CREIGHTON UNIVERSITY SCHOOL OF DENTISTRY
DEPARTMENT OF PERIODONTICS

STUDY PROTOCOL
Clinical Efficacy of easy graft Classic for the treatment of Peri-implantitis

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Contents

PROTOCOL SYNOPSIS

Protocol Number	1015456
Title	A STUDY TO DETERMINE EFFICACY OF EASY GRAFT CLASSIC FOR THE TREATMENT OF PERI-IMPLANTITIS
Subject Population	Subjects with history of Moderate to Severe Peri-implantitis
Objectives	TO ASSESS THE EFFECTVENESS OF EFFICACY OF EASY GRAFT CLASSIC
Number of Subjects	Maximum of 15 subjects
Number of Sites	Maximum 20 implants
Safety Endpoints	Assessments of subject safety will be based upon tabulations of the incidence of adverse events.
Efficacy Endpoints	Stability and health of the attachment apparatus at 6 and 12 months by measuring: • Change from baseline in probing depth • Change from baseline in clinical attachment level • Change from baseline in width of the keratinized tissue • Change from baseline in radiographic A) bone regeneration ; B) pathology • Esthetic satisfaction from baseline to 12 months, as assessed by both the examiner and the subject using the Visual Analog Scale (VAS), prior to and after viewing baseline photos • Subject pain/discomfort questionnaire

Study Design	This study will be "case series". Two periodontists will perform surgical procedures and record surgical measurements. The blinded examiner will perform all other clinical assessments. 15 subjects will be enrolled. Written informed consent will be obtained from each subject prior to any study related procedures. The study will follow subjects for safety and efficacy for 12 months after their surgical treatment. The day of surgery will be designated as Day 0. Subjects will have a guided bone regeneration surgery with GUIDOR® easy-graft® CLASSIC and GUIDOR® Bioabsorbable Membrane Matrix for the implants experiencing peri-implantitis. The surgical side will be assessed for osseous and implant surface anomalies. Intraoperative and postoperative measurements will be made and the flap will be closed with sutures.

1.0 BACKGROUND

Peri-implantitis is an infectious condition of the tissues around dental implants causing loss of supporting bone and clinical signs of inflammation such as bleeding and/or suppuration on probing). The prevalence of this disease regards almost 10% of implants and almost 20% of

patients[1,2]. Many factors influence and increase prevalence (and the risk) of peri-implantitis. Some of those are previous history of periodontitis, smoking, diabetes as well as the type and frequency of follow-up care. It is worth noting that the prevalence of peri-implantitis varies depending on the parameters used in scientific papers. Bone loss and/or probing depth threshold may vary among different authors modifying the case definition.

Different clinical protocols for treatment of peri-implantitis have been proposed, including mechanical debridement, the use of antiseptics and local or systemic antibiotics, as well as surgical access and regenerative procedures. Several attempts to combine the data of the available literature in a meta-analysis have failed in the past due to insufficient data.[3,4,5,6, 7, 8]

Mombelli et all, in their review[9] noted that almost all studies on the treatment of peri-implantitis in humans do not satisfy the strict criteria for a randomized controlled trial (RCT). The main limitation was the absence of a true control group (no treatment or placebo). Trials at the highest level of evidence compared test procedures, both of which had an unclear

[1] Mombelli A, Müller N, Cionca N. The epidemiology of periimplantitis. Clin Oral Implants Res 2012;23(suppl 6):67–76.
[2] Lee CT, Huang YW, Zhu L, Weltman R. Prevalences of peri-implantitis and peri-implant mucositis: systematic review and meta-analysis. J Dent. 2017 Jul;62:1-12. doi: 10.1016/j.jdent.2017.04.011. Epub 2017 May 3. Review.
[3] Klinge B, Gustafsson A, Berglundh T. A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. J Clin Periodontol 2002;29(suppl 3):213–225; discussion 232–213.
[5] Renvert S, Roos-Jansaker AM, Claffey N. Non-surgical treatment of peri-implant mucositis and peri-implantitis: A literature review. J Clin Periodontol 2008;35:305–315.
[6] Renvert S, Polyzois I, Claffey N. Surgical therapy for the control of peri-implantitis. Clin Oral Implants Res 2012;23(suppl 6):84–94.
[7] Muthukuru M, Zainvi A, Esplugues EO, Flemmig TF. Non-surgical therapy for the management of peri-implantitis: A systematic review. Clin Oral Implants Res 2012;23(suppl 6):77–83.
[8] Esposito M, Grusovin MG, Worthington HV. Treatment of periimplantitis: What interventions are effective? A Cochrane systematic review. Eur J Oral Implantol 2012;5(suppl):s21–s41.
[9]Mombelli A, Moene R, Decaillet F. Surgical treatments of periimplantitis. Eur J Oral Implantol 2012;5(suppl):s61–s70

outcome. As it is difficult to recruit sufficient numbers of patients with peri-implantitis to take part in a true randomized trial, some studies may have been underpowered.

In terms of outcomes, there is inconsistency about primary treatment goals and minimally required observation periods. A recent Cochrane systematic review [10] included nine randomized controlled trials in an attempt to identify the most effective interventions for treating peri-implantitis around osseointegrated oral implants. The authors concluded that there is no reliable evidence suggesting which could be the most effective interventions for treating peri-implantitis. A review by Heitz-Mayfield and Mombelli[11] covered reports that evaluated the effect of treatment, regardless if they were randomized trials or not. The available evidence does not provide specific recommendations or standard protocol for peri-implantitis treatment. Successful treatment outcomes at 12 months were reported in a majority of patients in 7 studies. Despite favorable short-term outcomes were reported in many studies, failure of treatment, progression or recurrence of disease and implant loss were reported too. The main limitation of systematic reviews is the heterogeneity in study design, length of follow-up, and exclusion/inclusion criteria.

[10]Esposito M, Grusovin MG, Worthington HV. Interventions for replacing missing teeth: Treatment of peri-implantitis. Cochrane Database Syst Rev 2012;1

[11]Heitz-Mayfield and Mombelli. The therapy of peri-implantitis: a systematic review. Int J Oral Maxillofac Implants. 2014;29 Suppl:325-45. doi: 0.11607/jomi.2014 suppl

Daugela et al[12] reported that in case of evident bone loss and pocket formation deeper than 5 mm, the surgical treatment seemed to be the only effective one in managing peri-implantitis defect. Surgical regenerative treatment resulted in predictable improvement of peri-implant clinical and radiographic parameters although this statement is limited on available studies without proper control arm, as at the time there is a lack of controlled studies comparing effectiveness of surgical regenerative and non-regenerative procedures to support scientific evidence if regenerative procedures provide better outcomes.

Currently there is a lack of clear recommendation regarding choice of biomaterials for peri-implant bone regeneration due to high heterogeneity among the studies. From the clinical point of view, surgical regenerative treatment is a relevant treatment option of intrabony defect component in addition to pre- and postsurgical hygiene maintenance phases and successful implant surface decontamination. Regenerative procedures, with the application of bone graft materials in combination or not with barrier membranes seem to give consistent results in the term of hard and soft tissues healing of the peri-implantitis defect.

Regenerative treatment of peri-implantitis lesions can be performed in cases with considerable pocket formation and bone loss after the acute infection has been resolved and proper oral hygiene has been instituted. Reported clinical studies indicate that considerable bone regeneration and re-osseointegration can be obtained by using various types of bone graft materials and membranes. Meta-analysis of latest systematic literature review [xi] revealed that

[12]Daugela P, et alSurgical Regenerative Treatments for Peri-Implantitis: Meta-analysis of Recent Findings in a Systematic Literature Review. J

the weighted mean of marginal bone level change was 1.97 mm, PD reduction was 2.78 mm and BOP reduced by 52.5% by treatment with regenerative treatment. However, a different compatibility between bone grafting material and chemically and mechanically decontaminated implant surface might bring a different clinical outcome.

As far as the use of alloplastic grafting material, only two papers were identified in the literature. Roos-Jansåker et al. [13], [14] evaluated regenerative treatment of peri-implantitis comparing a bone substitute with or without a barrier membrane. Peri-implant defects were treated with a phytogenic calcium carbonate bone substitute (Algipore) or with the bone substitute and a resorbable synthetic membrane (Osseoquest). Successful treatment outcome (no PD ≤ 5 and no further bone loss 12mo after treatment) was on 93% of patient treatment with bone substitute and membrane and 89% of patients treated with bone substitute only.

Schwarz et al [15] filled peri-implant defects with either a synthetic nano-crystalline hydroxyapatite (Ostim) or a bovine-derived xenogenic bone mineral (BioOss), and covered with a collagen membrane (Bio-Gide). Within the limits of the present case series they concluded that at 12 months after surgery both therapies resulted in clinically important PD reductions and CAL gains.

Oral Maxillofac Res 2016; 9 (3): e15

[13]Roos-Jansåker A-M, Renvert H, Lindahl C, Renvert S. Surgical treatment of peri-implantitis using a bone substitute with or without a resorbable membrane: A prospective cohort study. J Clin Periodontol 2007;34:625–632.

[14]Roos-Jansåker A-M, Lindahl C, Persson GR, Renvert S. Long-term stability of surgical bone regenerative procedures of peri-implantitis lesions in a prospective case-control study over 3 years. J Clin Periodontol 2011;38:590–597.

[15] Healing of intrabony peri-implantitis defects following application of a nanocrystalline hydroxyapatite (Ostim) or a bovine-derived xenograft (Bio-Oss) in combination with a collagen membrane (Bio-Gide). A case series. Schwarz F, Bieling K, Latz T, Nuesry E, Becker J J Clin Periodontol. 2006 Jul;33(7):491-9.

Due to scarcity of literature on the use of alloplast on peri-implant treatment, the purpose of the study is to assess the effectiveness of the novel in-situ hardening β -TCP material, Easy-Graft® CLASSIC and polylactide based biodegradable membrane, GUIDOR® Biodegradable Matrix Barrier, following clinically adequate decontamination procedures. The author thinks

that the specific properties of this grafting material may favor treatment of peri-implantitis. A recent study by Canullo[16] et al. analyzed the efficacy of Easy-Graft® CLASSIC on the treatment of peri-implantitis. After removal of granulomatous tissue and decontamination of the titanium exposed implant surface, Easy-Graft was placed on the defect as a protection from soft tissue invasion. The authors noted a pronounced increase in mucosal recession and clinical attachment level with stable peri-implant conditions at six and 12 months. Plaque index, bleeding on probing and probing depths values were significantly reduced at six and 12 months. Radiographic analysis demonstrated from partial to complete filling of the defect in all of the cases at six and 12 months.

Easy-graft remains moldable until it comes in contact with blood or tissue fluids. When the material is soaked in blood in bone defects it hardens in a few minutes to form stable porous scaffold for bone regeneration. This characteristic of graft material gives better handling for the clinician. The hardening of the material could provide an increased stability of the blood clot around implant defect and favor hard tissue deposition and maturation. The Easy-Graft® CLASSIC manufacturer recommends GUIDOR® Bioabsorbable Membrane Matrix to be used

[16] Canullo L, Peñarrocha Oltra D, Tallarico M, Aloy Prosper A, Chocer H, Peñarrocha Diago M. Surgical treatment of circumferential and semicircumferential defects due to periimplantitis: a prospective case series cohort study. J Oral Science Rehabilitation. 2016 Dec;2(4).

simultaneously in order to maximize its effects. The main difference between this proposed study and Canullo's will be the use of GUIDOR® Bioabsorbable Membrane Matrix in conjunction with Easy-Graft® CLASSIC

The authors of this present study considered the outcome of the peri-implant surgical therapy successful if: implant survival with no peri-implant probing depths (PD) ≥ 5 mm, with concomitant bleeding on probing (BOP) and no suppuration, in addition to no additional or progressive bone loss. If these criteria were met, it can be assumed that no further intervention other than nonsurgical maintenance care would be required, and the treatment outcome would therefore be regarded as successful.

2.0 SUMMARY AND STUDY RATIONALE

The present study was designed to demonstrate the EFFICACY OF EASY GRAFT CLASSIC FOR THE TREATMENT OF PERI-IMPLANTITIS.

Easy-graft® CLASSIC, is commercially available alloplastic bone graft granules consists of pure β -TCP, which has been commonly used for the indication of ridge preservation[17, 18], peri-implant bone augmentation[19], sinus elevation[20] and other treatment of intraoral / maxillofacial osseous defects[21]. It has unique handling capacity based on an extremely thin coating of the graft granules with poly(lactic-co-glycolic acid) (PLGA). PLGA is used as a raw material to manufacture dental membranes, suture materials and resorbable screws. Before application, the granules are mixed with BioLinker® which consists of water and N-Methyl-2-pyrrolidone (NMP). It is non-volatile solvent which has been in used in various medical products for more than 10 years. Easy-graft remains moldable until it comes in contact with blood or tissue fluids. When the material is soaked in blood in bone defects it hardens in a few minutes to form stable porous scaffold for bone regeneration. This characteristic of graft material gives better handling for the clinician.

Regenerative treatment of peri-implantitis lesions can be performed in cases with considerable pocket formation and bone loss after the acute infection has been resolved and proper oral hygiene has been instituted. Reported clinical studies indicate that

[17] Leventis MD, et.al. (2016) Minimally invasive alveolar ridge preservation utilizing an in situ hardening β-tricalcium phosphate bone substitute. A multicenter case series. Int J Dent. ID 5406736

[18] Schneider D, et.al. (2014) Labial soft tissue volume evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial. J Clin Periodontol. 41(6): 612-617.

[19] El Sayed et. al. (2015) After socket preservation of upper anterior teeth. Alexandria Dental Journal. 40: 79-85

[20] Troedhan A, et.al. (2015) Biomechanical Stability of Dental Implants in Augmented Maxillary Sites: Results of a Randomized Clinical Study with Four Different Biomaterials and PRF and a Biological View on Guided Bone Regeneration. BioMed Res Int. ID 850340

[21] Neumeyer S. et al. (2010) The use of polylactide-coated ß-TCP: Closure of oro-antral communications. Implants. 4:32-36

considerable bone regeneration and re-osseointegration can be obtained by using various types of bone graft materials and membranes. Meta-analysis of latest systematic literature review[22] revealed that the weighted mean of marginal bone level change was 1.97 mm, PD reduction was 2.78 mm and BOP reduced by 52.5% by treatment with regenerative treatment. However, a different compatibility between bone grafting material and chemically and mechanically decontaminated implant surface might bring a different clinical outcome. The purpose of the study is to assess the effectiveness of in-situ hardening β - TCP material, easy-graft CLASSIC, for the regenerative treatment of peri-implantitis with polylactide based biodegradable membrane (GUIDOR® Bio-resorbable Matrix Membrane) following clinically adequate decontamination procedures.

The day of surgery will be designated as Day 0. Subjects will have periodontal surgery based on the protocol of Guided Bone Regeneration. Subjects will have a guided bone regeneration surgery with GUIDOR® Bio-resorbable Matrix Membrane and Easy graft classic for the implants experiencing peri-implantitis. The surgical side will be assessed for osseous and implant surface anomalies. Intraoperative and postoperative measurements will be made and the flap will be closed with sutures.

[22] Daugela P, et al. (2016) Surgical regenerative treatment for peril-implantitis: Meta-analysis of recent findings in a systematic literature review. J Oral Maxillofac Res. 9 (3): e15

The preliminary phase of the study will comprise completion of medical and dental histories, signing of consent forms, obtaining radiographs and photographs, performing screening assessments to confirm eligibility, and instruction in oral hygiene techniques. Before the periodontal surgical procedure, subjects may undergo plaque removal, then root planing and scaling to the areas to be treated, if such treatment is indicated. The final esthetic outcome of the treated sites will be evaluated by the patients using the Visual Analog Scale (VAS) ranging from "Very Unsatisfied" to "Very Satisfied" (before and after viewing baseline photos). Other clinical assessments will include: subject pain/discomfort questionnaire, change in probing depth, change in clinical attachment level, change in width of keratinized tissue from baseline to 6 and 12 months and change in radiographic bone gain and pathology. Digital photographs will be obtained at each study visit and radiographs of the test sites will be made at the baseline, 6 and 12 month visits.

The primary efficacy parameters will include:

- Esthetic satisfaction from baseline to six months of all treated areas, as assessed by both the examiner and the subject using the Visual Analog Scale (VAS), prior to and after viewing baseline photos
- Subject pain/discomfort questionnaire
- Change from baseline in probing depth (PD) measured from the mucosal margin to the bottom of the probeable pocket

- Gingival recession (Rec) measured from the implant platform (IP) to the mucosal margin
- Change from baseline visit in clinical attachment level (CAL) measured from IP to the bottom of the probeable pocket
- Change from baseline in width of the keratinized tissue (KT)
- Change from baseline in radiographic a) bone gain; b) pathology

INVESTIGATIONAL DEVICE

GUIDOR® *easy-graft®* CLASSIC

GUIDOR® easy-graft® CLASSIC is bone grafting system contains: syringe containing beta-tricalcium phosphate (β-TCP) granules coated with poly (lactide-co-glycolide) (PLGA) and ampule containing BioLinker® Activator (N-methyl-2-pyrrolidone and water).

Easy-graft CLASSIC is a bio-resorbable, synthetic, porous bone graft substitute. It consists of two components: granules (supplied in syringe) and BioLinker activator (supplied in ampule). After mixing the components together, easy-graft CLASSIC forms a moldable mass that can be applied directly from the syringe into the bone defect. Easy-graft CLASSIC hardens in contact with body fluids, allowing a working time of approximately one minute after application into the bone defect. Easy-graft CLASSIC is provided in the particle size of 500 – 1000 µm. The scaffold is a biocompatible and osteoconductive that allows for complete resorption by the

body. β-TCP and PLGA are derived from synthetic raw materials. Easy-graft CLASSIC comes sterilized via gamma irradiation.

GUIDOR® Bio-resorbable Matrix Barrier

GUIDOR® Matrix Barrier are made of polylactic acid with a citric acid ester. It is double-layered; the external layer has large rectangular perforations which face the overlying soft tissues and permit connective tissue infiltration, while the inner layer has small circular perforations which face bone and inhibit fibrous tissue ingrowth. It maintains its barrier function for 6 weeks at least, with complete resorption occurring by 6 months. Available membrane dimensions are 15 mm x 20 mm or 20 mm x 28 mm. The membrane is provided in a transparent plastic tray in a sealed aluminum pouch. It comes sterilized via e-beam.

3.0 STUDY DESIGN

3.1 Overall Study Design

This study will be case series, with two periodontists and an examiner. Both of the periodontists will perform surgical procedures and record surgical measurements. The blinded examiner will perform all other clinical assessments. 15 subjects will be enrolled. Written informed consent will be obtained from each subject prior to any study related procedures.

The study will follow subjects for safety and efficacy for 6 and 12 months after their surgical treatment.

Screening will take place no more than 32 days prior to the first treatment and will include the clinical assessments required to confirm eligibility. Clinical photograph, radiographs of the implant treated, clinical measurements will be taken and recorded (Pocked Depth, Mucosal Recession, Clinical Attachment Level). Two to four (2-4) weeks prior to the first study treatment, subjects may undergo plaque removal and root planing and scaling to the areas to be treated, if appropriate. Also, they will receive personalized oral hygiene instructions to reach full-mouth plaque score (FMPS) <20% and full-mouth bleeding score (FMBS) <20%, which will be considered requirement for surgery to occur.

The day of surgery will be designated as Day 0. Subjects will have peri-implant regeneration surgery.

If possible, implant crown will be removed with attention not to damage it. Healing screw will be placed on the implants. Upon flap elevation and debridement of the peri implant lesion, the operator will record the type of bony defect associated to the treated implant (see Inclusion criteria 3). Titanium Implant surface will be debrided with rotating burs and brushes (PERI-SET Swden&Martina Inc.), and decontaminated with EDTA gel (Straumann® PrefGel. pH neutral, 24% EDTA) for 2 minutes and with the alternation of Perio-Flow Chlorhexidine mouthwash (GUM® ParoEx®, Chlorhexidine Gluconate Oral Rinse USP 0,12%, SUNSTAR) saline water and H_2O_2 using cotton pellets. After the completion of these procedures, Easy-graft® CLASSIC will be placed to fill the peri-implant defect.

GUIDOR® Bio-resorbable Matrix Membrane will be placed on top of the easy-graft classic. If the implant crown was successfully removed and healing screw placed, the implant will be covered by the flap and submerged. Intraoperative and postoperative measurements will be made and the flap will be closed with sutures. Patients will be instructed to take 500 mg of amoxicillin three times a day for 7 days, starting at least one hour prior the procedure.

Fifteen (15) male or female subjects, aged 21 to 85 years, will be recruited for the study from existing patient databases, as well as, from screenings of volunteers responding to advertisements, if necessary.

Objectives

The objectives of this study are to assess the EFFICACY OF EASY GRAFT CLASSIC FOR THE TREATMENT OF PERI-IMPLANTITIS.

3.2.1 Primary Efficacy Endpoints

- Change from baseline in probing depth
- Change from baseline in clinical attachment level
- Change from baseline in width of the keratinized tissue
- Change from baseline in radiographic a) bone gain; b) pathology
- Esthetic satisfaction from baseline to six months of all treated areas, as assessed by both the examiner and the subject using the Visual Analog Scale (VAS), prior to and after viewing baseline photos

- Subject pain/discomfort questionnaire

3.2.2 Study Duration

The duration of this study is to be twelve (12) months following the surgical procedure.

3.2.3 Study Timeline Summary

Screening	Baseline and Surgery	Post Treatment Evaluation	Post Treatment Evaluation	Post Treatment Evaluation	Post Treatment Evaluation	Post Treatment Evaluation
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Within 32 days of surgery	Day 0	Week 1 ± 3 days	Month 1 ±7 days	Month 3 ± 14 days	Month 6 ± 14 days	Month 12 ± 14 days

3.2.4 Safety Endpoints

Assessments of subject safety will include a tabulation of the incidence of adverse events. All treatment-related adverse events that occur up to 30 days excepting surgery related AEs within 48 hours after any treatment will be recorded, and all serious adverse events throughout the study will be recorded.

3.3 Subject Eligibility

3.3.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for the study:

1. Subject has read and signed the IRB approved consent form before treatment.
2. Subject must be age 21 or above.
3. Subject must be willing and able to follow study procedures and instructions.
4. Subject affected by moderate to severe peri-implant disease*.
5. Treated chronic periodontitis and proper periodontal maintenance care,

Dental implant must meet the following criteria to be selected for the study:

1. Implant presenting PD ≥ 6 mm
2. Radiographic implant bone loss more than 25% of the implant length (Apex of the implant to implant platform)[23].
3. Peri implant bone defect being a buccal dehiscence and semicircular bone resorption to the middle of the implant body, buccal dehiscence and circular bone resorption with lingual bone plate intact or circular bone resorption with buccal and lingual bone plates intact

[23] Froum SJ, Rosen PS. A proposed classification for peri-implantitis. Int J Periodontics Restorative Dent. 2012 Oct;32(5):533-40.

4. Single tooth implant restoration or implant supported fixed partial denture.

3.3.2 Exclusion Criteria

Subject with any of the following will not be eligible for the study:

- Subjects participating (currently or within 30 days prior to enrollment) in other clinical trials involving therapeutic intervention (either medical or dental).
- Subjects with poor oral hygiene as indicated by a score of greater than 50% on the O'Leary Plaque Index.
- Subjects with a systemic condition, which would preclude periodontal treatment, including but not limited to uncontrolled diabetes.
- Subjects with acute infectious lesions in the areas intended for treatment.
- Subjects taking chronic (i.e., > 2 weeks), therapeutic doses of medications known to affect bone metabolism such as nonsteroidal anti-inflammatory drugs or bisphosphonates. Prophylactic aspirin (≤ 325 mg q.d.) for cardiovascular indications will be permitted in subjects.
- Female subjects who are pregnant or lactating, or sexually-active female subjects who are of childbearing potential and are not using hormonal or barrier methods of birth control. (except for when a result of pregnancy test is negative)
- Subjects who are on any chronic antibiotic or steroidal therapy.

- Smoker using more than 10 cigarettes or equivalent per day.
- Smoker using cigar, smokeless tobacco use or e-cigarette.
- Subjects diagnosed with drug induced gingival hyperplasia (*e.g.* calcium channel blockers).
- Subjects with radiographic evidence of pathology in other areas of the mouth besides implant area to be treated.
- Implant mobility.
- Subjects with parafunctional habits and not wearing bite guard.
-

3.3.3 Investigator Training and Qualification

The investigator(s) will be trained before participation in the study during a site initiation by means of a detailed description of all study procedures including the methods of obtaining study endpoints (measurements). The examiner will be calibrated so that the difference is 1 mm or less between his or her measurements and the principal investigator. Each examiner will measure the recession depth on two subjects three times each during each calibration session. These measurements will be recorded on a case report form and analyzed to ensure each examiner's accuracy is 1 mm or less. Examiner recalibration will be performed at the six month follow-up visit to ensure that his or her accuracy in measuring recession depth remains within that limit. Any examiner who has greater than 1.0 mm variability

from the principal investigator will undergo retraining by the principal investigator, as necessary.

One examiner will make all the measurements for each subject. The investigator guarantees that the examiner, who has working experience with the probe, is well qualified. All investigators will be noted on the Investigator's Agreement and appropriate qualifications (CV and license) will be maintained in the investigator file.

3.3.4 Blinding and Probe Calibration

All study staff, with the exception of the treating clinician will be blinded to the treatment administered. Only calibrated UNC 15 probes will be used.

3.4 Study Procedures

3.4.1 Pre-Operative Treatment

Medical examination and past history as well as dental examination and past history will be completed at this stage.

Within 32 days prior to surgery, the subject will undergo plaque removal and the test sites will be undergo to root planing and scaling (if determined to be appropriate treatment by the investigator). Two to four (2-4) weeks prior to the first study treatment, subjects may undergo plaque removal and root planing and scaling to the areas to be treated, if

appropriate. Also, they will receive personalized oral hygiene instructions to reach full-mouth plaque score (FMPS) <20% and full-mouth bleeding score (FMBS) <20%, which will be considered requirement for surgery to occur.

3.4.2 Study Treatments

Screening will take place no more than 32 days prior to the first treatment and will include the clinical assessments required to confirm eligibility. Informed Consent Form will be signed at Screening Visit (Visit 1). Clinical photograph, radiographs of the implant treated, clinical measurements will be taken and recorded (Pocked Depth, Mucosal Recession, Clinical Attachment Level).

The day of surgery will be designated as Day 0. Subjects will have peri-implant regeneration surgery.

Whenever possible implant crown will be removed and cleaned. Healing screw will be placed on the implant. Upon flap elevation and debridement of the peri implant lesion, the operator will record the type of bony defect associated to the treated implant (see Inclusion criteria 3). Titanium Implant surface will be debrided with rotating burs and brushes (PERI-SET, Sweden&Martina Inc.), and decontaminated with EDTA (PrefGel: Straumann) for 2 minutes and with the alternation of Perio-Flow Chlorhexidine mouthwash (GUM® ParoEx®, Chlorhexidine Gluconate Oral Rinse USP 0,12% SUNSTAR), saline water and H_2O_2 using cotton pellets. After the completion of these procedures, Easy-graft® CLASSIC will be placed on the peri-implant defect surface. GUIDOR® Bio-resorbable Matrix Membrane will be

placed on top of the easy-graft classic and stabilized. If the implant crown was successfully removed, flaps will be primary closed and the implant will be covered completely. Second stage, minimally invasive surgery to gain access to the implant will be performed at 6 months. Intraoperative and postoperative measurements will be made and the flap will be closed with sutures. Patients will be instructed to take 500 mg of amoxicillin three times a day for 7 days, starting at least one hour prior the procedure.

Fifteen (15) male or female subjects, aged 21 to 85 years, will be recruited for the study from existing patient databases, as well as, from screenings of volunteers responding to advertisements, if necessary.

3.4.3 Other Therapy

No other dental therapies are permitted in conjunction with the study treatments, dental emergencies excluded (i.e. Acute abscesses, Pulpitis, tumors or oral lesions).

3.4.4 Postsurgical Care

Patients will be instructed to take 500 mg of amoxicillin three times a day for 7 days, starting at least one hour prior the procedure. In case of allergy to amoxicillin, patient will assume 300mg Clindamycin three times a day for 7 days. Subjects will be advised to follow good oral hygiene habits in all non-study sites by brushing twice daily using a soft bristled toothbrush, and flossing once per day. All subjects will be instructed to avoid brushing and avoid the use of interdental cleaning devices for the first seven days following the surgical

procedure. In addition, all subjects will be instructed to avoid chewing directly on the test sites and to avoid trauma to the test sites for the first week following the surgery. During that interval, the subjects will be instructed to rinse twice daily after meals with 0.12% chlorhexidine gluconate non-alcohol oral rinse. After the first week, the subjects will be instructed to resume gentle tooth brushing and interdental cleaning with dental floss and continue the 0.12% chlorohexidine gluconate oral rinse for the first 4 weeks following surgery. All subjects will receive local implant cleaning at the month 3, 6 and 12 follow up visits.

3.4.5 Management of Post-Surgical Oral Pain

Any pre-surgical pain medications should be recorded and noted as such (i.e. pre-surgical pain medication). Post-surgical pain can be divided into mild, moderate, and severe levels and requires a subjective assessment by the periodontists based on knowledge of the surgical procedure performed and the presenting signs and symptoms of the subject. Pain as a secondary outcome to an adverse event, such as infection, is to be excluded if pain is an expected outcome of such events. Treatment of the pain is usually the best indicator of pain intensity.

<u>MILD (Over-the Counter)</u>

Acetaminophen 250 or 500 mg.

Products include: Tylenol®, Datril®, Anacin®3

Ibuprofen

Products include: Motrin® 800 mg

MODERATE (Prescription Only)

Tylenol® No. 3 (codeine and acetaminophen)

Vicodin® (hydrocodone 5 mg and acetaminophen 500 mg)

Vicodin ES® (hydrocodone 7.5 mg and acetaminophen 750 mg)

Lortab® (hydrocodone 5 mg, 7.5 mg, 10 mg and acetaminophen 500 mg)

SEVERE (Prescription Only)

- Demerol® 50 mg (Meperidine)*
- Percocet® or Tylox® (oxycodone 5 mg and acetaminophen 500 mg)*

**Triplicate prescription where applicable*

3.4.6 Post-surgical Control, Professional Tooth Cleaning , Maintenance Care.

The objective of the post-operative appointments for professional tooth cleaning is both the removal of plaque and staining from the treated areas and the monitoring of the healing events. Post-surgical controls and professional tooth cleaning will be performed at s 3, 6 and 12 months post-surgical. At these appointments, the conditions of the soft tissue at the treated sites will be evaluated. The overall level of oral hygiene will be evaluated and reinstruction will be given as needed at all visits.

Instructions on post-operative care will be repeated at each appointment. In particular, the following points should be covered during the first month: (1) continue chlorhexidine rinses

(from surgery to four weeks post-op); (2) resume gentle brushing; and (3) avoid vigorous chewing on, or trauma to, the treated areas.

At week 6, subjects will be instructed to gradually resume interproximal cleaning, as well as chewing, in the treated areas. All subjects will be maintained by full mouth professional prophylaxis and calculus removal once every three months, excluding surgical sites which will be maintained supragingivally.

All treatment-related adverse events that occur up to 30 days excepting surgery related AEs within 48 hours after any treatment will be recorded in CRFs, and all serious adverse events throughout the study will be recorded.

3.5 Clinical Assessments

3.5.1 Summary of Clinical Assessments

All examinations and measurements will be performed in accordance with the Schedule of Events. Data will be collected and assessments will be made on study sites treated.

3.5.2 Primary Efficacy Assessment

- Esthetic satisfaction from baseline to 6 and 12 months of all treated areas, as assessed by both the examiner and the subject using the Visual Analog Scale (VAS), prior to and after viewing baseline photos
- Subject pain/discomfort questionnaire

- Change from baseline in probing depth
- Change from baseline visit in clinical attachment level
- Change from baseline visit in width of the keratinized tissue
- Change from baseline in radiographic a) bone gain; B) pathology

3.5.3 Probing Depths

Clinical probing depths of the periodontal sulcus will be measured using the a UNC 15 periodontal probe. Measurements will be performed without local anesthesia at six (6) locations around each study tooth. The number of additional locations to be measured around each experimental site will be determined by the extent and morphology of the area. Interproximal pocket depths will be recorded at the deepest point probable at the contact points from both buccal and lingual aspects. Buccal and lingual pocket depth measurements will be recorded at the mid-buccal and mid-lingual sites. All pocket depth measurements will be rounded down to the nearest mm and recorded. In conjunction with recording the pocket depths, any bleeding from the periodontal pockets will be indicated by marking an asterisk on the figure recorded for the depth measurement for that same pocket.

3.5.4 O'Leary Plaque Index

The plaque index is determined by scoring the percentage of individual tooth surfaces with plaque. The following procedure will be followed:

Apply disclosing solution to all exposed tooth surfaces.

Rinse to remove any excess solution.

Examine each tooth surface (mesial, distal, facial, lingual) at the dento-gingival junction for presence of plaque.

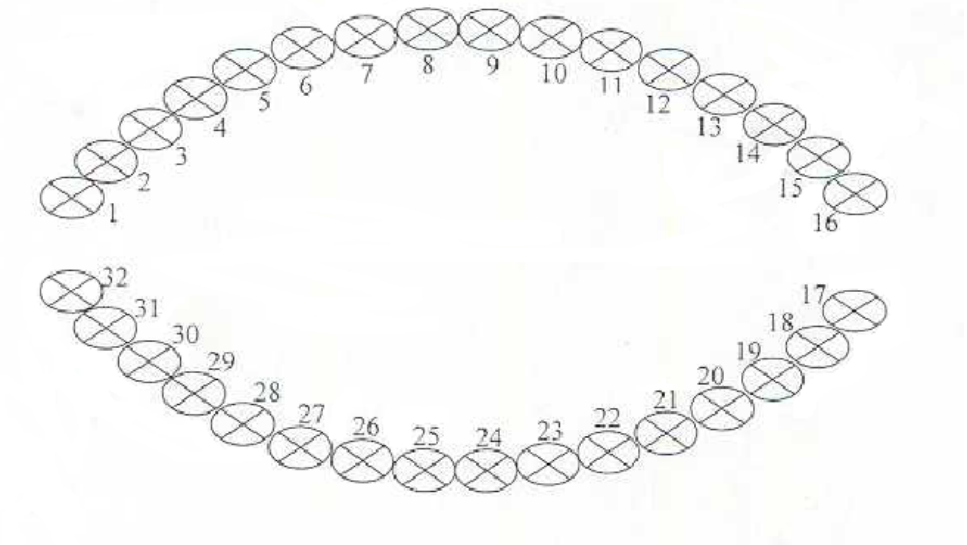
Presence of plaque at the dento-gingival junction is indicated by making a dash in the appropriate spaces on the plaque control record diagram (see Figure 1).

If a tooth is missing, draw a line through the tooth on the diagram. Missing teeth should not be counted in the total number of surfaces scored.

Calculate the plaque index by dividing the number of surfaces with plaque by the total number of surfaces scored, and then multiply by 100 to obtain a percentage.

Figure 1 Plaque Control Record

3.5.5 Laboratory Assessments



The following laboratory assessments will be conducted at screening:

- Urine pregnancy test (females of child-bearing potential only)

3.6 **Schedule of Investigational Events**

3.6.1 Screening Visit (Visit 1)

At the screening visit the following procedures and assessments will be performed within 32 days prior to surgery:

- Informed Consent
- Subject registration
- Medical history collection and physical examination:
    - Record of past therapy
    - Urine pregnancy test (females of child-bearing potential only)
    - Medications
- Dental history collection
    - Record of past therapy
- Screening assessments to determine eligibility:
    - O'Leary Plaque Index
    - Probing depths
    - Implant mobility,
    - Clinical attachment level
    - Obtain baseline radiographs of study sites
- Dental cleaning

- Oral hygiene instruction
- Supragingival plaque control, as appropriate
- Examiner and subject baseline esthetic satisfaction VAS assessments
- Radiographs of all target study sites

3.6.2 Baseline/Treatment (Visit 2)

Visit 2 may occur concurrently with Visit 1. If separate visits are to occur, Visit 2 must occur within 32 days of the screening examine.

- Examiner calibration (for first 2 subjects enrolled only)
- Preoperative and Intraoperative digital photographs
- Concomitant medications
- Surgical procedure
- Post-operative instructions
- Collection of any Adverse Events

3.6.3 Post op - Week 1 (Visit 3)

- An Investigator will rate and record the judgment of healing
- Study personnel will obtain clinical photographs of surgical sites taking care not to place apical tension on flap

- Post-operative instructions (e.g. Chlorhexidine rinse) and pain management according to standard procedures
- Complete Pain Rating Scale
- Rate and record color and texture of treated areas
- Adverse event review
- Concomitant medication review
- Suture removal according to healing
- Measurement of width of keratinized tissue
- Pain Medication review

3.6.4 Post op – 1 Month (Visit 4)

- Rate and record the color and texture of treated areas
- Digital photographs
- Rate and record judgment of healing
- Clinical attachment level
- The examiner and subject esthetic satisfaction VAS assessments (before and after viewing baseline photos)
- Supragingival plaque control as indicated
- Oral hygiene instruction
- Complete pain rating scale
- Concomitant medications

- Collection of Adverse Events
- Pain medication review

3.6.5 3-Months Follow up (Visit 5)

At the month 3 visit (Day 90 ± 14 days) the following procedures and assessments will be performed:

- Rate and record the color and texture of treated areas
- Digital photographs
- Rate and record judgment of healing
- Measurement of width of keratinized tissue
- Clinical attachment level
- The examiner and subject esthetic satisfaction VAS assessments (before and after viewing baseline photos)
- Supragingival plaque control as indicated
- Oral hygiene instruction
- Complete pain rating scale
- Concomitant medications
- Collection of Adverse Events
- Pain medication review
- Implant area professional cleaning

3.6.6 6 Months Follow up. (Visit 6)

Subjects will return to the clinic for a study visit 6 months (± 14 days) after surgery. The following procedures and assessments will be performed at this visit:

- Digital photographs
- Radiographs of all treated sites
- The examiner and subject esthetic satisfaction VAS assessments (before and after viewing baseline photos)
- Rate and record the color and texture of treated areas
- Rate and record judgment of healing
- Measurement of width of keratinized tissue
- Clinical attachment level
- Supragingival plaque control as indicated
- Oral hygiene instruction
- Complete pain rating scale
- Concomitant medications
- Probing depth
- Collection of Adverse Events
- Pain medication review
- Adverse Events review
- Implant area professional cleaning

3.6.7 12 Months Follow up. (Visit 7)

Subjects will return to the clinic for a study visit 6 months (± 14 days) after surgery. The following procedures and assessments will be performed at this visit:

- Digital photographs
- Radiographs of all treated sites
- The examiner and subject esthetic satisfaction VAS assessments (before and after viewing baseline photos)
- Rate and record the color and texture of treated areas
- Rate and record judgment of healing
- Measurement of width of keratinized tissue
- Clinical attachment level
- Supragingival plaque control as indicated
- Oral hygiene instruction
- Complete pain rating scale
- Concomitant medications
- Probing depth
- Collection of Adverse Events
- Pain medication review
- Adverse Events review
- Implant area professional cleaning

3.7 **Summary of Clinical Assessments (revised by UoC to meet assessment for implant tooth)**

All examinations and measurements will be accomplished in accordance with the Schedule of Procedures (See Study Flowchart).

Oral Hygiene Status

Plaque recorded as present (1) or not present (0) on buccal and lingual surfaces of study teeth only

Bleeding following Angulated Probing

Bleeding will be registered at the surgical sites by means of pulling a probe with 60° angle to the root surface along the gingival margin.

Probing Pocket Depth

Distance of probe penetration (UNC 15 periodontal probe), measured from the gingival margin to the bottom of the probable pocket of the buccal surface to the nearest 0.5 mm.

Probing Proximal Pocket Depth

Distance of probe penetration (UNC 15 periodontal probe), measured from the gingival margin to the bottom of the probable pocket of the mesial and distal surface to the nearest 0.5 mm.

Clinical Attachment Level (CAL)

Distance of probe penetration (UNC 15 periodontal probe) measured from fixed reference point to the nearest 0.5 mm.

Proximal Probing Attachment Loss

Distance of probe penetration (UNC 15 periodontal probe) measured from fixed reference point at the mesial and distal aspect of the tooth to the nearest 0.5 mm.

Recession Depth

The distance between the fixed reference point and the soft tissue margin, measured to the nearest 0.5 mm with a UNC 15 periodontal probe. At the 6 and 12 month visit, tissue coronal to the fixed reference point will be recorded as a negative measurement

Width of Keratinized Tissue

The distance between the free gingival margin and the muco-gingival junction, measured to the nearest 0.5 mm with a graded periodontal probe. To facilitate the identification of the muco-gingival line, a probe may be used horizontally to move the mucosa in a coronal direction, creating a fold at the muco-gingival junction. Shiller's Iodine Solution may also be used to identify the muco-gingival junction

Examination of Defects During Surgery

After the flaps have been raised and the area debrided, characterization of the morphology and measurements of the defects are made, with the UNC 15 periodontal probe, and recorded as follows:

Alveolar Bone Level (Before and after osteoplasty if needed)

Notation of intra marrow penetration of alveolar crest

Notation of alveolar crest topography and whether osteoplasty was to be performed to refine contours.

Clinical Photographs

Clinical photographs will be taken of each tooth involved in the study before, during and after surgery, at Weeks 1, and 6 post surgery and at the 3, and 6 month follow-up examinations.

Post-Op Discomfort and Satisfaction Questionnaires

The subject's satisfaction with respect to postoperative discomfort between test and control quadrants will be evaluated by asking the subject about pain, bleeding, swelling and sensitivity using 10 cm visual analogue scale (See Appendix 1).

Procedure/ Assessment	Visit 1 Screen 0-32 Days Prior Surgery	Visit 2 Day 0	Visit 3 Post-op Day 7	Visit 4 1 Month 42± 7 Days	Visit 5 Month 3 90± 14 Days	Visit 6 Month 6 ±14 Days	Visit 7 Month 12 ±14 Days
Informed Consent	**X**						
Eligibility/ Study Lesion Identification, Subject Registration	**X**						
Demographics/Dental/Medical History	**X**						
O'Leary Plaque Index	**X**					**X**	**X**
Probing Depths	**X**					**X**	**X**
Pregnancy Test	**X**[1]						
Radiographic Exam	**X**					**X**	**X**
Dental Cleaning	**X**				**X**	**X**	**X**

Digital Photos		X	X	X	X	X	X
Examiner and Subject GORS and VAS of esthetic satisfaction		X	X	X	X	X	X
Plaque Control/Oral Hygiene Instruction	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Clinical Attachment level	X					X	X
Examiner calibration		X					
Easy Graft Classic surgery		X					
Second stage surgery for submerged implants only						X	
Rate and record Judgment of Healing			X	X	X	X	X
Pain Rating Scale			X	X	X	X	X
Color and Texture			X	X	X	X	X
Width of Keratinized Tissue				X	X	X	X

1. In females of child-bearing potential only

3.7 Radiography

Radiographs will be taken using a modified Rinn system in order to obtain radiographs with minimum projection error. Rinn system is a radiograph sensor holder that favors a standard system to have reproducible radiograph images. We will customize this holder in order to reproduce standard radiographic image. Evaluable bitewings radiographs will be taken in each of the tooth regions included in the study.

3.7.1 Exposure

Intraoral film, 24 × 40 mm, from the same batch will be used.

3.7.2 Processing

Digital X-ray system will be used.

3.7.3 Handling

Study radiographs are stored in Axium system.

3.7.4 Radiographic assessment

Intra-oral biewing radiographs will be obtained at baseline, at 6 and 12 months. These radiographs should be taken using device to standardize during course of the study 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.

Once the exposure parameters are selected they should not be changed during the course of the study. Send the image files to the central reading center at each study site for analysis following the instructions.

3.7.5 Derivation or calculation of variable

Image processing software is used to capture measurements (MiPACS Dental Enterprise). Measurement tool will be calibrated with a 1 millimeter radiographic image.

The measurements are taken from a stationary landmark (Distal and Mesial portion of implant platform - Bd_p and Bm_p) to the mesial and distal bone crest of osseous defect in millimeters (Bd_a and Bm_a). In order to calculate percentage of bone fill (or residual defect) this last measured will be compared with implant length noted on the chart.

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.

- Linear bone change (distal) = $Bd_{p(0,6,12)} – Bd_{a(0,6,12)}$
- Linear bone change (mesial) = $Bm_{p(0,6,12)} – Bm_{a(0,6,12)}$

Where $_{(0,6,12)}$ is the measure at baseline, 6 and 12 months.

3.8 Discontinuation of Treatment

Subjects may be withdrawn from the study prior to completion of treatment for the following reasons:

- Subject withdrawal of consent
- Investigator's decision
- Death
- Poor maintenance of oral hygiene
- Lack of compliance
- Discontinues Orthodontics treatment and/or other treatments on study site(s) and adjacent teeth

When a subject is terminated from the study prior to completion of treatment, the subject will continue to be evaluated as scheduled. Attempts will be made to perform all follow-up assessments and procedures required by the protocol.

4.0 ADVERSE EVENTS

Recording and Reporting Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject of a clinical investigation administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the use of an investigational product, whether or not related to use of the product.

Recording Adverse Events

All adverse events occurring after surgical procedure will be collected during the entire trial. Each adverse event will be followed until the adverse event has resolved or stabilized. During visits, subjects should be encouraged to report adverse events spontaneously or in response to general, non-directed questioning.

- Standard medical terminology for the AE and the associated body system
- Description of adverse event and clinical consequences
- Date and time of onset
- Date and time of resolution of the adverse event
- Whether or not the event is ongoing
- Severity of the event
- Relationship between the adverse event and the investigational agent or related procedure
- Description of any therapy administered and associated outcome (actions required)
- Outcome of the AE
- Whether or not the effect was serious and/or unanticipated

  All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and on the adverse event case report form.

Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

Each adverse event should be reported separately. For example, "nausea and vomiting" should be recorded as two (2) separate events.

Grading Adverse Events

Common Terminology Criteria for Adverse Events v3.0, (on the NCI website, http://ctep.info.nih.gov) will be used to grade all toxicities/adverse events. Adverse events not included in the CTCAE v.3.0 should be reported with common medical terminology and graded according to definitions in the CTC Manual.

Assigning Relationship of Adverse Events to Treatment

A relationship must be assigned by the investigator to each reported adverse event, and will be documented as follows:

- *Unrelated* The event is clearly due to causes other than the study treatment.
- *Unlikely* Toxicity is doubtfully related to the study treatment. The event was most likely related to other factors such as the subject's clinical state, concomitant drugs or other therapeutic interventions.
- *Possible* The event follows a reasonable temporal sequence from the time of study treatment administration, but could have been produced by

other or factors such as the subject's clinical state, therapeutic interventions concomitant drugs.

- *Probable* The event follows a reasonable temporal sequence from the time of study treatment, and follows a known response pattern to treatment. The toxicity cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs.
- *Definite* The event follows a reasonable temporal sequence from the time of study treatment administration, follows a known response pattern to the study treatment, cannot be reasonably explained by other factors such as the subject's condition, concomitant drugs or therapeutic interventions, AND either occurs immediately following administration of the study treatment, improves on stopping the study treatment, or reappears on re-exposure.

Serious Adverse Events

Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any event meeting any of the following criteria:

- Is life-threatening or fatal
- Requires, or significantly prolongs, inpatient hospitalization
- Results in persistent or significant disability and/or incapacity
- Is a congenital anomaly or birth defect
- Requires medical or surgical intervention to prevent one of the outcomes listed above

SAE report to Sponsor and IRB

Investigators and other study site personnel must inform appropriate Sponsor representatives of any SAE that occurs during the course of the study within one day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The Sponsor representative will work with the Investigator to compile all the necessary information and ensure that the appropriate Sponsor personnel receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

If an AE becomes a SAE, this and other relevant follow-up information must also be provided to Sponsor within one day for all fatal and life-threatening cases and by day five for all other SAEs.

The Investigator is responsible for informing the ethics committee of SAEs as per local requirements.

SUNSTAR IS RESPONSIBLE FOR INFORMING THE REGULATORY AUTHORITY OF DEVICE RELATED SAES AS PER REQUIREMENTS.

5.0 STATISTICAL AND ANALYTICAL PLAN

Intent to Treat Population

The primary efficacy analysis and summaries will be performed on the "intent to treat" (ITT) population, defined as all subjects who successfully completed the screening to enter this trial.

Safety Population

All safety summaries and analyses will be performed on the safety population, defined to be all subjects.

Evaluable Population

All secondary efficacy analyses will be performed on an evaluable population, defined to be all subjects who received surgical treatment in accordance with the protocol.

Subjects exiting after undergoing surgery, but before month 6 due to treatment-related adverse events will be included in the evaluable population. Subjects that do not complete the assessments due to satisfaction with treatment will also be included in the evaluable population. All attempts will be made to collect complete follow-up evaluations for these subjects despite study exit. These subjects will be included in the analysis based on the assessments that are completed.

Subjects will be deemed non-evaluable if they do not meet the eligibility criteria as outlined in the protocol. Other reasons to be considered non-evaluable include protocol violations, as described below, and any actions that compromise the effectiveness of the treatment, for non-efficacy or safety related reasons.

Protocol violators consist of subjects who do not comply with the protocol in terms of treatment administration, visit timing, and/or assessment compliance. Each protocol violation will be discussed between Investigators and the Sponsor to evaluate the impact on the statistical assessment before performing the analyses.

Missing Data

It is not anticipated that many subjects will exit the study prematurely or will miss visits. The reasons for early termination, along with the timing of the early terminations will be provided.

Subjects missing a baseline evaluation will be discussed between Investigators and the Sponsor to evaluate the impact on the statistical assessment before performing the analyses

Assessment of Safety

Adverse events with an onset within 30 days of any surgical treatment will be recorded and tabulated. All adverse events will be tabulated by first occurrence of the event, maximum severity, and strongest relationship to study treatment by body system.

6.0 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

6.1 IRB Requirements

United States Federal regulations require that all investigational studies be conducted under the auspices of an Institutional Review Board (IRB), as defined in the Code of Federal Regulations, Title 21, Part 56. This committee, the makeup of which must conform to the Federal, State and local guidelines regarding such, will approve all aspects of the Study, including said Protocol and Informed Consents to be used, prior to initiation. The formal written approval notice must be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IRB member has a conflicting interest, abstention of that individual from voting should be documented. The investigator will provide the sponsor with a copy of the communication from the Committee to investigator indicating approval of the protocol and consent form. All changes to the protocol and consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

The investigator must also report to the IRB, at least annually, on the progress of the investigation. Continuing IRB review should be documented by a letter from the IRB. Notification to the IRB by the investigator within three months after completion, termination, or discontinuation of the study at the specific site must be documented.

6.2 Protocol Amendments

Amendments will originate from the sponsor and will be provided to the investigator for submission to his or her IRB for its review and approval prior to implementation. It should be noted that when an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the informed consent should be revised and if applicable, subject's consent to continue participation should again be obtained.

No deviations from the protocol should be made except in emergency situations where alternative treatment is necessary for the protection, proper care and wellbeing of subjects. In situations requiring a departure from the protocol, the investigator or other physician in attendance will contact the sponsor's clinical representative by fax or telephone. If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the sponsor's clinical representative must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The case report form and source document will describe any departure from the protocol and the circumstances requiring it.

6.3 Informed Consent

In accordance with the Code of Federal Regulations, Title 21, Part 50.20 the investigator will be responsible for obtaining an Informed Consent, signed by the subject or legally authorized representative, from every subject prior to his/her participation in the study. The consent form that is used must be the current version and must be approved by both the reviewing IRB and by the sponsor. Informed consent will be obtained from the subject after a full explanation of the purpose of the study, risks and discomforts involved, potential benefits, etc. have been provided by the investigator both verbally and in writing. The original signed copy of the informed consent must be maintained in the institution's records, and is subject to inspection by a sponsor representative.

APPENDIX I: QUESTIONNAIRES/SURVEYS

1. Examiner's Judgment of Healing
2. Pain Visual Analogue Scales
3. Discomfort and Satisfaction Questionnaire
4. Color and Texture Scale
5. Inflammation Score

EXAMINER'S JUDGMENT OF HEALING

(circle response)

Upper Right Quadrant:

Much worse than expected	Worse than expected	As Expected	Better than expected	Much better than expected

---

Upper Left Quadrant:

Much worse than expected	Worse than expected	As Expected	Better than expected	Much better than expected

---

Lower Right Quadrant:

Much worse than expected	Worse than expected	As Expected	Better than expected	Much better than expected

_____

Lower Left Quadrant:

Much worse than expected	Worse than expected	As Expected	Better than expected	Much better than expected

_____

PAIN VISUAL ANALOGUE SCALES

Please have patient complete the scales below by drawing a single vertical line across each scale at the point corresponding to the patient's level of pain.

Upper Right Quadrant

_____

No Pain Extreme Pain

Upper Left Quadrant

_____

No Pain Extreme Pain

Lower Right Quadrants

_____

No Pain Extreme Pain

Lower Left Quadrant

_____

No Pain Extreme Pain

DISCOMFORT & ESTHETIC SATISFACTION QUESTIONNAIRE: Maxillae

Category	Right Quadrant	Left Quadrant
Sensitivity	None Mild Moderate* Severe* Duration:_____	None Mild Moderate* Severe* Duration:_____
Bleeding	None Mild Moderate* Severe*	None Mild Moderate* Severe*

	Duration:_____	Duration:_____
Swelling	None Mild Moderate* Severe* Duration:_____	None Mild Moderate* Severe* Duration:_____

(*Record as Adverse Event)

Has the patient experienced any other differences between the Left and Right Study sites?

□ Y □ N

If Yes, explain:_____

Overall, how satisfied is the patient with the **appearance** of the study sites?

Right Study Site

□ Very Satisfied □ Satisfied □ Neither □ Unsatisfied □ Very Unsatisfied

Left Study Site

□ Very Satisfied □ Satisfied □ Neither □ Unsatisfied □ Very Unsatisfied

If not satisfied, please explain: _____

Overall, which side did the patient experience the most discomfort? □ Right □ Left

Examiner's signature: _____Date:_____

Color and texture will be scored in relation to adjacent tissues as follows:

DISCOMFORT & SATISFACTION QUESTIONNAIRE: Mandible

Category	Right Quadrant	Left Quadrant
Sensitivity	None Mild Moderate* Severe* Duration:_____	None Mild Moderate* Severe* Duration:_____
Bleeding	None Mild Moderate* Severe* Duration:_____	None Mild Moderate* Severe* Duration:_____
Swelling	None Mild Moderate* Severe* Duration:_____	None Mild Moderate* Severe* Duration:_____

(*Record as Adverse Event)

Has the patient experienced any other differences between the Left and Right Study sites?

□ Y □ N

If Yes, explain:_____

Overall, how satisfied is the patient with the **appearance** of the study sites?

Right Study Site

□ Very Satisfied □ Satisfied □ Neither □ Unsatisfied □ Very Unsatisfied

Left Study Site

□ Very Satisfied □ Satisfied □ Neither □ Unsatisfied □ Very Unsatisfied

If not satisfied, please explain: _____

Overall, which side did the patient experience the most discomfort? □ Right □ Left

Examiner's signature: _____Date:_____