regulatory filing in Japan; however, the data analysis has not been completed at this time.

This study will be the first to examine the effectiveness and safety of the investigational device in adult subjects with a periodontal intrabony defect and connective tissue loss.

3.4 Mode of Action

The principal mode of action of β-TCP is as an osteoconductive bone void filler. The device physically fills bone defects providing a matrix or scaffold for bone formation. By filling the defect it also prevents the collapse of the soft tissues into the bone defect and its porous nature facilitates stabilization of the blood clot. The microstructure of the β-TCP allows roughness of its surface which provides more opportunities for cells to attach and grow on its surface. The pores inside of the particle are interconnected allowing for cell migration and angiogenesis which further enhance bone ingrowth.

Regarding [redacted] GFeBGS, the rh-bFGF enhances the β-TCP's physical and biological actions by promoting cellular ingrowth into a periodontal defect and bone matrix. Furthermore, the recent beagle studies showed that rh-bFGF could significantly promote both periodontal ligament and cementum maturation, while retarding epithelial migration. An increase in new bone formation was also observed [(4)].

3.5 Potential Risks

3.5.1 Potential Risks Associated With The Procedure

Potential risks to a subject participating in this trial include those associated with any routine periodontal reconstructive surgery. The following risks are associated with the periodontal flap procedure: post-surgical inflammation, fever, pain, local irritation, redness, swelling, pus, and

superficial post-surgical infection. If any of these adverse events occur, it is expected that they will resolve over time as the wound heals and with appropriate post-surgical treatment.

Excessive bleeding caused by blood vessel damage, nerve damage, damage to the surrounding soft connective tissue and dehiscence may result from the surgical procedure.

Additional potential risks are associated with the use of local anesthesia or IV sedation and include allergic reaction, toxic effects on the cardiovascular and central nervous system including symptoms such as dizziness, tinnitus, visual disturbances, respiratory distress, tachycardia and seizures, Vasovagal episodes including lowered heart rate, lowered blood pressure and fainting but the likelihood of occurrence is minimal (less than 1%). Note: For a complete list of risks associated with the drugs, Investigators should review the package inserts of the drugs.

Investigators selected to participate in this study will have extensive previous experience with the procedures. Additionally, all Investigators will be trained on how to reduce the severity of risks by the Principal Investigator prior to study initiation. In order to minimize the risk of post-surgical infection, 0.12% chlorhexidine rinse will be prescribed to subjects. Subject education of the post-surgical procedures will also minimize the potential hazards. Therefore, possibility of the above-mentioned adverse events will be minimized.

3.5.2 Potential Risks Associated With β-TCP

β-TCP is a ceramic bone graft material used in a variety of orthopedic and dental applications since 1981. The β-TCP material used in the [redacted] GFeBGS product is [redacted] as a bone void filler. Although a few adverse events have been reported in orthopedic applications, no adverse reactions have been reported from the use of β-TCP products in dental applications in the FDA MAUDE database. The β-TCP used in GFeBGS has undergone biocompatibility testing in conformance with the International Standard ISO-10993 and was determined to be biocompatible.

3.5.3 Potential Risks Associated With rh-bFGF in GFeBGS

The rh-bFGF based product has been approved for treatment of dermal ulcers by the Japanese authority and in clinically used since 2001 with minimal adverse events reported in the post marketing surveillance report to the Pharmaceuticals and Medical Devices Agency for 8 years. Most of the adverse events were related to the skin and subcutaneous tissue and the administration site. There were rare reports of malignant tumors in the follow-up period whose causal relationship with the product could not be denied due to insufficient information. The safety and toxicological testing on rh-bFGF includes single dose toxicity, repeating dose toxicity, reproductive development toxicity, genetic toxicity (mutagenicity), local irritation, antigenicity, pyrogen test, skin carcinogenesis initiation, skin carcinogenesis promotion, effects on human tumor cells, effects on mouse melanoma cells, evaluation using a two-step model of hepatocarcinogenesis, *in vitro* transform study. No adverse events were observed throughout this series of studies. In summary, the safety, toxicity and biocompatibility data suggest that an rh-bFGF-based product is sufficiently safe for conducting a human clinical trial.

However, the risk of promotion of cancer in a remote location cannot be denied because rh-bFGF has a promotional effect to accelerate a proliferation of various kinds of cells including several human tumor cell lines. Even though the probability of this risk is very low, its severity is considerable if it were to occur. To minimize the cancer promotion risk, the subjects with a history of oral cancer or having any other history of cancer (except for prostatic and skin cancer more than 5 years after treatment and skin cancer) are excluded in this study. If precancerous conditions of the mucous membrane are found in the oral cavity, it will be thoroughly examined and diagnosed before enrollment of the patient in this study. If the Investigator is unable to make a definitive diagnosis of the oral lesion, the Investigator will consult with an oral pathologist or a qualified specialist. Also, Investigators will be well trained about the proper preparation and use of GFeBGS before initiation of the study.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective:

To obtain dosing data on [redacted] Growth Factor enhanced Bone Graft Substitute (GFeBGS) for the treatment of periodontal intrabony defects and to help guide the selection of dosing for future study.

4.1.2 Secondary Objective:

To determine the capacity of the [redacted] Growth Factor enhanced Bone Graft Substitute (GFeBGS) to accelerate and enhance the periodontal wound healing process.

4.2 Endpoints

4.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite endpoint that considers radiographic and clinical measurements at six months post-implantation: the amount of linear bone growth (LBG), which is assessed with the use of radiographs, and the regain from baseline of clinical attachment level (ΔCAL), which is assessed clinically. Linear bone growth (LBG) in a vertical and horizontal direction will be determined radiographically at six months post-implantation. The clinical attachment level (CAL) is the distance from the cemento-enamel junction (CEJ) (or other fixed reference point) generally along the long axis of the tooth to the deepest extent of the periodontal pocket.

4.2.2 Secondary Effectiveness Endpoints

The secondary endpoints evaluated and compared among treatments will include:

- Mean ΔCAL at three and six months post-implantation;
- LBG at six months post-implantation;
- Percent bone fill (%BF) at six months post-implantation;
- Composite endpoint combining ΔCAL and %BF at six months post-implantation;
- Probing Depth Reduction (PDR) at three and six months post-implantation;

- Change in Gingival Recession (ΔGR) from baseline at three and six months post-implantation;
- Wound-Healing (WH) scale at two and four weeks post-implantation:
- Gingival wound evaluation at two and four weeks post-implantation; and
- Bleeding on probing (BOP) at three months post-implantation.

4.2.3 Safety Endpoints

Safety will be monitored throughout the trial by assessing the incidence, timing, and severity of Adverse Events. Adverse events with clinical signs or symptoms will be collected when volunteered by subjects and/or observed by Investigators. Additionally, blood serum collected at two and four weeks visits will be analyzed for antibody formation against rh-bFGF. Subjects with an increase of specific antibody production against rh-bFGF will have blood serum collected at subsequent follow-up visits for testing until their results return to baseline values. If a subject is diagnosed with a precancerous lesion such as leukoplakia after the study starts, it will be biopsied as appropriate for further analyses. Also, radiographs obtained at three and six months post-implantation will be reviewed and compared to baseline to detect adverse events such as ankylosis, root resorption or other abnormal events in the bony architecture at the site.

5.0 STUDY DESIGN AND DESCRIPTION

5.1 Study Design

This will be a prospective, randomized, double-blinded, controlled, multi-center, dose-verification clinical study in subjects who require surgical intervention to treat a qualifying periodontal defect. A total of 94 subjects will be randomized to obtain at least 80 evaluable subjects in anticipation of a 15% dropout rate. This study will be conducted in six sites in the United States.

The duration of the study for each subject will be six months following implantation of the study device.

Subjects will participate in a Screening Period lasting up to 2.5 months. Subjects must have been diagnosed to have at least one periodontally related osseous defect to be treated by periodontal reconstructive surgery. Subjects must be systemically healthy and not have any sites suffering from localized juvenile periodontitis. Subjects must not partake in the daily use of smokeless chewing tobacco, pipe or cigar smoking, or smoke more than 10 cigarettes a day or the equivalent.

After a successful screening, eligible subjects will be randomized using variable block sizes for the four treatment groups. The study will be stratified to control for potential differences in healing rates and responses in the treatment based on smoking habits (between non-smokers and moderate smokers).

The treatment groups are:

Treatment I: β-TCP alone (active control)
Treatment II: [redacted] GFeBGS: consisting of β-TCP and 0.1% rh-bFGF
Treatment III: [redacted] GFeBGS: consisting of β-TCP and 0.3% rh-bFGF
Treatment IV: [redacted] GFeBGS: consisting of β-TCP and 0.4% rh-bFGF

Subjects will be evaluated at 2 and 4 weeks and 3 and 6 months following surgery (see Figure 5).

Figure 5 Schematic of Study Visits and Windows

	Screening period	Pre-treatment procedures			Treatment/ Post-treatment follow-up period				
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Procedure	Screening	Pre-treatment	Pre-treatment	Baseline	Surgery	Wk 2	Wk 4 (1 Mo)	3 Mo (12 Wk)	6 Mo/ Early termination (24 Wk)
Schedule	<-3 Mo	-2 Mo (≥2Wks before Baseline)*		-2 Wks					
Windows		(-2 days)*			Day 1	±3 days	±3 days	±7 days	±7 days

***** Pre-treatment should be performed at least two weeks prior to the Baseline Visit. The study visit window is -2 days; therefore teeth in the target quadrant must undergo all required scaling and planing no more than two months and 2 days prior to surgery.

5.2 Justification for Study Design and Endpoints

5.2.1 Study Design

The randomization of the investigational device kits will be performed by [redacted] for the allocation of subjects at each investigational site. Subjects will be randomized to one of four groups so that treatment is balanced within each center by block randomization method stratified by smoking status. Enrollment will be defined as randomization to one of the above-mentioned study arms (Treatment I ~ IV). The randomization will be performed intraoperatively after surgeons confirm if the probing bone depth and the number of bony wall of defect of the target site meets the inclusion criteria (greater than 4 mm and at least one bony wall).

The active control arm (β-TCP alone) will be used for comparisons to three test groups with different rh-bFGF concentrations (0.1%, 0.3% and 0.4%) in order to determine the optimal concentration of rh-bFGF in combination with β-TCP to treat a qualifying periodontal defect.

5.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite endpoint that considers radiographic and clinical measurements at six months post-implantation: the amount of linear bone growth (LBG), which is assessed with the use of radiographs, and the regain from baseline of clinical attachment level (ΔCAL), which is assessed clinically. LBG is a representative measurement of alveolar bone re-growth that is measured in a vertical and horizontal direction using radiographs. The clinical attachment level (CAL) is the distance from the cemento-enamel junction (CEJ) (or other fixed

reference point) generally along the long axis of the tooth to the deepest extent of the periodontal pocket. CAL is the established clinical parameter to be used for evaluation of connective tissue regeneration and 1.5 mm is the historically established level of clinical efficacy for guided tissue regeneration (GTR) products that attempt to regenerate periodontal structures. The success criteria are a minimum of 1.5 mm for ΔCAL and a minimum of 1 mm for LBG. Both the ΔCAL and LBG must meet the success criteria for a subject to be considered a success.

LBG was selected as a component of the primary endpoint because it was shown to be the most sensitive measurement of alveolar bone re-growth in a recent trial for a different bone graft substitution used in a similar indication[6], The soft tissue and bone components are each important to a clinically successful outcome and periodontitis, which by definition affects both the connective tissue like periodontal ligament and alveolar bone, is an established fact. Furthermore, in Sunstar dog studies, it was also demonstrated that β-TCP itself achieved a good bone regeneration but not cementum. Rh-bFGF must contribute to not only bone regeneration but also new cementum and matured periodontal ligament regenerations. Therefore, to determine whether this product achieves the regeneration of all periodontal tissues, the composite endpoint combining clinical parameter (ΔCAL) with radiographic parameter (LBG) was selected as the primary endpoint.

Standardized periapical radiographs will be performed using Rinn positioning instruments and thermoplastic impression tabs. One standardized intra-oral periapical radiograph obtained at baseline and at 6 months will be assessed. These radiographs should be taken perpendicularly with a standardized long-cone parallel technique and should image the target tooth (or teeth) and at least 2 mm on either side of the osseous defect. A standardizing technique will be used to produce repeatable diagnostic quality radiographs with close to identical geometry and image clarity (see Section 8.2.3 Radiographic Quality Assessment and Calibration).

5.2.3 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints will include:

- ΔCAL from baseline at three months and ΔCAL at three and six months post-implantation - CAL is theoretically calculated by addition of PD and GR. The mean change in CAL is compared to a historically established level (1.5 mm) of clinical effectiveness at three months post-implantation, and the mean ΔCAL between study treatments are compared at three and six months post-implantation;
- LBG at six months post-implantation;
- Percent bone fill (%BF) at six months post-implantation;
- Composite endpoint combining ΔCAL and %BF at six months post-surgery - The success criteria are a minimum of 1.5 mm for ΔCAL and a minimum of 10% for %BF. Both the ΔCAL and %BF must meet the success criteria for a subject to be considered a success;

- Probing Depth Reduction (PDR) from baseline at three and six months post-implantation - PDR is the difference between the PD (pocket depth) at baseline, three months and six months. PD is the distance from the gingival margin generally along the long axis of the tooth to the deepest extent of the periodontal pocket;
- Change in Gingival Recession (ΔGR) from baseline at three and six months post-implantation - GR at three and six months post-implantation: GR is the distance from the free gingival margin to the CEJ;
- Wound-Healing (WH) scale two and four weeks post-implantation - A wound-healing scale modified from the index described by Lobene *et al*. (1986) [7] will be used to assess wound healing during the first four weeks post-implantation. The assessment will be made of the gingival tissues superficial to the grafted osseous defect using the scale is shown below:

  0 = Absence of inflammation, normal healthy appearance to the tissues superficial to the graft;

  1 = Mild inflammation, slight marginal change in color (e.g. redness), little change in texture of any portion of the marginal or papillary gingival unit superficial to the graft;

  2 = Mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit;

  3 = Moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal or papillary unit, bleeding on gentle palpation; and

  4 = Severe inflammation; marked redness, edema, and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion.
- Gingival wound evaluation – evaluated as closed, open <2 mm or open ≥ 2 mm at two and four weeks post-implantation;
- Bleeding on probing (BOP) at three months post-implantation - Presence or absence of bleeding on probing at each site, recorded 10 seconds after probing of the particular quadrant.

All secondary endpoints will be evaluated by treatment group.

ΔCAL at three and six months, and LBG and %BF at six months were set as secondary endpoints to evaluate the effectiveness over time of the investigational product on both new connective tissue attachment and bone regeneration, respectively. BOP will be assessed to evaluate the effect of the investigational product on periodontal tissue inflammation. PD and GR will be assessed to evaluate tissue levels. WH scale and gingival wound evaluation will be assessed to evaluate the effect of the investigational device on the wound healing process.

Standardized radiographs will be obtained at baseline and three and six months post-implantation. These radiographs will be analyzed for bone growth as well as adverse events.

5.2.4 Safety Endpoints

Safety will be monitored throughout the study by assessing the incidence, timing, and severity of Adverse Events. Adverse events with clinical signs or symptoms will be collected when volunteered by subjects and/or observed by Investigators. Additionally, blood serum collected at two and four weeks post-implantation will be analyzed for antibody formation against rh-bFGF. Subjects with increase of specific antibody production against rh-bFGF will have blood serum collected at subsequent follow-up visits for testing until their results return to baseline values. If a subject is diagnosed with a precancerous lesion such as leukoplakia after the study starts, it will be biopsied as appropriate for further analyses. Also, radiographs obtained at three and six months post-implantation will be reviewed and compared to baseline to detect adverse events such as ankylosis, root resorption or other abnormal events in the bony architecture at the site.

5.3 Premature Termination or Suspension of Study or Investigational Site

5.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied and require temporary suspension or early termination of the study.

1. New information or other evaluation regarding the safety or effectiveness of the device that indicates a change in the known risk/benefit profile for the device, such that the risk/benefit is no longer acceptable for subjects participating in the study.
2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
3. Sponsor decides to terminate the study.

5.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

An investigational site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of GCP, the protocol, or the contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

5.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will

be followed by applicable investigational sites during the course of termination or study suspension.

6.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

6.1 Inclusion Criteria

Subjects must meet all of the following criteria to be entered into the study:

1. Male or female, age of 25 and older
2. Must have read, understood, and signed a consent form
3. Must be able and willing to follow study procedures and instructions
4. Must have undergone thorough scaling and root planing of the target tooth and be expected to demonstrate good plaque control after instruction in oral hygiene
5. The target tooth must exhibit the following:
    - A pocket depth of 7 mm or greater
    - After surgical debridement, 4 mm or greater intrabony defect with at least 1 bony wall
    - Sufficient keratinized tissue to allow complete tissue coverage of the defect
    - Radiographic base of defect at least 3 mm coronal to the apex of the tooth

6.2 Exclusion Criteria

1. Failure to maintain adequate oral hygiene during the screening phase
2. Women of child-bearing potential
3. A history within the last 6 months of HIV, Type IV heart disease, or end-stage renal disease
4. A history of oral cancer or any other cancer (exception: subjects with a history of skin cancers such as squamous and basal carcinoma with end of treatment at least 6 months ago and/or prostate cancer with end of treatment at least 5 years ago may be enrolled)
5. A history within 12 months of previous open flap periodontal surgery on the study tooth.
6. A diagnosis of pre-malignant oral lesion(s)
7. A traumatic occlusion of the target tooth
8. Target "study" tooth exhibiting Grade III mobility
9. Maxillary molars or maxillary first premolar with a prominent mesial concavity
10. Study tooth exhibiting a Class II or greater furcation defect
11. Clinical or radiographic signs of untreated acute or chronic periapical infection at the surgical site, apical pathology, root fracture, severe root irregularities, cemental pearls, cervical enamel projections not easily removed by odontoplasty, untreated carious lesions at the cemento-enamel junction (CEJ) or on the root surface, or restorations with open or otherwise defective margins at or below the CEJ
12. A history within the last 6 months of the daily use of any tobacco products besides cigarettes (smokeless chewing tobacco, pipe or cigar smoking), or of smoking more than 10 cigarettes per

day

13. Subjects participating in other clinical trials within 30 days of enrollment
14. Subjects having uncontrolled endocrine-induced diseases (e.g. uncontrolled diabetes mellitus and hyperparathyroidism)
15. Subjects undergoing current therapy with systemic steroids or other drugs that significantly alter bone metabolism
16. Subjects with Localized Juvenile Periodontitis (LJP) sites in the oral cavity

6.3 Excluded Medications and Treatments

6.3.1 Excluded Medications

Subjects may not use systemic corticosteroids during four weeks from the day of the treatment (surgery). Representative systemic corticosteroids listed in the ADA/PDR Guide to Dental Therapeutics 5th Edition [8] are: hydrocortisone, fludrocortisone, methylprednisolone, prednisolone, prednisone, betamethasone and dexamethasone.

Corticosteroids may disturb the wound healing due to the inhibitory effect on cell proliferation and immune response to infection and therefore, effect the evaluation of effectiveness of GFeBGS.

Also, subjects may not be treated with intravenous bisphosphonates during the study period. The Food and Drug Administration and Novartis Pharmaceuticals Corporation have each issued a drug precaution to health professionals regarding a condition known as Osteonecrosis of the Jaw (ONJ). This condition has been observed in cancer patients who undergo invasive dental procedures such as dental implants or tooth extractions while receiving treatment with intravenous bisphosphonates. The American Association of Periodontology suggests that invasive dental procedures should be avoided unless absolutely necessary in patients who are receiving intravenous bisphosphonates therapy. Two intravenous bisphosphonates are marketed by Novartis under the trade names *Aredia* and *Zometa. Bonefos* is another brand of intravenous bisphosphonates marketed by Schering AG.

Other medications which the patient has already been taking as a treatment of periodontitis before enrollment into the study may be continued during the study period as long as the medications remain necessary. Also subjects may take new medications during the study whenever the Investigator decides that the medications are necessary to treat a condition that would otherwise be a contraindication and/or to treat adverse events. Medications other than systemic corticosteroids have little impact on the evaluation of effectiveness of GFeBGS.

Non-steroidal anti-inflammatory drugs (NSAIDs) also will not be allowed to treat post-surgical conditions such as pain because they may affect wound healing and tissue regeneration through the

anti-inflammatory effect. However, acetaminophen products (prescription or over-the-counter) are allowed because the mechanism of pain relief is not mediated by anti-inflammatory effect.

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

6.3.2 Excluded Treatment

Temporary splints may not be used on the study tooth unless the subject already has used the splint before study participation.

The study-treated tooth will not receive any surgical treatments besides the study treatment from the day of the treatment (surgery) until the study ends. Also, no surgical treatments involving implantation of biologic bone grafting material will be allowed in teeth adjacent to the study-treated tooth for the duration of the study. Additionally, no bone grafting materials may be implanted on adjacent teeth in the interproximal space. Surgical treatments at the adjacent teeth and/or the study-treated tooth may disturb the wound healing, and have an impact on the evaluation of effectiveness and safety of GFeBGS.

However, scaling and root planing will be allowed in teeth adjacent to the study-treated site as these procedures are expected to have little impact on the evaluation of safety and effectiveness of GFeBGS.

6.4 Criteria of Failures (Discontinuation or Withdrawal of a Subject)

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded on the Subject Discontinuation/Withdrawal form (CRF 10) using the following categories:

1. Pre-treatment event or adverse event (AE). The subject has experienced a pre-treatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pre-treatment event or AE.
2. Major protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and that continued participation would pose an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e. withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The Sponsor, IRB or regulatory agency terminates the study.
6. Subject does not meet eligibility requirements at Visit 5 and has not signed the informed consent for enrollment in the study.
7. Unexpected surgery is required including rescue treatment of the target tooth.
8. Excluded medication is required including rescue treatment of the target tooth.
9. Unexpected amount of loss of the device from the target tooth.
10. Unacceptable safety risk develops.
11. Other. Note: The specific reasons should be recorded in the "specify" field of the CRF.

6.5 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 6.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. If a subject is discontinued or withdrawn due to an adverse event, the Sponsor should be notified immediately.

Efforts will be made to avoid any subjects being lost to follow-up during the conduct of the study. Before subjects are considered lost to follow-up, a minimum of 2 documented telephone contact attempts and 1 certified letter within 6 weeks of the most recent planned study visit must be sent in an effort to contact subjects.

7.0 INVESTIGATIONAL DEVICE DESCRIPTION

7.1 Investigational Device

7.1.1 Manufacturing, Packaging, and Labeling

7.1.1.1 Description of Investigational Device

1. Components

The investigational device, [redacted] GFeBGS, is supplied in a kit which consists of three components and one accessory:

- 1 each sterile β-TCP in a portion cup
- 1 each vial that contains a sterile lyophilized cake with rh-bFGF.
- 1 each sterile HPC solution in a syringe
- 1 each 18G blunt needle

2. Product code: [redacted]
3. Generic name:

rh-bFGF: trafermin (genetic recombinant)

β- TCP: β- tricalcium phosphate

4. Molecular formula:

rh-bFGF: $C_{764}H_{1201}N_{217}O_{219}S_6$ (Protein composed of 154 amino acids) or

$C_{761}H_{1196}N_{216}O_{218}S_6$ (Protein composed of 153 amino acids)

β- TCP: $Ca_3(PO_4)_2$

5. Molecular weight:

rh-bFGF: 17,122.67 (Protein composed of 154 amino acids) or

17,051.59 (Protein composed of 153 amino acids)

β- TCP: 310.18

6. Content of active ingredients

- Treatment I: β-TCP with 0.5 mg trafermin-containing lyophilized rh-FGF (final conc. 0.1%)
- Treatment II: β-TCP with 1.5 mg trafermin-containing lyophilized rh-FGF (final conc. 0.3%)
- Treatment III: β-TCP with 2.0 mg trafermin-containing lyophilized rh-FGF (final conc. 0.4%)

- Treatment IV: β-TCP with lyophilized vial (Active control)

7.1.1.2 Investigational Device Preparation Procedure

A copy of the Instructions for Use is provided in Appendix E.

7.1.1.3 Contents of Carton

The investigational and active control devices are packaged identically. The kit components are sterile. The kit is non-sterile.

- 1 sterile vial containing lyophilized cake with or without the Growth Factor (rh-bFGF)
- 1 sterile cup containing 0.5 cc of β-TCP granules
- 1 sterile syringe containing 0.5 ml of 1% HPC solution
- 1 sterile 18G blunt needle

Storage condition: 2-8ºC, in a dry place. Do not freeze.

7.1.2 Storage

All investigational devices must be kept in an appropriate, limited-access, secure place until implanted in a study subject or returned to the Sponsor or designee for destruction. All investigational devices must be stored under the conditions specified on the label, and remain in the original container until dispensed. The temperature of the device storage area must be maintained at 2-8°C (36-46°F). The investigational device should not be frozen. The temperature of the device storage area must be logged daily.

Investigational devices should not be used after the expiration date unless subsequent extensions are confirmed by the Sponsor.

Once the β-TCP granules and the rh-bFGF solution are mixed, it should be applied to the surgical site within 5 minutes. Otherwise, it should not be used and should be destroyed following the instructions provided in the Instructions for Use. Note that the product disposition must be designated as destroyed in the Inventory Accountability Log.

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7.2 Randomization Code Creation and Storage

The investigational device kits are assembled by a clinical supplies vendor [redacted] and are visually identical. The randomization code will be created by [redacted] as the Sponsor's designee. Block randomization will be stratified by smoking status (non-smoker or smoker). The randomization schedule will be provided to the Investigator as a list of sequential product numbers on the label of the carton box

assigned by [redacted]. In the event that devices must be disposed of, replacement devices will be made available.

7.3 Investigational Device Blind Maintenance

Each carton box has a label with a scratch off seal masking the identity of the study treatment contained in the box. The seal is not to be scratched off except in the case of an emergency. During regularly scheduled monitoring visits, a study monitor will perform an inventory of investigational device kits and verify that none of the seals have been scratched off.

All unassigned kits will be counted and returned to [redacted] before study closure. All of used kit package containing the empty container of each component also will be returned to [redacted] before study closure.

7.4 Unblinding Procedure

The blinded information can be revealed in emergency situations only. In such an emergency, the Primary Investigator at the investigational site will break the blind information for only the subject involved by scratching off the seal on that subject's box. The Primary Investigator is instructed to notify the Sponsor immediately in case of such an emergency.

7.5 Accountability and Return of Investigational Device

Upon receipt of investigational device kit delivered by [redacted], the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity received matches the quantity listed as shipped on the packing list, the investigational device kits are received within the labeled storage conditions, and are in good condition. If quantity and conditions are acceptable, the Investigator should acknowledge the receipt of the shipment to [redacted] according to the instructions provided by [redacted]. If there are any discrepancies between the packing list versus the actual product received, [redacted] must be contacted to resolve the issue. The Investigator or designee must maintain 100% accountability for investigational device kits received and dispensed during his or her entire participation in the study. If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The Investigator or designee must record the current inventory of the investigational device kits on a Device Inventory Log. The following information will be recorded at a minimum: protocol number and title, name of Investigator, investigational site, product number, including the initials of the person receiving the investigational device kit. The log should include all required information as a separate entry for each subject who is implanted with the contents of the investigational device kit.

Before the investigational device kits are returned to [redacted] and at appropriate intervals, a clinical monitor will perform the investigational device kits accountability and reconciliation process. The Investigator will retain a copy of the documentation regarding the investigational device kits

accountability including return, and/or destruction of the kits, and originals will be sent to [redacted].

8.0 STUDY PLAN

8.1 Study Procedures

The following sections describe the study procedures and data to be collected. Subjects will be assessed at the screening (Visit 1) and baseline (Visit 4) visits to determine and confirm eligibility. The identified target teeth at the screening visit (Visit 1) will be reconfirmed intra-operatively at the surgery visit (Visit 5), and one eligible tooth will be selected to receive the study treatment. Within 2 months prior to the study treatment, each subject will undergo thorough scaling and planing of all teeth in the target tooth's quadrant to control the disease process and minimize lesion variability (Visit 2 and if necessary, Visit 3). Note that a patient may have already undergone scaling and planing prior to screening. After study treatment, each subject will be monitored at periodic intervals to assess safety and effectiveness for at least six months. The Schedule of Study Procedures is located in Appendix A.

The Investigator and all study personnel will be blinded to the treatment. Only calibrated Examiners who are different from the surgeon performing the implantation should carry out the clinical evaluations to assess the study safety and effectiveness parameters. See Section 8.2 for calibration details.

8.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 14.2.

Two informed consents are proposed in this study. Informed consent for screening must be obtained prior to the subject undergoing screening (Visit 1). In addition, those subjects that meet the screening requirements must complete an informed consent for enrollment into the study (Visit 4). A unique subject identification number (subject screening number) will be assigned to each subject at the time that informed consent for screening is obtained. A different, unique subject identification number (subject enrollment number) will be assigned to each subject at the time that informed consent for enrollment is obtained. This subject enrollment number will be used throughout the study.

8.1.2 Clinical Outcomes

The Investigator and other qualified site personnel (i.e. Dentist, Dental Hygienist) will perform the clinical examinations using the following methods at the examination visits. Clinical Measurement will be performed throughout pre-treatment, baseline and post-treatment follow-up visits during the trial. Intra-Surgical Measurement will be performed at Visit 5 only.

Only calibrated North Carolina 15 mm periodontal probes will be used. The measurements will be rounded off to the nearest millimeter (0.5 mm is to be rounded up). Clinical probing measurements will be made at the mid-facial, mesial and distal line angles and at mid-lingual, mesial, distal line angles with a calibrated probe. The measurements will be made at these standard locations to the deepest part of the defect.

Clinical Measurement

- Pocket depth (PD): From free gingival margin to the base of the pocket
- Clinical attachment level (CAL): will be calculated by adding PD and GR.
- Gingival recession (GR): From the free gingival margin to the CEJ

Intra-Surgical Measurement (Visit 5 only)

- Alveolar crest height (ACH): From cemento-enamel junction to alveolar crest (CEJ-AC)
- Base of defect from CEJ (BD): From cemento-enamel junction to the base of osseous defect (CEJ-BD)
- Vertical bone defect depth at its deepest location (vBD): vBD will be calculated by subtracting ACH from BD

8.1.3 Radiologic Outcomes

The radiographic assessments include standardized periapical radiographs using Rinn positioning instruments and thermoplastic impression tabs. One standardized intra-oral periapical radiograph will be obtained at baseline and again at 3 and 6 months. These radiographs should be taken perpendicularly with a standardized long-cone parallel technique and should image the target tooth and at least 2 mm on either side of the osseous defect. The following standardizing technique will produce repeatable diagnostic quality radiographs with close to identical geometry and image clarity.

8.1.3.1 Assemble the needed materials

- A patient-specific reusable bite registration is used as a positioning guide.
- Rinn film holder and positioning apparatus are used to maintain beam direction.
- A digital sensor or a phosphor plate radiography system.
- One image of a current US penny for calibration of the system.

8.1.3.2 Obtain the Image

- The sensor or phosphor plate should be positioned in an alignment device for the system that will align it parallel to the long axis of the tooth. The x-ray beam must be angled perpendicular to the capturing device.
- Expose the film/sensor.
- Save the digital image as a TIFF file using the following file naming protocol:
    - File naming protocol: investigational site number (xxx), subject enrollment number (xx), target tooth number (xx), date (mmddyy) and image number with each entry separated by a period
    - For example, a radiograph taken at investigational site 03 on patient number 03-001-209 of target tooth #2 on 4-15-11 should be labeled: 03-001-209.02.041511

- Send the image files to University of Alabama Birmingham (UAB) for analysis following the UAB instructions.

Once the exposure parameters are selected they should not be changed during the course of the study.

8.1.3.3 Radiographic Image Processing and Outcomes Assessment

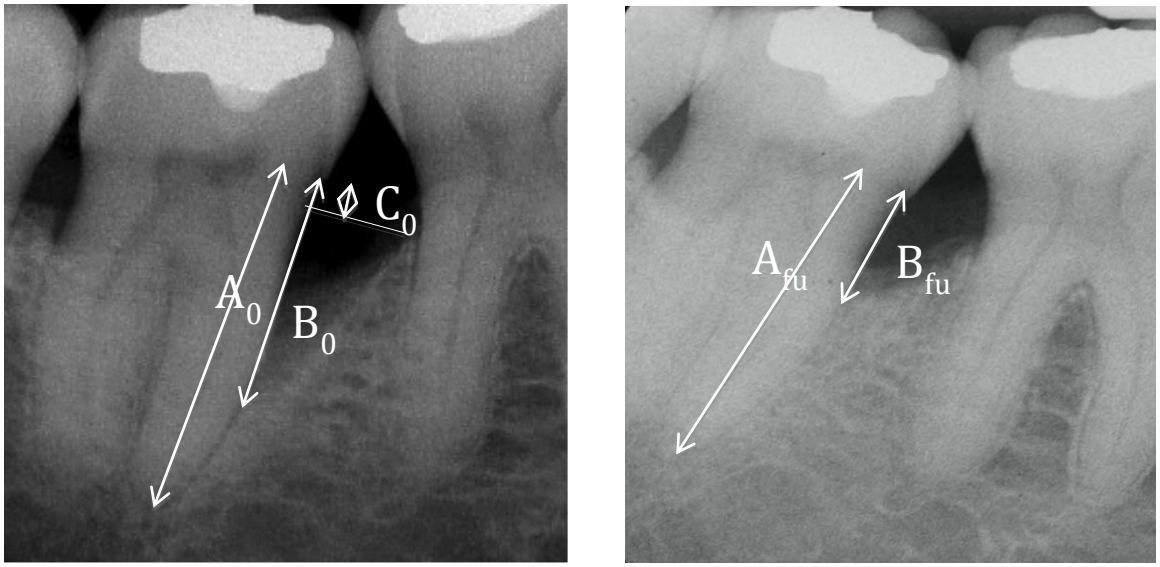
Coded radiographic images will be sent to the reading center at UAB where they are given a unique identifier and logged into an electronic file. Subsequent images are matched to the identifier and a digit added which identifies the follow-up sequence (i.e. 6, post-baseline).

Baseline images are saved in an electronic study file and linear measurements, in millimeters, of bone height along mesial and/or distal root surfaces of the defect site are captured and entered into a database.

Image processing software is used to capture measurements. First, the image of the penny will be used for the conversion of pixels to millimeters for every system. The number of pixels per millimeter is calculated by dividing the measurement of the penny in pixels by the known diameter of a penny of 19.2 mm. If all parameters of the system stay the same from radiograph to radiograph, the image of the penny should only be submitted once. However, if any parts of the system change (i.e. the sensor or capturing device, scanner or capturing software), a new penny radiograph should be submitted.

Then, measurements are taken from a stationary landmark (CEJ) to the base of the defect; to the crest of bone, and to the apex of the longest root in millimeters. All measurements are taken parallel to the long axis of the tooth. The measurements are shown in Figures 8 a and b. A_0 is the root length at baseline, B_0 is the measurement form the CEJ to the base of the defect at baseline, and C_0 is the CEJ to the crest of the defect projected onto the root surface (Figure 8, left). At follow up, the A and B measurements are repeated (Figure 8, right).

Figure 8 Measurements on Radiographs at Baseline and 6 Months Post-surgery



Subsequent images are logged in and saved to the file. Linear measurements of bone height along root surfaces are made using the same method as the original defect. Bone height changes and percent bone fill estimates, based on loss or gain (resorption or osseous recontouring) of bone from baseline images are computed and entered onto the Independent Radiological Evaluation form (CRF 11).

Measurements to the root apex taken from baseline images are used to correct for any geometric distortion (elongation/foreshortening) of subsequent images and the percent of distortion (plus or minus) as well as percent of bone fill are computed using established formulae.

Linear bone change = $B_0 - B_{fu}$

Percent bone fill = $(B_0 - B_{fu})/(B_0 - C_0)$

Note: It is not appropriate to include in the calculation of %BF the distance from the CEJ to the crest of the defect projected onto the root surface. If it were included, an increase in crest height would result in a decrease in the calculated %BF while a decrease would result in an increase in the calculated %BF.

8.1.4 Procedures for Clinical Laboratory Samples

Serum will be collected before the surgery at Visit 5 (Baseline), Visit 6 (2 weeks post-surgery) and Visit 7 (4 weeks post-surgery) in accordance with acceptable laboratory procedures. Subjects with an increase of specific antibody production against rh-bFGF will have blood serum collected for testing at subsequent follow-up visits until their results return to baseline values. The maximum volume of blood at any single visit is approximately 4 ml to isolate 2 ml of serum, and the approximate total volume of blood for the study is 12 ml. Details of these procedures, storage condition of the serum samples and shipping instruction will be given in the laboratory manual provided by [redacted]. The serum samples will be stored in a freezer at the site or a commercial laboratory. Within two weeks of the collection of the Visit 7 sample for a subject, all three samples for that subject will be shipped to the central laboratory. If serum is collected at subsequent visits, the site will ship each serum sample to the central laboratory within two weeks of its collection.

The central laboratory, [redacted], will perform ELISA assay for total serum antibody level of IgG, IgA and IgM for rh-bFGF upon receipt of the serum samples from investigational sites. The ELISA assay method will be established and validated by [redacted] before testing the clinical samples. If an increase in the rh-bFGF specific antibody level is detected in a serum sample, the neutralizing activity of the antibody will be measured. The site will be notified that an additional blood serum sample from that subject will be required at the next visit. The results of laboratory tests will be sent to the data management vendor. [redacted] will bank all serum samples until Sunstar notifies them that the FDA has reviewed and approved the assays.

8.1.5 Pregnancy

The safety impact of neutralizing antibody to rh-bFGF on fetuses has not been established by preclinical study. Therefore, any potential subject of childbearing potential will not be allowed to continue with the screening process. At screening (Visit 1), Investigators will ask female subjects about their child bearing potential and will exclude all who report a childbearing potential. If any subject has an unanticipated pregnancy after receiving the study treatment, it should be reported using a Protocol Deviation form (CRF 9) and the subject may remain in the study.

8.1.6 Documentation of Screening Failure

Investigators must account for all subjects who sign informed consent for screening at Visit 1 (Screening). If the subject is found to be not eligible prior to randomization, the Investigator should complete the Screening Failure Log.

Subject screening numbers assigned to subjects who fail screening should not be reused.

8.2 Examiner Calibration

8.2.1 Training of Surgeons, and Training of Examiners

One to two periodontists from each investigational site will be trained to perform the surgeries. One individual will be designated as the primary surgeon and should perform most of the procedures. The other individual will be the back-up and may also perform any non-examiner procedures when the primary clinician is not available. All surgeons must have ample experience in periodontal regenerative procedures and receive training. Surgeons will be trained on the surgical technique, end point of root debridement, handling and placement of test materials and suturing technique. To insure standardization of the surgical procedures, training will be conducted to thoroughly review all aspects of the pre-surgical, surgical and post-surgical phases of the trial. This training will be carried out prior to the beginning of the trial.

In addition, two examiners (dentists or hygienists) will be trained on baseline, interim and final evaluation measurements, exclusive of clinical photographs. The examiners should be different individuals from the surgeons. The same examiner, if possible, should perform all measurements on a particular subject, *i.e.* baseline, interim, and final evaluation measurements, exclusive of clinical photographs.

8.2.2 Intra-Examiner Reproducibility

All Examiners from the investigational sites will go through a training and calibration exercise before they may participate in the study. This will involve first a classroom discussion of the clinical criteria and scales that will be used followed by demonstration and measurement using volunteer patients. A "gold standard" periodontist or hygienist will first make clinical measurements on the patients, followed by each examiner. These measurements will then be repeated. Inter- and intra-examiner correlations will then be calculated. This process will be repeated until each examiner is correlated to the gold standard examiner.

8.2.3 Radiographic Quality Assurance and Calibration

The independent radiographic center will conduct quality assurance and calibration procedures according to their procedures.

8.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

8.3.1 Visit 1: Screening

After the Informed Consent for Screening is signed and a screening number is assigned, the screening assessment will be performed. It includes an oral, medical (including a complete record of current medications) and demographic history, smoking history and identification of one or more target teeth and bone defect(s). Note that only one tooth per subject may receive treatment

with the investigational product. However, the final study eligibility of a tooth cannot be determined until the surgery is underway. Therefore, identification of additional target teeth increases the likelihood that the subject will not be excluded from the study during surgery.

A periapical radiograph may be taken as necessary to ensure that all target teeth meet the inclusion and exclusion criteria (see Sections 6.1 and 6.2). If the subject satisfies all inclusion and exclusion criteria, one or more target teeth that meet the eligibility criteria will be identified. To be included in the study, a subject must undergo thorough scaling and planing of all teeth in the target tooth's quadrant within 2 months prior to the surgical procedure. If more than one target tooth is selected in more than one quadrant, each quadrant with a target tooth will undergo scaling and planing. Note that scaling and planing will be performed in other quadrants as necessary to treat disease. If scaling and planing are necessary, it should be performed at least two weeks prior to the Baseline Visit (Visit 4). If tissue inflammation caused by the pre-surgical treatment is observed at the Baseline Visit (Visit 4), the Baseline Visit should be postponed until the inflammation subsides.

A summary of all procedures to be performed is listed below.

Summary of Procedures/Measurements**:**

- Informed consent for screening must be obtained according to the process described in Section 14.2
- Complete Screening Assessment (CRF 1) and Pre-enrollment Eligibility and Assignment (CRF 2) forms
- Identify a single or, if possible, multiple target teeth
- Determine initial subject eligibility
    - If not eligible, subject is a screen failure and should be documented on the Screening Failure Log
    - If eligible, continue the visit
- Determine if 1 or 2 scaling and planing procedures and/or sustained oral hygiene instructions are necessary
    - If yes, schedule the procedure(s)
    - If no, Visit 4 (Baseline) may be conducted at the end of this visit
- If necessary:
    - Perform supragingival prophylaxis
    - Provide oral hygiene instructions
    - Obtain a full set of radiographs or a panorex
    - Complete a full mouth periodontal chart

- Obtain a periapical (PA) radiograph of the target tooth or teeth

8.3.2 Visits 2 and 3: Pre-Treatment Procedures

All subjects must receive a thorough scaling and root planing of all teeth in the target tooth's quadrant within 2 months before the surgical procedure. If more than one target tooth is selected in more than one quadrant, each quadrant with a target tooth will undergo scaling and planing. Note that scaling and planing will be performed in other quadrants as necessary to treat disease. If scaling and planing are necessary, it should be performed at least two weeks prior to the Baseline Visit (Visit 4). If tissue inflammation caused by the pre-surgical treatment is observed at the Baseline Visit (Visit 4), the Baseline Visit should be postponed until the inflammation subsides. The subjects will be instructed in oral hygiene including tooth brushing, and interproximal oral hygiene devices, as needed. Subjects are expected to demonstrate good plaque control prior to the surgical intervention.

A summary of all procedures to be performed is listed below.

Summary of Procedures/Measurements**:**

- Perform thorough scaling and planing of all teeth using local anesthetic as necessary
- Provide oral hygiene instructions

8.3.3 Visit 4: Baseline Examination

Visits 1(Screening) and 4 (Baseline) may occur on the same day if pre-treatment procedures (Visits 2 and 3) are not necessary. Visit 4 (Baseline) may be performed after the final pre-treatment (Visit 2 or 3) has been completed if the final pre-treatment visit occurs within 2 weeks before surgical treatment. If the window between Visit 4 (Baseline) and 5 (Surgery) is greater than 2 weeks but less than or equal to 4 weeks, the baseline measurements do not have to be re-measured. However, if the window between Visit 4 and 5 is greater than 4 weeks, the baseline measurements must be measured again at next clinic visit (Visit 5 or an unscheduled visit before Visit 5) and recorded on CRF 12: Re-measurement of Baseline Measurements. Additionally, the eligibility of the target tooth should be re-verified at this visit.

If Visit 4 (Baseline) does not occur on the same day of Visit 1 (Screening), the subject eligibility should be verified again at this visit.

Visits 4 (Baseline) and 5 (Surgery) may be performed on the same day.

A summary of all procedures to be performed is listed below.

Summary of Procedures/Measurements**:**

- Confirm subject eligibility (if this visit is not the same day of Visit 1-Screening)
- Informed Consent for Enrollment must be obtained according to the process described in Section 14.2
- Detailed probing measurements of the potential study teeth sites including:

- CAL (calculation)
- PD
- GR
- BOP

- Full set of radiographs or a panorex (if none available within past 6 months) ;
- Full mouth periodontal pocket depth charting except for 3rd molar (if none available from last 6 months);
- Standardized PA radiograph of potential target teeth (if none available within 2 months of Visit 5 - Surgery; see Section 8.1.3 Radiologic Outcomes);
- Confirm eligibility of all target teeth;
- If more than one target tooth is identified, the Investigator will rank the eligible target teeth in order of most severe disease coupled with the most favorable environment. The following criteria, listed in order of importance, will be used to determine the ranking:

  1. Deepest intrabony defect based on radiographic measurement
  2. Smallest vertical angle (smallest coronal width) of defect based on radiographic measurement
  3. Single-rooted
  4. Adjacent teeth have the most healthy periodontal condition (based on amount of bone loss, clinical attachment level and pocket depth)

  Thus, eligible target teeth will be ranked numerically starting with "1".
- Record tobacco use
- Oral hygiene instruction (as necessary)
- Concomitant medication review

8.3.4 Visit 5: Periodontal Surgery and Implantation of Investigational Device

Pre-surgical procedure:

- Collect blood serum sample for rh-bFGF antibody; and,

Periodontal surgery:

Beginning with the target tooth ranked as the most severe disease, the area selected for surgery is anesthetized. Following intracrevicular incisions, buccal and lingual full-thickness horizontal (mucoperiosteal) flaps are raised extending at least one tooth mesial and distal to the treated tooth. In case of a missing proximal tooth, the flap is extended at least 6 mm proximal to allow easier management and placement of the test material. Care is taken to preserve as much as possible of the keratinized gingival connective tissue in the flap. A horizontal releasing incision will be performed in order to facilitate coronal displacement of the flap, if it is applicable. The inner

surface of the flap may be carefully instrumented to remove dento-gingival epithelium and granulation tissue.

Following the reflection of the mucoperiosteal flap, all granulation tissue associated with the osseous defect is removed. Meticulous root planing should be performed to remove subgingival soft and hard deposits on the root surfaces. Magnification aids and fiber optic lights for additional illumination should be utilized. Additionally, both hand and ultrasonic instruments are to be used to assure thorough degranulation and root planing.

The area is rinsed with sterile saline. Examination of the defect and adjacent root surfaces should be performed to detect pathological conditions such as root fracture, severe root irregularities, cemental pearls or cervical enamel projections not easily removed by odontoplasty, root caries or subgingival and/or open restoration margins at the CEJ. These abnormalities must be successfully treated prior to proceeding or the subject will be excluded from the study.

Direct measurements of the intra-bony defect will be performed, as soon as the defect is thoroughly debrided, using a calibrated probe scoring the following dimensions:

- vBD (must be 4 mm or greater);
- W, the width of the defect from the root surface to the farthest bone wall; and
- The predominant number of bone walls present (i.e. 1-3)

At this point, final eligibility of the target tooth will be confirmed on the basis of the acceptable depth of the defect and the number of bone walls.

If the target tooth does not meet the inclusion criteria, the tooth will not receive the study treatment and standard care will be provided. If additional target teeth were identified during the screening process, the previous steps (up to determination of the final eligibility) will be performed on the next target tooth in order of ranking until a target tooth is deemed eligible or all have failed to meet the eligibility criteria. If all target teeth fail to meet the eligibility criteria, complete the Screening Failure Log and provide standard care.

If the target tooth meets the eligibility criteria, the steps below will be followed. Note that only one tooth per subject may receive treatment with the investigational product.

Decorticate cleaned defect with small round bar, and add neutral EDTA to condition the roots. The EDTA should be carefully applied to the tooth root surface with a small brush or other instrument avoiding excessive running of the paste onto the bone surfaces. After two minutes, the EDTA is removed using irrigation and suction.

<u>Randomization</u>

The subject is randomly assigned to a treatment group and the specified investigational device kit identified by the sequential product numbers on the label of the box is retrieved.

<u>Implantation:</u>

Following debridement of the periodontal defect, conditioning of the root surfaces with EDTA and measurements, the assistant opens the carton containing the investigational device ([redacted] GFeBGS) kit. All kits contain the β-TCP bone substitute. All kits will also have a vial with a lyophilized cake with or without rh-bFGF and a syringe containing a 1% HPC solution for reconstitution of lyophilized material. The vials are visually identical so the Investigators are unaware of the treatment assignment. The reconstituted solution in the vial should be left alone for a few minutes to release bubbles. Then the solution is mixed with the β-TCP bone matrix in the sterile container using a sterile instrument so that the graft particles are fully and rapidly saturated. The graft materials mixed with the solution should be implanted into the defect site within 5 minutes after mixing to avoid the nonspecific binding of rh-bFGF to the container. Please see Appendix E: Instructions for Use. During this time, the conditioned root surfaces are thoroughly rinsed and air-dried. The hydrated graft is then added into the osseous defect. The tissue flaps are coronally displaced and secured with interdental sutures (Gore-Tex® suture CV-5) in an attempt to achieve complete coverage of the surgical site.

Specific information related to the surgery, i.e. syringe number and approximate amount of product placed in the periodontal defect is then recorded on the Surgical Procedure form (CRF 4).

The subject should be instructed not to brush or floss the surgical site until the sutures are removed. Sutures will be removed at 2-3 weeks, when the clinician judges that the flap has become stabilized by healing. Subjects will be instructed to rinse with alcohol–free chlorhexidine (CHX) rinse (0.12%) twice daily for 2 weeks, and then once per day until the Visit 7 (4-wk post-operative visit). Note that subjects with dental work that predisposes them to staining will be instructed to swab CHX on the surgical site instead of rinsing with it.

Subjects will be treated with systemic application of antibiotics for post-surgery infection prophylaxis and will be instructed to take acetaminophen, if necessary, for pain relief after surgery. No NSAIDs or surgical dressing will be used.

If any adverse events occurred during the surgery, complete the Adverse Events form (CRF 8). If the subject was withdrawn from the study during the surgery, complete the Subject Discontinuation/Withdrawal form (CRF 10).

Photography**:**

Five clinical photographs of the target tooth should be taken at the following times:

- Before surgery;
- After flap reflection, debridement and root planing;
- With a probe in place vertically to the base of the defect;
- After the device is placed in the defect; and,
- After soft tissue closure

Post-surgical Care:

Analgesics prescribed will be recorded. All adverse events must be recorded.

8.3.5 Visits 6 and 7: Follow-up Evaluations

Subjects will be seen for post-operative evaluations at 2 and 4 weeks post-surgery (± 3 days). Sutures will be removed approximately 2 weeks post-surgery when the clinician judges that the flap has become stabilized by healing. Blood will be collected and prophylaxis for staining due to CHX rinsing or swabbing will be performed. Wound healing and the condition of the soft tissues in the surgical site will be examined by visual inspection and very gentle palpation. A secondary endpoint, WH score, will be recorded to reflect the extent of healing (WH) at the surgical site. Deep scaling of the target tooth should not be performed for the duration of the study and no additional implantation of the investigational product is allowed. Note that if a subject is diagnosed with a precancerous lesion such as leukoplakia after the study starts, it will be biopsied as appropriate for further analyses. A summary of all procedures to be performed is listed below:

Summary of Procedures/Measurements:

- Determine the WH score and evaluate the gingival wound
- Photographs of surgical site
- Supragingival cleansing by hand of surgical site
- Record date of suture removal and the number of days of work missed (if appropriate) on the Follow-up Evaluation form (CRF 5)
- Oral hygiene instruction and prophylaxis for staining due to CHX rinse or swab (as necessary)
- Concomitant medication review, especially number and type of analgesics
- Adverse Events review. Complete the Adverse Events form (CRF 8) if necessary
- Collect blood serum sample for rh-bFGF antibody

8.3.6 Visits 8 and 9: Subsequent Follow-up or Early Termination Evaluations

Subsequent follow-up visits occur at 3 and 6 months (final evaluation) post-surgery (± one week). During these visits, photographs are taken and the endpoint measurements of clinical attachment level (CAL), probing pocket depth (PD) and gingival recession (GR) will be assessed in the surgery site. Subjects with an increase of specific antibody production against rh-bFGF at Visit 7 will have blood serum collected at until their results return to baseline values. Deep scaling of the target tooth should not be performed for the duration of the study and no additional implantation of the investigational product is allowed. Note that this visit is also conducted for early termination. Note that if a subject is diagnosed with a precancerous lesion such as leukoplakia after the study starts, it will be biopsied as appropriate for further analyses. A summary of all procedures to be performed is listed below:

Summary of Procedures/Measurements:

- Detailed probing measurements of the target tooth including:
  - CAL (calculation)
  - PD
  - GR
  - BOP
- Photographs of surgical site
- Routine supragingival prophylaxis
- Standardized PA radiograph of surgical site (see Section 8.1.3)
- Only at 3 months post-implantation: Oral hygiene instruction and full-mouth prophylaxis for staining due to CHX rinse or swab
- Record tobacco use on the Subsequent Follow-up Evaluation form (CRF 6)
- Concomitant medication review, especially number and type of analgesics since the last visit
- Complete the Subsequent Follow-up Evaluation form (CRF 6)
- Adverse Events review. Complete the Adverse Events form (CRF 8) if necessary
- If necessary, collect blood serum sample for rh-bFGF antibody

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject; it does not necessarily have to have a causal relationship with the investigational device.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational device, whether or not it is considered related to the investigational device.

9.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of pre-existing condition of periodontitis. (Intermittent events for pre-existing conditions underlying disease should not be considered AEs.)
- Necessitate unexpected surgical intervention and/or medication.
- Be considered unfavorable by the Investigator for any reason.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Worsening or changes in severity of AEs:

- If the subject experiences a worsening or complication of an AE after any change, the worsening or complication should be recorded as a change to an existing AE.
- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

9.1.3 Expected AEs

Following the periodontal flap procedure, pain, swelling, soreness, erythema, edema, bleeding and temporary numbness are expected to occur 80% to 100% of the time. These sequelae are related to the surgical procedure, not the product and typically resolve over time as the wound heals. Occasionally (less than 5% of the time), fever, pus and infection of the surgical site may occur as post-surgical adverse events.

In addition, headaches, tooth pain and tooth disorder (less than 10%) were reported as AEs related to periodontal grafting procedures in the summary of effectiveness and safety data for a similar product (GEM 21S ™).

9.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse event that:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
4. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
5. Results in persistent or significant DISABILITY/INCAPACITY.
6. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
7. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

9.1.5 Unanticipated Adverse Device Effects

The investigational device exemption (IDE) regulations define an Unanticipated Adverse Device Effect (UADE) as "any serious adverse effect (SAE) on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

9.1.6 Severity of AEs

The different categories of intensity (severity) are characterized as follows:

DEGREE	DESCRIPTION
Mild:	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.

Moderate:	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe:	Cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study device; treatment for symptom(s) may be given and/or subject hospitalized.

9.1.7 Causality of AEs

The relationship of each AE to investigational device will be assessed using the following categories:

RELATIONSHIP	DESCRIPTION
Not related	Any reaction that does not follow reasonable temporal sequence from administration of study device AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Unlikely	Any reaction that does not follow a reasonable temporal sequence from administration of study device or that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Likely	A reaction that follows a reasonable temporal sequence from administration of study device OR that follows a known response pattern to the suspected device AND that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Definite	A reaction that follows a reasonable temporal sequence from administration of study device AND that follows a known response pattern to the suspected device AND that recurs with rechallenge, and/or is improved by removing the device.

9.2 Procedures

9.2.1 Collection and Reporting of AEs

9.2.1.1 AE Collection Period

Collection of AEs will commence from Visit 5 (Surgery) when the subject is administered the investigational device. Routine collection of AEs will continue until the Final Visit or Early Termination (Visit 9).

9.2.1.2 AE Reporting

At each study visit beginning with the Surgical Visit (Visit 5), the Investigator will assess whether any AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects should be instructed to report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the investigational device or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE form, whether or not the Investigator concludes that the event is related to the investigational device. If the treatment involves surgical intervention, the Surgical Intervention form (CRF 7) must be completed. The following information will be documented for each adverse event:

- Event type
- Start and stop date
- Severity
- Investigator's opinion of the causal relationship between the event and investigational device (Section 9.1.7)
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Action concerning investigational device
- Outcome of event
- Severity (Section 9.1.6)

9.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An AE form must be completed and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject enrollment number
- Investigator's name
- Causality assessment

The Sponsor should be notified of the SAE within 24 hours.

Any SAE spontaneously reported to the Investigator after the subject has completed the study should be reported to the Sponsor if considered related to study participation.

9.3 Follow-up of SAEs

If information that is not available at the time of the first report becomes available at a later date, the Investigator should update the AE form and/or provide other written documentation to the Sponsor within 24 hours of receipt. Copies of any relevant data from the hospital notes (.eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

9.3.1 Safety Reporting to Investigators, IRBs and Regulatory Authorities

In accordance with US regulations, Investigators are required to submit a report of an Unanticipated Adverse Device Effect (UADE) to the Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event.

The Sponsor will be responsible for reporting all (UADEs) to regulatory authorities, Investigators and IRBs as applicable. The Sponsor or Sponsor's designee shall report the results of such evaluation to FDA and to all reviewing IRB's and participating Investigators within 10 working days after the Sponsor first receives notice of the effect.

10.0 DATA HANDLING AND RECORD KEEPING

10.1 eCRFs

The Sponsor or its designee will supply investigative sites with access to electronic case report forms (eCRF) via a web-based electronic data capture system. Complete data for each subject are to be entered on all required forms. A representation of the eCRFs is provided in Appendix F.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the Sponsor (or designees) and will be answered by the investigational site. Data problems will be addressed in calls to the Investigational Sites and during monitoring visits.

Corrections to eCRFs can be made at any time. If the eCRF to be changed has already been electronically signed by the Investigator, a reason for the change must be provided. The eCRF status will then change, requiring the Investigator to resign the eCRF.

The Principal Investigator must review the eCRFs for completeness and accuracy and must electronically sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

All data files will be secured to ensure confidentiality.

The Investigator is to maintain all source documents as required by the protocol, including supporting medical records and Informed Consents. The source documents will be used at the regular monitoring visits to verify information submitted on the eCRFs.

10.2 Visit Boundaries and Missed Visits

Figure 5 defines the tolerance range for each follow-up visit. A visit that occurs outside of the specified range will be coded using the closest follow-up window and identified as a protocol deviation on the Protocol Deviation form (CRF 9).

10.3 Subjects Lost-to-Follow-Up

A subject will be considered lost-to-follow-up from the last missed clinical evaluation if all reasonable efforts made to contact the subject and request his/her continued participation in the study have failed. Telephone and written attempts will be made to locate and return such individuals to care. At least two certified letters must be sent. In instances where the individual cannot be located or traced, the circumstances leading to lost-to-follow-up status will be documented. All attempts to contact the subject will be documented. When all attempts have failed and a subject is lost-to-follow-up, a Subject Discontinuation/Withdrawal form (CRF 10) must be completed.

Study ID numbers assigned to subjects who are discontinued will not be reassigned to newly enrolled subjects. Whenever possible, subjects who have been discontinued for reasons other than

lost-to-follow-up will be contacted and requested to participate in ongoing safety data assessments conducted by phone.

10.4 Screened Subjects Who are Not Enrolled

Only data for enrolled subjects will be monitored and entered into the database. Subjects who are screened for the study but are not enrolled for any reason will not be followed and the Sponsor will not evaluate their data. The sites may retain the screening documents for these subjects, at their discretion.

10.5 Record Retention

The Investigator agrees to keep the records stipulated in Section 10.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms) and query responses, and detailed records of investigational device disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Refer to the Investigator Agreement for the Sponsor's requirements on record retention. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11.0 INVESTIGATOR RESPONSIBILITIES AND OBLIGATIONS

11.1 Investigator Responsibilities

The Investigator is responsible for obtaining the initial and continuing review and approval from the authorized IRB for the institution (site) at which the proposed clinical investigation is to be conducted. The Investigator is responsible for ensuring that the investigation is conducted according to the Investigator Agreement, this Investigational Plan and applicable FDA regulations as required. Investigator responsibilities are defined in Title 21 of the US Code of Federal Regulations Part 812, Subpart E.

The Investigator is responsible for ensuring that informed consent is obtained from each study subject prior to the initiation of any study procedures.

The Investigator shall permit the device to be used only under his / her supervision. Upon completion or termination of this study, or at Sponsor's request, the Investigator shall return to the Sponsor any remaining unused devices or otherwise dispose of the device as the Sponsor directs.

11.2 Investigator Records

The Investigator will maintain complete, accurate and current study records, including the following materials:

1) Correspondence with the Sponsor, the Clinical Monitor, the Medical Monitor, other Investigators, the IRB, or the FDA;
2) Accountability of records of receipt, use, and disposition of all investigational devices and other study materials that are consigned to a site including:
    a) The type and quantity of the device, the dates of its receipt, and the batch number or code mark;
    b) The names of all persons who received, used, or disposed of each device; and
    c) The number of devices that have been repaired, returned to the Sponsor, or otherwise disposed of, and the reason for such action;
3) Study Subject Records, including Informed Consent forms, copies of all source documents and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.), and records of exposure of each study subject to the device;
4) Documentation of any use of the device without Informed Consent. A brief description of the circumstances justifying the failure to obtain Informed Consent and written concurrence of a licensed dentist are required;
5) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated);

6) Current study protocol and protocol deviation log, with dates and details of any reason for deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects;
7) The approved blank Informed Consent form;
8) Certification that the Investigational Plan has been approved by all of the necessary approving authorities; and
9) Signed Investigator's Agreements
10) CV's of the Principal Investigator and all participating Co-Investigators attached.
11) Signed Financial Disclosure
12) Copies of hospital certification and clinical laboratory certification, if applicable.

These records shall be maintained for a period of 2 years after the latter of the following two dates:

i) the date on which the investigation is terminated or completed; or
ii) the date that the records are no longer required for purposes of supporting a premarket approval application or notice of completion of a product development protocol.

11.3 Investigator Reports

The Investigator will be responsible for the following reports:

Unanticipated Adverse Device Effect: An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, or any life threatening problem or death caused by, or associated with the device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this investigational plan; or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of the subjects.

Withdrawal of IRB Approval: The Investigator shall report to the Sponsor within 5 working days if, for any reason, the IRB withdraws approval to conduct the investigation. The report will include a complete description of the reason(s) for which approval was withdrawn.

Deviations from the Investigational Plan: The Investigator shall notify the Sponsor and the reviewing IRB of any changes in, or deviations from, the Investigational Plan to protect the life or physical well being of the Subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurs. Except in such emergency, prior approval by the Sponsor is required for changes in or deviations from the plan; and, if these changes or deviations may affect the scientific soundness of the plan, or the rights, safety or welfare of the subjects, FDA and / or IRB approval also is required.

Use of Device without Informed Consent: No Subject may be treated with the device without prior Informed Consent. Such treatment constitutes a violation of federal regulations. If the Investigator treats a Subject with the device without prior Informed Consent, that Investigator must report this use to the Sponsor and the reviewing IRB within 5 working days after use occurs.

Progress Reports: The Investigator is required to submit annual progress reports to the study Sponsor, to the Clinical Monitor and to the reviewing IRB. Reports must include the number of study subjects, a summary of all follow up evaluations, a summary of all adverse events and a general description of the study's progress.

Final Report: The Investigator will submit a final report to the Sponsor and to the IRB within 3 months of termination of the study or termination of that Investigator's participation in the study.

Other Reports: Upon request of the Sponsor, the FDA or the IRB, the Investigator shall provide accurate, complete and current information.

11.4 Investigator Agreement

An example of the agreements to be entered into by all Investigators to comply with Investigator obligations is provided as an attachment to the written protocol. Please refer to Appendix B to review the Sample Investigator's Agreement.

11.5 Financial Disclosure by Clinical Investigators

Pursuant to 21 CFR part 54 and prior to the initiation of the study, each Investigator must disclose certain financial arrangements that may exist between that Investigator and Sunstar Americas, the manufacturer of the [redacted] Growth Factor Enhanced Bone Graft Substitute. This information will be collected from each Investigator, maintained in confidential files by the Principal Investigator and will be available for review by FDA upon request.

The Sponsor will provide sample informed consents for screening and enrollment (see Appendices C and D, respectively) to each site for review and approval by the local Institutional Review Board (IRB), any changes made to the consents must be approved by the Sponsor. All subjects must sign the IRB approved informed consents prior to screening and the initiation of any study-related procedures, and enrollment in the study.

Additionally, each subject must consent to data transfers affected by HIPAA. Due to the differences in state regulations affecting HIPAA, sites may supply their local consent document or language for inclusion in the study informed consent document.

Final Report: The Investigator will submit a final report to the Sponsor and to the IRB within 3 months of termination of the study or termination of that Investigator's participation in the study.

Other Reports: Upon request of the Sponsor, the FDA or the IRB, the Investigator shall provide accurate, complete and current information.

12.0 STATISTICAL METHODS

Data will be summarized for each treatment group separately. The analyses will be performed by comparing the data for the active control group to each of the treatment groups.

12.1 Statistical and Analytical Plans

Primary Effectiveness Endpoints:

The primary effectiveness outcome in this trial is the radiographic and clinical composite which is a combination of an amount of linear bone growth (LBG) and change of clinical attachment level (CAL) clinically measured from baseline at the six month post-implantation. The thresholds to be used are 1.5 mm for ΔCAL and 1 mm for LBG.

Secondary Effectiveness Endpoints:
There are nine secondary effectiveness outcomes which are described in Section 5.2.3.

12.1.1 Hypothesis Testing

As this is a feasibility study, formal hypothesis tests for the purposes of regulatory approval or labeling claims will not be performed. Nonetheless, for internal purposes, statistical hypothesis tests may be performed as follows.

A two-sided superiority hypothesis test follows for the composite success percent endpoint:

H_0: $p_G - p_C = 0$, versus
H_a: $p_G - p_C \neq 0$

where p_G and p_C are the respective percents of subjects achieving success as specified above for [redacted] GFeBGS and Active control treatment groups. This hypothesis testing format will be used for the other effectiveness endpoints measured as success outcomes.

The two-sided superiority hypothesis test is the following for the continuous and percent based measures relative to baseline:

H_0: $\Delta_G - \Delta_C = 0$, versus
H_a: $\Delta_G - \Delta_C \neq 0$

where Δ_G and Δ_C are the respective mean changes in outcomes relative to baseline for [redacted] GFeBGS and Active control treatment groups. The same hypothesis testing format will be used for other continuous effectiveness endpoints.

For each primary and secondary effectiveness endpoint, an alpha level of 0.05 will be used.

12.1.2 Sample Size Determination

Since this is a feasibility study, the overall sample size was selected based on a combination of regulatory, logistical, and statistical considerations. While formal hypothesis testing for the primary effectiveness endpoint is not expected to be conclusive, the analysis of change in LBG is expected to provide more power as it is based on a continuous outcome. An assessment of the planned sample size based on this endpoint follows.

Sample size was determined based on a two-sided two sample unequal variance t-test with an overall 5% significance level for comparison of [redacted] GFeBGS versus Active control using the following assumptions:

- 1:1 randomization for GFeBGS and Active control (equal allocation of subjects to the control and each of the three treatment group separately, n1=n2=n3=n4 resulting in a 1:1:1:1 randomization allocation)
- Power = 80% for the secondary effectiveness endpoint of LBG
- δ = 1.70 mm mean advantages in the change from baseline in LBG to be tested in favor of GFeBGS (3.00 mm) versus Active control (1.30 mm)
- Corresponding standard deviations (SDs) are projected to be 1.20 and 2.30 mm for the GFeBGS and Active control groups respectively
- 15% dropout rate by 6 month post-surgery.

With a minimum of 20 patients per treatment group, the power is at least 80% to detect a difference of 1.70 mm based on a two sample unequal variance t-test.

12.1.3 Analysis Populations

Three populations will be considered in this study as follows.

Intent-to-Treat (ITT) population: The ITT population is defined as all randomized patients who receive the study therapy. All effectiveness analyses will be performed using the ITT population as randomized. The ITT population will be used for all primary effectiveness analyses.

Modified ITT (mITT) population: The mITT population is defined as all ITT patients who were eligible, received the study treatment as randomized (*e.g*. 0.3% GFeBGS when randomized to 0.3% GFeBGS), received the treatment as specified in the protocol, had at least one post-baseline evaluation, and maintained the evaluator treatment blind. The mITT population will be used for all confirmatory effectiveness analyses.

Safety population: The safety population is defined as all patients receiving any study therapy. Safety analyses will be based on the actual treatment administered. The safety population will be used for all safety analysis.

12.1.4 Missing, Used and Unscheduled Data

The numbers of patients screened, randomized, treated, eligible, completing each visit, and completing the study will be reported overall and by treatment group, and then for each investigational site by treatment group.

12.1.5 Patient and Visit Deviations

Patients will be evaluated to assess eligibility, treatment compliance, visit compliance, and other protocol deviations such as excessive smoking, poor dental care, concurrent medical conditions impacting effectiveness or safety evaluations, and missed visits. Any post-baseline visits occurring more than two weeks outside of study visit windows will be reported. Withdrawals due to lack of effectiveness or adverse events will also be reported as well as the timing of such events. Dropouts will also be reported as well as the nature and timing of such dropouts for any reason. A 15% allowance has been made for dropouts; treatment assignments for dropouts will not be recycled. All patients will be included in all analyses to the fullest extent possible; no data will be carried forward.

12.1.6 Analysis Approach

Demographics and Baseline Characteristics

Differences between the four study treatment groups in continuous baseline characteristics (i.e. age, percent bone required to be regenerated) will be analyzed using ANOVA. Differences between treatment groups in categorical baseline characteristics (i.e. gender, race, smoking history) will be analyzed using a two-sided, generalized, Fisher Exact test. Differences between ordinal outcomes (i.e. number of teeth to be implanted) will be analyzed using a singly ordered exact Kruskal-Wallis test as a global test of equality. Analyses will account for baseline smoking habit.

If any treatment groups are found to be imbalanced with respect to any baseline covariates based on test at a 0.05 alpha level, impact to the comparisons between the study treatment groups will be investigated by including those covariates in sensitivity analyses for the binary effectiveness analyses using a logistic regression model and for continuous effectiveness endpoints using an ANCOVA model.

12.1.7 Missing Data Strategies

Given the nature of the study, very few dropouts (<5%) are expected. This is a consequence of the close bond that develop between study Investigator teams and their patients, which will be observed and reinforced through the Study Monitors assigned to respective sites. In the event that there are any missing data, the percents with missing data will be compared using a two-sided Fisher Exact test; the reason for withdrawal will be presented to see if any treatment group or site pattern exists. While the primary analysis will be based on all available data with no imputation performed, sensitivity analyses will be performed to assess the potential impact of missing data.

This will include an analysis where missing data is treated as a success, an analysis where missing data is treated as a failure, and finally an analysis where missing data in the control group is treated as a success and missing data in the GFeBGS group is treated as a failure.

12.1.8 Primary Effectiveness Analysis

Comparisons will be made between the control group and each of the treatment groups using 2x2 tables. Superiority for the composite endpoint will be tested using a logistic regression model to include age (< 50 versus ≥ 50 years) and smoking status (never or not within the last 6 months vs. any within the last 6 months) at the time of randomization as the baseline covariates. The two-sided 95% lower bound for the LSMEAN difference for each of the three GFeBGS treatment groups minus the Active control will need to exceed 0% to achieve superiority. An unadjusted logistic regression model for the primary composite endpoint will also be performed.

Superiority will also be tested using an exact two-sided 95% lower confidence bound for the difference in success percents. The two-sided 95% lower bound for each of the three GFeBGS treatment groups minus Active control difference must be ≥ 0% to achieve superiority.

Additional logistic regression models will also evaluate any additional covariates found to be imbalanced ($p \leq 0.05$) at baseline.

12.1.9 Secondary Effectiveness Analysis

Superiority will be tested for the continuous effectiveness endpoints (e.g. ΔCAL, LBG, %BF, PD) using an ANCOVA model with the same baseline covariates as specified above and in addition, the corresponding baseline value for each endpoint. The ANCOVA model will include the same covariates as for the primary effectiveness endpoint. The two-sided 95% lower bound for the LSMEAN difference between each of the three GFeBGS treatment groups minus Active control will need to exceed 0 to achieve superiority.

Additional ANCOVA models will also evaluate any additional covariates found to be imbalanced ($p \leq 0.05$) at baseline.

Effectiveness outcomes will be displayed at every visit in order to characterize the time of onset and duration of effectiveness throughout the study. Results will be displayed for subjects who complete the study as planned as well as for those withdrawn early; the patterns of withdrawal will be displayed for each study treatment group to assess if reasons withdrawn were different in any respect.

Analyses will also be conducted for the other effectiveness endpoints inclusive of PDR, GR, WH, and BOP; the second composite endpoint (ΔCAL, %BF) will be analyzed in the same manner as for the first composite endpoint. In general, for continuous variables, the mean, median, standard deviation, minimum and maximum values will be displayed; for ordinal and categorical variables,

frequencies and percentages will be displayed. When relevant, the mean changes from pre-operative baseline will be computed for all treatment groups at each visit through study exit; an unpaired t-test will be used to test for improvement between the treatment groups while a paired t-test will be used to test for improvement within the treatment groups. Superiority will be tested for continuous outcomes using an unpaired t-test by examining the two-sided 95% lower bound for the difference between GFeBGS minus Active control to test if the lower bound exceeds 0. The percents achieving predefined effectiveness milestones will be displayed at each post-baseline time through each stage; a two-sided Fisher Exact test will be used to test for superiority.

12.1.10 Dose Selection

Dose selection for future study will be based on an analysis of the primary composite endpoint. Five different dose response patterns will be examined and modeled statistically, with the dose selected based on the best model fit. Specifically, we will perform a logistic regression of the primary composite endpoint and apply linear contrasts to the model according to the following five dose response patterns for success:

1. An increase in a linear manner from the Treatment I to Treatment IV groups
2. A plateau in the Treatment II group, with similar performance in groups II through IV
3. A plateau in the Treatment III group, with similar performance in group IV
4. An apex in the Treatment III group; best performance in group III, lower performance in the other groups
5. An apex in the Treatment IV group; best performance in group IV, lower performance in the other groups

For each contrast, the Wald test statistic will be computed and the pattern that corresponds to the largest value of the Wald statistic will be considered the best fit and guide the selection of the optimal dose.

For patterns where there is insufficient data to distinguish between effective doses, patterns 2 and 3 for example, the 0.3% rh-bFGF dose may be selected based on prior data and pre-clinical testing.

12.1.11 Safety Analysis

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and additional pre-specified codes for device-specific local AEs or classified using a pre-specified ordinal scale. The classes of AEs will be summarized by type (by organ class and preferred term), incidence, timing (intra-operative, post-operative), severity, and relationship to study treatment for each treatment group; event counts will also be summarized by system organ class and preferred term. All AEs will also be sorted into local vs. systemic events. Patients reporting multiple

episodes will be counted once under the worst severity and the strongest relationship, respectively. In addition, SAEs will be presented by relationship to study treatment.

Local events, clinical signs or symptoms, rh-bFGF antibody above baseline, and delayed healing will also be assessed. The subject-level incidence of these outcomes will be analyzed using a two-sided Fisher Exact test while the event-level incidence will be analyzed using a Wilcoxon test.

Safety analyses will be performed on the ITT population receiving any study treatment.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Investigational Site Monitoring Visits

Each investigational site will be monitored on site, to ensure that the study is conducted in full compliance with the study protocol and in compliance with the FDA Guidelines for the Monitoring of Clinical Investigations (February,1988), Good Clinical Practices and Sunstar policies and procedures.

[redacted]. will conduct regular clinical monitoring visits to each investigational site. Before beginning data collection for a given site, the site and personnel to be involved in the study at that site will be visited. The objectives of this pre-study visit are:

- to confirm that the Investigator and study personnel fully understand the Clinical Investigation Plan, the data collection procedures and the requirements to be met before starting the study;
- to confirm that the Investigator and study personnel fully understand the procedures related to the selection of study subjects for this study; and
- to confirm that the Investigator and study personnel have appropriate knowledge, experience and equipment to comply with the study requirements. Observations made during a pre-study visit will be documented by means of a pre-study monitoring report.

To ensure that the Investigators and their staffs understand and accept their defined responsibilities, the Clinical Monitor will maintain regular correspondence and perform periodic site visits during the course of the study to verify the continued acceptability of the facilities, compliance with the Investigational Plan, conditions of the IRB and requirements of the IDE regulations, complete documentation and reporting of any complications and Unanticipated Adverse Device Effects, and the maintenance of complete records. Clinical monitoring will include review and resolution of missing or inconsistent results, source document checks (i.e., comparison of submitted study results to original reports) to assure the accuracy of the reported data, review of the device inventory log and review of the investigational device storage conditions. The Clinical Monitor will also conduct a site close out visit. The Clinical Monitor will evaluate and summarize the results of each site visit in written reports, identifying any repeated data problems with the Investigator and specifying recommendations for resolution of noted deficiencies.

13.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that would require deviation from protocol-specified procedures, the Investigator should consult with the Dental Director (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The investigational sites also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the investigational device is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments. If the investigational site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all study documents.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Section 11.0. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

14.1 IRB Approval

IRBs must be constituted according to the applicable requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or for the protocol's review and approval. This protocol, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the investigational device kits or study specific screening activity). The IRB approval must refer to the study by the exact protocol title, number, and version date; identify versions of other documents (e.g. informed consent form) reviewed; and state the approval date. The Sponsor or its designee will ship the investigational device kits once the Sponsor has confirmed the adequacy of investigational site's regulatory documentation and the Sponsor has received approval from the FDA to begin the trial. Until the site receives notification from the Sponsor or designee, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB and submission of the Investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and Sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB approval of the informed consent form and if applicable, the subject authorization form. The informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form will be stored in the investigational site's file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

14.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g. FDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e. subject name, address, and other identifier fields not collected on the subject's eCRFs).

15.0 REFERENCES

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