

# SUNSTAR

## CLINICAL STUDY PROTOCOL

Study Product:	GUIDOR® easy-graft® CLASSIC
Study Code:	CLP-2015-12-17-1
Date:	Jan. 22, 2016
Version	1.1

NCT#: NCT02702609

---

PROSPECTIVE, COMPARATIVE ASSESSMENT OF  
ALVEOLAR RIDGE PRESERVATION USING GUIDOR®  
EASY-GRAFT® CLASSIC IN ATRAUMATIC  
EXTRACTION SOCKET

---

---

## PROTOCOL SYNOPSIS

---

### Coordinating Investigator

Dr. Hanae Saito, Assistant Professor at University of Maryland

### Study center(s) and number of subjects planned

The study will include a total of 44 subjects equally distributed at two centers:

Center 1: Professor Mark Reynolds, University of Maryland, USA

Center 2: Professor Georgia K. Johnson, University of Iowa, USA

### Study timetable

Estimated date of first subject enrolled	April 2016
Estimated date of last subject completed implant placement	April 2017
Estimated date of last subject completed follow-up period	September 2018

### Objectives

The primary objective of this study is to investigate linear and volumetric osseous changes at 4 months following ridge preservation by calculating horizontal and vertical bone changes via cone beam computed tomography (CBCT).

The secondary objectives of the study are to evaluate:

- New bone replacement/remaining graft residuals at re-entry (histomorphometric assessment).
- Change in mesial and distal marginal bone loss on periapical radiographs from baseline to re-entry.
- Change in mesial and distal marginal bone loss on periapical radiographs from crown delivery to 6 months and to 12 months after the crown delivery (follow-up observation).

### Study design

The study is designed as a randomized controlled clinical trial. Patients will be assigned for ridge preservation of a single extraction socket site to treatment group A (GUIDOR® easy-graft CLASSIC) or group B (Freeze-dried bone allograft (FDBA) with collagen plug).

## CONFIDENTIAL

The study will involve a ridge preservation procedure and the follow-up observation period in 12 months after delivery of implant-supported prosthesis. The study randomization key will be opened after completion of re-entry visit of all patients for analysis of the primary endpoint. However, examiners and central reading centers will have to be masked until the end of study.

### Target subject population

Patients in need of ridge preservation prior to dental implant therapy in a single extraction socket in premolars and molars except for third molar will be included.

### Investigational product

GUIDOR® easy-graft CLASSIC is a bone graft substitute consisting of pure beta-triphosphate calcium ( $\beta$ -TCP) coated by poly (lactic-co-glycolic acid) (PLGA) and BioLinker™. BioLinker™ is comprised of N-methyl-2-pyrrolidone (NMP). The particle size is 500– 1000  $\mu$ m and is sterilized by gamma sterilization process. The mixture of grafting material and BioLinker get hardening into a stable, porous immediately after the mixture contacts blood or body fluid in a defect.

### Comparator, dosage, and mode of administration

Mineralized cortical freeze-dried particulate bone allograft (FDBA) has a particle size of 250-1000  $\mu$ m (Lifenet). It is sterilized via Allowash XG® technology.

Collagen plug (Zimmer Dental Inc.), is made from a bovine type I collagen. The resorption period is 10-14 days.

### Duration of treatment

The study will be a five month follow up to re-entry for implant placement. The treatment period includes ridge preservation followed by implant placement 5 months later. Follow-up visits following the ridge preservation will occur at one week, two weeks, 4 weeks, 2 months, 4 months (CBCT) and 5 months (re-entry and implant placement).

Follow-up observation after the implant placement will occur at the crown delivery, 6 months and 12 months.

### Outcome variables

#### Efficacy

##### Primary outcome variable:

- Linear and volumetric horizontal and vertical bone changes at 4 months

##### Secondary outcome variables:

- Qualitative histology: new bone and residual graft particles

## CONFIDENTIAL

- Mesial and distal marginal bone loss on periapical radiographs at reentry and follow-up period after crown delivery.

### **Safety**

- Complications
- Adverse events

### **Statistical methods**

The primary outcome variables of dimensional horizontal and vertical bone changes will be analyzed by Wilcoxon rank sum test.

The secondary outcome variable assessing new bone formation and residual graft particles, and mesial/distal bone loss will be analyzed by Wilcoxon rank sum test.

---

# 1 INTRODUCTION

---

## 1.1 Background

---

A horizontal loss of some 15% of the original width of the alveolar ridge already occurs in the first 6–8 weeks after tooth loss. A broad systematic analysis of the relevant literature showed that vertical loss in the first 6 months equals about 1.2 mm which is about 11–22% of the original height (1). With physiological loss of hard and soft tissue following tooth extraction, the conditions deteriorate for proper axial alignment of the implant and aesthetically pleasing prosthetic treatment (2, 3).

To minimize alveolar atrophy in the course of wound healing, method has been described that is summarized under the terms “ridge preservation”. This typically involves filling the extraction socket with bone or bone graft substitute and/or covering it with a membrane. When a tooth is extracted atraumatically without raising a flap the bone graft substitute can be plugged by a collagen plug. The primary objective of ridge preservation is preserving the alveolar ridge volume. A systematic literature analysis shows that ridge preservation procedures are effective. With ridge preservation procedures, alveolar atrophy in the first 6 months after tooth extraction is significantly lower than atrophy in non-treated control groups (4).

Evidence-based reviews have shown positive outcomes using a broad range of grafting materials, including autogenous bone, allografts, and xenografts in ridge preservation procedures (5, 6). Synthetic bone grafting materials are made from mineral raw materials. The most-used materials are  $\beta$ -tricalcium phosphate ( $\beta$ -TCP), hydroxyapatite (HA) and biphasic calcium phosphate. Human bone consists of approximately 60-70% of a modified hydroxyapatite (HA) and 30-40% of organic constituents and water, this material can give bone its strength (7, 8).

Easy-graft® CLASSIC, is commercially available alloplastic bone graft granules consists of pure  $\beta$ -TCP, which has been commonly used for the indication of ridge preservation (9). It has unique handling capacity based on an extremely thin coating of the graft granules with poly(lactic-co-glycolic acid) (PLGA). In medicine, PLGA is used 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.

The pilot case study aiming to evaluate the performance of easy-graft CLASSIC in extraction socket ridge preservation has been conducted by University of Maryland School of Dentistry (IRB# HP00063203). The interim observation of the study indicates that the effectiveness of easy-graft CLASSIC is not inferior to those of other leading bone graft substitutes even when easy-graft is used without a membrane or a plug

covering the defect site. It is beneficial to both dentists and patients to avoid additional treatment time and a cost of membrane or a plug.

The purpose of study is to evaluate two different treatment approaches using easy-graft CLASSIC for comparative effectiveness to freeze-dried bone allograft (FDBA) with collagen plug (Collagen Plug, Zimmer Dental Inc.) in ridge preservation when the study tooth is extracted atraumatically. Furthermore, implant stability will be observed in the follow-up period.

---

## 2 STUDY OBJECTIVES

---

### 2.1 Primary objective

The primary objective is to assess horizontal and vertical linear and volumetric osseous changes after single tooth extraction and the application of two different ridge preservation techniques, via DICOM data analysis. The changes from baseline to four months will be compared. Radiographic measurements will be obtained from DICOM data files acquired by CBCT imaging.

**Hypothesis:** The treatment group with easy-graft CLASSIC is superior or at least not inferior to the control treatment group (FDBA with collagen plug).

### 2.2 Secondary objectives

Secondary objectives of the study are to evaluate and compare:

- New bone replacement/remaining graft residuals at re-entry (histomorphometric assessment).
- Change of mesial and distal marginal bone loss on periapical radiographs from baseline to re-entry.
- Change of mesial and distal marginal bone loss on periapical radiographs from crown delivery to 6 months and to 12 months after the crown delivery (follow-up observation).

---

## 3 STUDY PLAN AND PROCEDURES

---

### 3.1 Overall study design and flow chart

---

The study is designed as a randomized control prospective study with two study centers.

The study population will consist of individuals requiring ridge preservation prior to dental implant therapy in a single tooth extraction socket in premolars and molars except for third molars.

A total of 44 subjects will be randomized to obtain at least 40 evaluable subjects in anticipation of a 10% dropout rate. 44 evaluable subjects will be enrolled at two centers. Each subject will be randomized into one of two groups: group A (GUIDOR® easy-graft CLASSIC) and group B (FDBA and collagen plug). Each center will enroll 22 evaluable subjects, 11 per group ideally.

The ridge preservation study will be a 5-month follow-up with 9 main clinic visits to re-entry/implant placement. Three additional clinic visits for the observation period will be scheduled after crown delivery to the study site.

#### 3.1.1 Visit 1: Screening

Subjects in need of ridge preservation of a single tooth extraction socket in premolars or molars prior to dental implant surgery that are deemed eligible by meeting inclusion and exclusion criteria will be considered for treatment in this study. Third molars will be excluded as a study site.

Screening process will include evaluation of general dental and systemic health. It will also include a clinical and radiographic assessment of the potential study site and the adjacent teeth. Pre-existing intraoral (periapical) radiograph can be used but must not be older than 6 months. All women except for postmenopausal women will require a negative urine human chorionic gonadotropin (HCG) test result prior to inclusion in the study to rule out pregnancy. Postmenopausal is considered when the patient has not had her period for an entire year. Eligible subjects will immediately be scheduled for Visit 2 provided that they fulfill all inclusion and none of the exclusion criterion.

#### 3.1.2 Visit 2: Enrollment

Visit 1 (Screening) and Visit 2 (Enrollment) may occur on the same day. Individuals meeting all inclusion and none of the exclusion criteria and that have signed all appropriate consent forms will be further evaluated. Before any assessment or examination is carried out for study purposes the subject must have been informed orally and in writing about the study, and have signed the appropriate consent forms. Informed consent for the research study will be given and signed on paper, as well as

## CONFIDENTIAL

HIPAA authorization, if not already obtained. Subjects will also be asked to sign informed consent documents.

Subjects meeting all inclusion and none of the exclusion criteria will be randomly allocated to Group A or B. Subjects with smoking habit will be stratified to be distributed equally to two treatment groups.

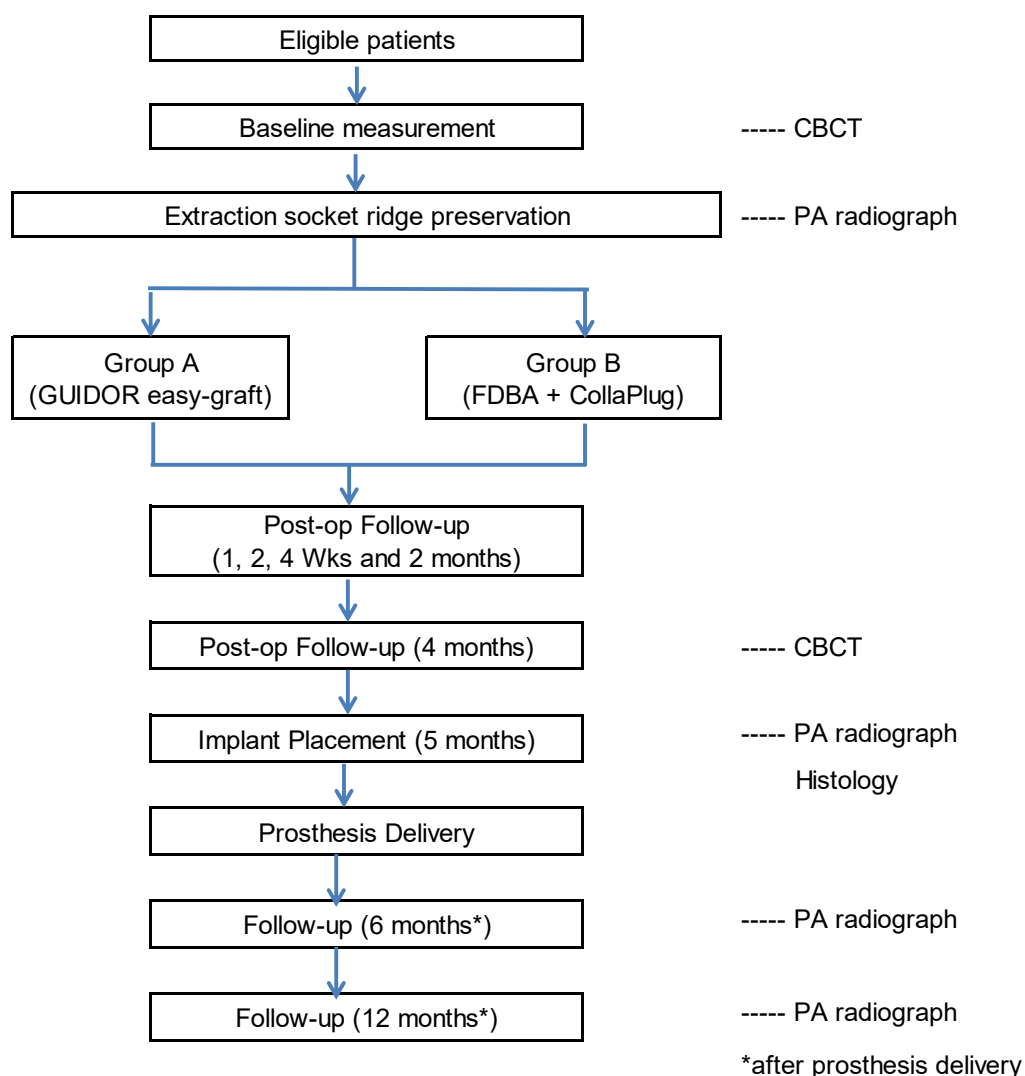
### Cone beam computed tomography (CBCT) imaging

Small segmental cone beam computed tomography (CBCT) imaging will be obtained for all patients 4 months following the ridge preservation surgical procedure. Images will provide baseline data for horizontal and vertical bone locations.

A CBCT scan will be obtained using i-CAT Next Generation (Imaging Sciences International Inc., Hatfield, PA, USA) or equivalent system. Only the arch that contains the site of interest will be scanned to minimize the radiation exposure. Based on previous investigations, the field of view will be approximately 6 cm and the machine settings will be fixed at 120 kVp and 18.66 mAs for all scans.

Subject with intact ridge verified with CBCT scan is eligible to be enrolled to the study (If not, Screen failure).



**Figure 1 Study flow chart**

### 3.1.3 Visit 3: Extraction Tooth and Socket Ridge Preservation

Visit 2 (Enrollment) and Visit 3 (Surgery) may occur on the same day.

#### Pre-Surgical, Surgical, and Post-Surgical Care (at surgical appointment)

Pre-surgical, surgical and post-surgical care will be given at the discretion of the Investigator and recorded in appropriate sections in the CRF:

- Antibiotics
- Analgesics

## CONFIDENTIAL

- Sedation
- Anaesthesia

### *Antibiotics:*

Post-surgical antibiotic coverage will be provided to patients. The regimen is left up to the surgeon's discretion.

### *Analgesics:*

The regimen is left up to the surgeon's discretion.

### *Sedation:*

The regimen is left up to the surgeon's discretion.

### *Anesthesia:*

The regimen is left up to the surgeon's discretion.

## Pre-Surgical Procedures

Buccal and occlusal photographs of the planned surgical site will be obtained. Width of keratinized mucosa on the buccal and thickness of the buccal and lingual mucosa will be measured by a caliper. Standardized periapical radiograph of a target tooth will be taken.

## Surgical Procedure

After administration of local anesthesia, the tooth will be extracted without raising a mucoperiosteal flap. A minimally invasive extraction procedure helps protection and preservation of the surrounding socket bone. Horizontal bucco-lingual ridge width at crest will be measured intraoperatively and recorded in CRF. The bucco-lingual width will be measured intraoperatively using a pointy caliper. The width will be measured 1mm apical to the alveolar crest level.

If fenestration and/or dehiscence are present when the marginal bone is sounded by a periodontal probe through the sulcus around the tooth or fracture of the buccal bone is noted upon extraction, the subject will be excluded from the study and treated as a normal patient of the clinic (Incorrect enrollment).

After thorough debridement of granulated tissue and rinsing with sterile saline the prepared easy-graft® CLASSIC (Group A) or FDBA (Group B) will be grafted to the socket defect. Easy-graft CLASSIC should be prepared according to manufacturer's instruction. FDBA will be rehydrated by sterile saline before grafting.

The graft materials will be condensed to achieve a fill of the socket to level of crestal bone.

## CONFIDENTIAL

A bioabsorbable collagen wound dressing (Collagen Plug, Zimmer Dental Inc.) will be placed on the top of the graft (FDBA) and secured with sutures. (Group B).

### Post-Surgical Procedures

Buccal and occlusal photographs of the surgical site will be obtained. Post-operative medications will be prescribed. An intraoral PA radiograph will be taken in order to assess ridge preservation surgery.

#### 3.1.4 Visit 4: Post-Operative Visit (7 days $\pm$ 2 days)

Buccal and occlusal photographs of the surgical site will be obtained. Gentle debridement and oral hygiene instruction will be provided. AEs will be recorded.

#### 3.1.5 Visit 5: Post-Operative Visit (14 days $\pm$ 2 days)

Remaining suture material will be removed (only Group B). Buccal and occlusal photographs of the surgical site will be obtained. AEs will be recorded.

#### 3.1.6 Visit 6: Post-Operative Visit (28 days $\pm$ 2 days)

Buccal and occlusal photographs of the surgical site will be obtained. Gentle debridement and oral hygiene instruction will be provided. AEs will be recorded.

#### 3.1.7 Visit 7: Post-Operative Visit (2 months $\pm$ 4 days)

Buccal and occlusal photographs of the surgical site will be obtained. Gentle debridement and oral hygiene instruction will be provided. AEs will be recorded.

#### 3.1.8 Visit 8: Post-Operative Visit (4 months $\pm$ 7 days)

In this visit, a second segmental CBCT scan will be obtained for all patients, using the same settings employed at baseline, as detailed in above. Images will provide post-ridge preservation data for horizontal and vertical bone locations. Buccal and occlusal photographs of the surgical site will be obtained. AEs will be recorded.

#### 3.1.9 Visit 9: Re-entry and Dental Implant Placement (5 months $\pm$ 14 days)

### Pre-Surgical, Surgical, and Post-Surgical Care

See Section 3.1.3.

### Pre-Surgical Procedures

Buccal and occlusal photographs of the surgical site will be obtained. Standardized periapical radiograph of a target tooth will be taken.

## CONFIDENTIAL

If the bucco-lingual ridge width is judged not enough for implant placement the subject will be terminated from the study and will receive an appropriate treatment and followed according to the clinic's routines.

### Surgical Procedure

Implant placement is made per standard procedure. For patients in each treatment group, a trephine drill will be used to harvest a core of bone for descriptive histology. A trephine drill will be used to harvest a core of bone corresponding with the planned implant length. A trephine drill of 2.8 mm in diameter will be used as the first choice. If another diameter has to be used a diameter of the trephine will be recorded in CRF. A length of a trephine will be up to 8 mm. Following harvesting, the trephined bone core will immediately be transferred to a solution of 10% neutral buffered formalin (NBF). These samples are to be used for histomorphometric assessment. Bone Density Classification (Misch Classification)(10) will be evaluated and recorded in CRF.

Selection of implant system will be left to the judgment of study sites; however the same system should be used in all the cases treated at the site. Implant site preparation and placement will proceed according to the implant system manufacturer recommendations.

When one-stage approach is chosen, a healing abutment will be placed to finger tightness. Depending on the buccal soft tissue thickness, the crestal tissue will either be removed or deepithelialized and inverted to the buccal to increase the soft tissue thickness. When two-stage procedure is chosen, a cover screw will be placed and stay buried and left to heal. Once healed, a second surgery is performed to attach an abutment for securing the crown in place. Selection of approach will be left up to the dentist's discretion.

### Post-Surgical Procedures

An intraoral periapical radiograph will be obtained immediately postoperatively to assess the depth and angulation of dental implant placement. Buccal and occlusal photographs of the surgical site will be obtained. An intraoral PA will be taken in order to assessment of implant placement. Post-surgical AEs will be recorded.

Post-operative medications will be prescribed.

#### 3.1.10 Visit 10: Prosthesis Delivery

Visit 10 will be scheduled on the day of prosthesis delivery or at least 14 days after prosthesis delivery. Buccal and occlusal photographs of the surgical site will be obtained.

Standardized periapical radiograph of a study site will be taken following prosthesis was delivered. Plaque Index (modified Queegley- Hein) of teeth adjacent to the study site and

## CONFIDENTIAL

bleeding on probing on the study site will be evaluated and recorded in CRF. AEs will be recorded.

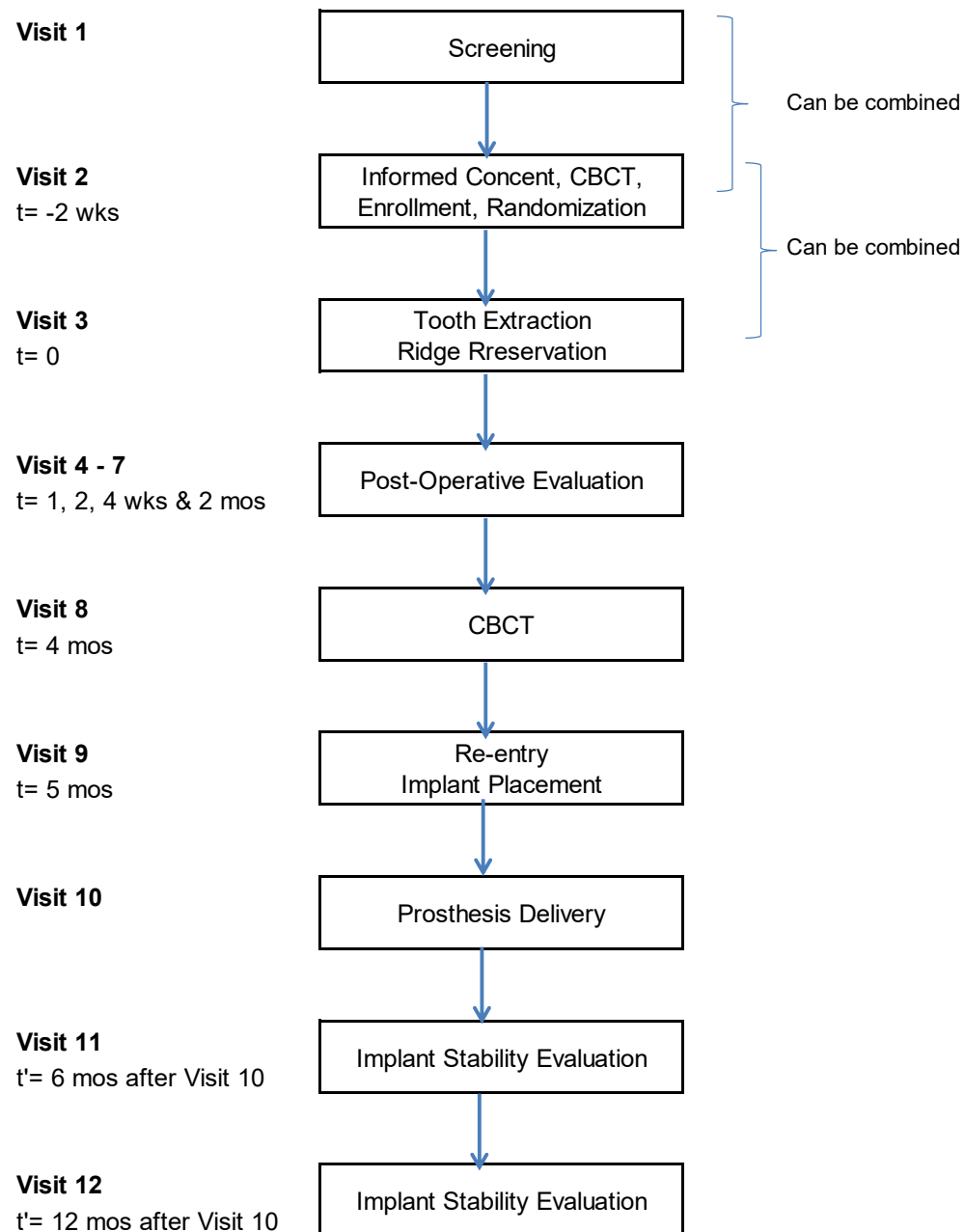
### 3.1.11 Visit 11: Follow-Up Visit (6 months $\pm$ 14 days after Prosthesis Delivery)

Buccal and occlusal photographs of the surgical site will be obtained. Standardized periapical radiograph of a target tooth will be taken. Standardized periapical radiograph of a study site will be taken following prosthesis was delivered. Plaque Index (modified Quegley- Hein, 1970) of teeth adjacent to the study site and bleeding on probing on the study site will be evaluated and recorded in CRF. AEs will be recorded.

### 3.1.12 Visit 12: Follow-Up Visit (12 months $\pm$ 28 days after Prosthesis Delivery)

Buccal and occlusal photographs of the surgical site will be obtained. Standardized periapical radiograph of a target tooth will be taken. Standardized periapical radiograph of a study site will be taken following prosthesis was delivered. Plaque Index (modified Quegley- Hein, 1970) of teeth adjacent to the study site and bleeding on probing on the study site will be evaluated and recorded in CRF. AEs will be recorded.

**Figure 2 Appointment flow chart**



**Table 1 Study plan**

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Description	Screening	Enrolment	Ridge preservation	Post-op	Post-op	Post-op	Post-op	Post-op (CBCT)	Implant placement	Prostheses delivery	Follow-up	Follow-up
Visit Window		-2w>	0	1w±2d	2w±2d	4w±2d	2m±4d	4m±1w	5m±2w	0	6m±2w	1Y±4w
Patient Information												
Informed consent		X										
Patient demographics	X											
Medical/surgical history	X											
Oral examination	X											
Inclusion/exclusion criteria		X										
Treatment												
Clinical photography			X	X	X	X	X	X	X	X	X	X
Tooth extraction / Ridge preservation			X									
Suture removal					X							
Trephined bone sample									X			
Implant placement									X			
Assessment												
CBCT (ridge dimensions)		(X) <sup>1</sup>						X				
Standardized PA radiograph			X						X	X	X	X
Bone density classification									X			
Histology									X			
Other												
Width of keratinized mucosa			X									
Horizontal ridge width			X									
Wound dehiscence				X	X	X	X	X				
Adverse events/Adverse device effects			X	X	X	X	X	X	X	X	X	X

1.Pre-existing CBCT taken for the treatment planning are available.

## 3.2 Rationale and risk/benefit assessment

---

It is necessary to further define the effects of different grafting materials on clinical outcomes following ridge preservation. This study will employ gold standard methods of evaluation efficacy and safety conforming to that stipulated of the medical, clinical research, and regulatory communities to demonstrate clinical benefit of GUIDOR® easy-graft CLASSIC. The study has been designed to treat a clinical scenario commonly encountered in clinical practice.

The patients will benefit from a preserved alveolar ridge dimension to permit dental implant placement. The public will benefit from the study results which will help to refine the knowledge of bone preservation and healing following ridge preservation with different grafting material. This will help aid clinicians in the selection of materials to optimize their clinical outcomes of treatment. The study also includes dental implant placement and acquisition of data that will help to define the effect that different grafting materials have on implant stability at time of placement and follow-up period for one year after the implant placement. Data acquisition includes minimally invasive collection methods, both before and after the surgical procedures.

### 3.2.1 Study selection record

Investigator(s) will keep a record of subjects who were considered for enrollment but were never enrolled (e.g., subject screening log). This information is necessary to establish that the subject population was selected without bias.

### 3.2.2 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Provision of informed consent
2. At least 18 years old
3. In need of one posterior tooth, excluding third molar molars, planned for extraction and replacement with a dental implant (If the subject requires two adjacent socket preservation, they can still be enrolled in the study but only one site will be used for the study)
4. Intact ridge as verified with cone-beam CT scan
5. At least one natural tooth adjacent to the study site present.

### 3.2.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Insufficient interocclusal space to allow for implant supported prosthesis
2. Dehiscence or fenestration identified at the time of reviewing CBCT.
3. No previous interventions performed involving soft and/or bone grafting



## CONFIDENTIAL

4. Non-treated caries or uncontrolled periodontal disease present affecting the teeth in adjacent to study site
5. Any of natural teeth adjacent to the study site presents active periapical endodontic lesion ("active periapical endodontic lesion" will be determined per consultation by endodontics specialist).
6. Adjacent tooth (mesial and distal) to study site was extracted within last 6 months
7. Smoker using more than 10 cigarettes or equivalent per day
8. Smokeless tobacco use or e-cigarette use
9. Current alcohol or drug abuser
10. Systemic or local disease or condition that would compromise post-operative healing and/or osseointegration e.g. uncontrolled diabetes
11. Need for systemic corticosteroids or any other medication that would influence post-operative healing and/or osseointegration
12. Pregnancy, as indicated by positive urine human chorionic gonadotropin (HCG) test result.
13. Unable or unwilling to return for follow-up visits for a period of 5 months
14. Unlikely to be able to comply with study procedures according to Investigators judgement
15. Subject in other clinical trials

### 3.2.4 Restrictions

Subjects will be advised of the following restrictions during the study period:

- Bridge or denture involving the study site is not allowed except for Essex type appliance as long as it does not touch the surgical site.
- To avoid disruption of wound healing during the initial study period the subject should have a restricted diet for at least 14 days (printed instructions will be distributed to the subjects at Visit 3 per institutional standard of care).
- For current smokers, no more than 10 cigarettes per day are allowed.

### 3.2.5 Discontinuation of subjects from treatment or assessment

#### Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or Sponsor

- Severe non-compliance to protocol as judged by the investigator and/or Sponsor
- Incorrect enrolment (i.e., the subject does not meet the required inclusion/exclusion criteria for the study)
  - If a dehiscence and/or a fenestration are observed intraoperatively upon tooth extraction, the subject will be excluded.
- Subject received further dental therapy on study site or adjacent teeth without consent of investigator (e.g. new crown, periodontal surgery, or orthodontics on adjacent teeth)
- Subject lost to follow-up

#### Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any AEs or ADEs. If possible, they should be seen and assessed by an investigator(s). Ongoing AEs and ADEs should be followed up.

A subject will be classified as lost to follow up only if, he/she has failed to return to the required study visits and his/her dental status remains unknown, despite multiple attempts to contact the subject via telephone, fax, email, certified letter and through subject locator agencies (if allowed per national regulation).

#### Procedures for handling incorrect enrolled subjects

Subjects not meeting the inclusion/exclusion criteria for a study should, under no circumstances, be enrolled into the study - there can be no exceptions to this rule. When subjects not meeting the study criteria are enrolled in error, or if subjects subsequently fail to meet the criteria for the study after enrollment, they will be excluded from the study and from the analyses.

If subjects are excluded intraoperatively (e.g. dehiscence), the subjects will receive a standard grafting treatment at no cost. However, an implant placement at the site will be at the patient's cost.

### 3.3 Treatments

---

#### 3.3.1 Identity of investigational product and comparators

GUIDOR® easy-graft CLASSIC is bone grafting system contains: syringe containing beta-tricalcium phosphate ( $\beta$ -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 bioresorbable, 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  $\mu$ m. Easy-graft CLASSIC is a biocompatible and osteoconductive material that allows for complete resorption by

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

Collagen Plug, Zimmer Dental Inc. is made from type I bovine collagen. Collagen Plug is a biocompatible, sterile resorbable highly porous collagen wound dressing for bleeding control, stabilizing the blood clot, and protecting the wound bed. Its dimensions are 10mm X 20 mm and have a resorption period of 10-14 days.

Lifenet Health® mineralized cortical freeze-dried particulate bone allograft (FDBA) has a particle size of 250-1000  $\mu$ m. It is sterilized via Allowash XG® technology, consisting of rigorous screening and assessment of donor tissues; cleaning with hypotonic solutions and antimicrobial reagents; decontamination, disinfection, and cleaning regimens with hydrogen peroxide and isopropanol alcohol solutions; and terminal sterilization with gamma irradiation. The particulate material comes packaged in a sterile vial in a blister pack.

### 3.3.2 Labeling

All grafting materials will be labelled as follows:

- “Reference number”
- “Lot number”
- “Expiration date”

All dental implant materials will be labeled as follows:

- “Reference number”
- “Lot number”
- “Expiration date”
- “Single use”
- “Sterile”

The reference number and lot numbers will be recorded in clinical records (source data) and CRF.

### 3.3.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. Descriptions of the appropriate storage and shipment conditions are specified on the study product label and product information.

### 3.3.4 Accountability

Distributed study products will be used for this study in accordance with the study protocol. All product deliveries, distributions and dispositions will be confirmed by the investigator or delegate, and recorded in the log.

## 3.4 Method of assigning subjects to treatment groups

---

Screening numbers will be assigned at day of screening (Visit 1). Subjects at center 1 will receive numbers starting at S101 and subjects at center 2 will receive numbers starting at S201. Subject numbers (subject ID) will be consecutively allocated in series at day of inclusion (Visit 2). Subjects at center 1 will receive numbers starting

at 101 and subjects at center 2 will receive numbers starting at 201. Enrollment will continue until 22 subjects at each center have been allocated a subject ID. If a subject discontinues, the subject number will not be reused.

Subjects will be randomized strictly sequentially at enrollment (Visit 2). The randomization schedule will be generated using a validated system under the responsibility of the data management team. The randomization procedure will be concealed. Randomization will be stratified by center and smoking habit, i.e. each center will have 11 subjects in each group A and B, respectively with an equal number of subjects with current tobacco consumption per group. The allocation will be revealed to the clinician only following tooth extraction for ridge preservation.

### 3.5 Pre-study, concomitant and post-study treatment(s)

---

Systemic corticosteroids or any other medication that would compromise post-operative healing and/or bone healing are not allowed.

After surgery, mouth rinsing with 0.12% non-alcohol chlorhexidine rinse will be subscribed according to local routines.

Subjects will be given post-surgical instructions with regards to diet and oral hygiene. Oral hygiene instructions will be given to the subjects at all study visits.

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication must be recorded in the appropriate sections of the CRF. This includes all medication administered pre-surgical, during surgery and post-surgical.

---

## 4 MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

---

### 4.1 Screening and demographic measurements

---

The following data will be recorded via a standard CRF:

- Date of birth
- Sex
- Race
- Relevant medical and surgical history
- Medication
- Oral examination
- Local condition of alveolus and adjacent teeth
  - Periodontal disease
  - Bone loss
  - Caries
  - Endodontic treatment
  - Existing periapical radiolucency
- Tobacco use
- Reason for tooth extraction
- Previous bone graft, soft tissue graft, or apical surgery
- Opposing tooth contact in maximum intercuspation

### 4.2 Efficacy

---

#### 4.2.1 Primary outcome variable

##### 4.2.1.1 Dimensional osseous changes

The amount of horizontal and vertical bone changes will be calculated using data from DICOM images acquired by CBCT using 3D software.

##### *4.2.1.1.1 Methods of assessment*

CBCT scans will be obtained at baseline and 4 months following ridge preservation (Visit 8). Linear measurements will be done at the University of Iowa by a single, calibrated examiner. Volumetric assessments will be performed by an external reading center in Georgia that is associated with the University of Iowa. All examiners will be masked for the therapy applied in each case.

For the horizontal and vertical measurements a plane of reference will be set to allow for reproducible and reliable assessments (in mm) between both baseline and 4-month datasets.

Volumetric assessments will be performed using a specific software (Simplant 16 Pro) via selection of a region of interest (ROI) that includes only hard tissues. The same segmentation settings of the ROI selected in the baseline scan will be transferred to the 4-month reconstruction in order to generate comparable volumes. Volume

measurements will be expressed in cc, which allows for a calculation of the % of volumetric reduction that took place from baseline until one month prior to surgical re-entry.

#### *4.2.1.1.2 Derivation or calculation of variable*

The mid-alveolar point positioned on a tangent drawn from the mesial and distal adjacent tooth CEJs will be used as a reference point for assessment of dimensional bone changes in the Z-axis (bone width) and Y-axis (bone height). The changes in the bone dimensions between baseline (Visit 2) and 4 months (Visit 8) will be measured. The change for each study site will be compared longitudinally and the average for each treatment group will be calculated and compared among treatment groups.

### 4.2.2 Secondary outcome variables

#### 4.2.2.1 Qualitative histological evaluation

A core of bone from the defect sites will be harvested for qualitative histological assessment.

##### *4.2.2.1.1 Methods of assessment*

Trephined bone cores will be obtained from a subset of patients from each treatment group (Visit 9). Tissues stored in 10% neutral buffered formalin (NBF) will be fixed for at least 7 days. All bone core samples will be sent to University of Maryland. The samples will be subsequently rinsed in phosphate buffered solution (PBS) and demineralized by immersion in ethylenediaminetetraacetic acid (EDTA) for a minimum of 5 weeks. Cores will be embedded in paraffin, sectioned along a transverse plane, and stained with conventional hematoxylin and eosin (H&E) technique, and coverslipped for qualitative histologic analysis.

Images of sections will be taken with microscope and connected with digital camera. Quantitative assessment of newly formed bone and, residual bone graft particles and non-mineralized tissue on histological section with H&E staining will be performed at least 5 images randomly chosen in the same section and analyzed with recommended software. The assessment will be performed by the central reader at University of Maryland.

#### 4.2.2.2 Mesial and distal marginal bone loss on standardized periapical radiographs

The marginal bone loss of the study defect is the change on standardized periapical radiographs between baseline and re-entry (Visit 9), and between crown delivery (Visit 10) and at 12 months after the crown delivery (Visit 12).

##### *4.2.2.2.1 Methods of assessment*

Intra-oral periapical radiographs will be obtained at baseline, at 5 months (re-entry), at crown delivery and at 12 months after the crown delivery. 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.

#### 4.2.2.2.2 *Derivation or calculation of variable*

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.

The measurements are taken from a stationary landmark (e.g. the mesial and/or distal adjacent tooth CEJs) to the crest of and distal marginal bone, to the crest and bottom of osseous defect and to the apex of the longest root of mesial and/or distal adjacent tooth in millimeters.  $Ad_0$  is the root length of distal adjacent tooth at baseline;  $Bd_0$  is the measurement from the CEJ to the crest of distal marginal bone at baseline. All measurements are taken parallel to the long axis of the adjacent tooth.

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.

Measurements to the root apex taken from baseline images ( $Ad_0$ ,  $Am_0$ ) are used to correct for any geometric distortion (elongation/foreshortening) of subsequent images.

Linear bone change (distal) =  $Bd_0 - Bd_{5m}$

Linear bone change (mesial) =  $Bm_0 - Bm_{5m}$

### 4.3 Safety measurements and variables

---

The methods for collecting safety data are described below.

### 4.3.1 Adverse Events

#### 4.3.1.1 Definitions

The definitions of AEs, ADEs and Serious Adverse Events (SAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

#### **Adverse Event**

An AE is any untoward and unintended medical occurrence in a subject. This definition does not imply that there is a relationship between the AE and the medical device under investigation. An AE which is possibly related, is one that may have been caused by the medical device, or treatment, however there is insufficient information to determine the likelihood of this possibility.

- Possibly related: temporal relationship of the onset of the event, relative to the use/administration of the medical device, is reasonable but the event could have been due to another, equally likely cause.
- Non-related (unlikely): temporal relationship of the onset of the event, relative to the use/administration of the medical device, is not reasonable or another cause can itself explain the occurrence of the event.

Ambiguous cases should be considered as possibly related.

#### **Adverse Device Effect**

An ADE is any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use of the medical device or any event that is a result of a user error. This definition also includes treatment- or procedure-related events. ADEs can only occur from the time of medical device use/administration. Here the event is related to the use of the medical device where there is a probable/definite relationship that the event may have been caused by the medical device, or treatment.

- Probably related: temporal relationship of the onset of the event, relative to the use/administration of the medical device, is reasonable and the event is more likely explained by the medical device/treatment than by any other cause.
- Definitely related: temporal relationship of the onset of the event, relative to the use/administration of the medical device, is reasonable and there is no other cause to explain the event.

Expected post-surgical events (i.e.. pain, swelling, bleeding and edema) on the study site within 7 days following surgeries will be excluded from AE/ADE.

#### **Serious Adverse Event**

A SAE is an AE/ADE occurring during any study phase of the medical device that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above



## CONFIDENTIAL

If a non-related AE becomes serious, i.e. fulfilling one or more of the above criteria, action should be taken as for any other SAE.

### 4.3.1.2 Recording of Adverse Events and Adverse Device Effects

At each visit, scheduled or unscheduled, the subject will be asked an open question; "Have you had any health problems since the previous visit?"

All health problems, reported by the subject or found at the clinic visit, where the investigator believes the event "possibly" has been caused by the investigational medical device or treatment, must be recorded in the CRF as AEs, specifying time of onset, action taken, outcome and whether it constitutes a SAE or not. Non-related AEs must be recorded in the CRF together with a short description and whether it constitutes a SAE or not.

All health problems, reported by the subject or found at the clinic visit, where the investigator believes the event "probably/definitely" has been caused by the investigational medical device or treatment, must be recorded in the CRF as AEs and ADEs, specifying time of onset, action taken, outcome and whether it constitutes a SAE or not.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 8.2, Pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a medical device under study may have interfered with the effectiveness of a contraceptive medication.

### 4.3.1.3 Reporting of Serious Adverse Events

#### **Timelines for reporting of SAEs**

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 or ADE 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 DATA MANAGEMENT

---

### 5.1 Data handling

---

Sponsor or the designee will supply investigative sites with access to electronic case report forms (eCRF) via a web-based electronic data capture system. The eCRF will be completed for each included patient. The completed eCRFs will not be made available in any form to third parties without written permission from Sponsor.

All data from source documents will be entered into the eCRF database. The data entry will be verified by means of double data entry or proofreading by each clinical site. Before database lock, both manual and computerized validation tests will be performed and, if necessary, data queries will be sent to the investigator for clarification. Should questionable data be detected during the validation process, written queries will be raised as result of this validation. The study site personnel are required to resolve any such queries. The eCRFs will be retained for 10 years.

At the end of the study, Sponsor or the representative will perform final validation checks, including central consistency checks, after which Clean File will be declared and the database locked.

### 5.2 Record retention

---

To enable evaluations and/or audits from regulatory agencies or Sponsor and its representatives, the investigator agrees to keep records in the Investigator's Study File (ISF), including the identification list of the participating patients, all original signed Informed Consent forms, and detailed records of medical device disposition. To comply with international regulations, the investigator should retain the records for 10 years.

---

## 6 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

---

### 6.1 Statistical evaluation – general aspects

---

A comprehensive Statistical Analysis Plan (SAP) may be prepared before database lock. If prepared, the SAP will be kept as an appendix to the Data Management Plan. When using the terminology descriptive statistics it means that number of patients, mean, median, standard deviation, minimum and maximum values will be presented for continuous data and frequencies and percentages for categorical data.

If nothing else is stated, descriptive statistics will be given for each variable in the study and p-values may be complemented by confidence intervals as appropriate. All p-values presented will be two-sided. A p-value less than 5% will be called “statistically significant” but all conclusions will be based on the primary objective and hence multiplicity is accounted for even though careful interpretations are necessary as multiple tests are performed.

#### 6.1.1 Demographics and other baseline characteristics

Demographics and other baseline characteristics will be presented by means of descriptive statistics (by group and in total). Continuous variables will be presented by means of number of observations (N), minimum (min), median, maximum (max), mean, and standard deviation (std). Discrete variables will be presented by frequency and percentage.

#### 6.1.2 Covariates and prognostic variables

No covariates are judged to influence the outcome of the primary or any of the secondary variables.

#### 6.1.3 Handling of dropouts and missing data

Patients dropping out from the trial prior to study end will not be replaced. Data totally missing will not be estimated.

#### 6.1.4 Multicenter

This study is a multicenter study. However, there is not a priori reason to suspect that there will be any qualitative differences between the centers regarding any of the efficacy variables or regarding the safety variables. Therefore, the primary statistical analyses will not include center in the model.

In order to harmonize the use and handling of the graft materials and dental implant systems, training will be conducted prior to study start at each center.

#### 6.1.5 Subgroup analyses

Subgroup analysis is not planned.

## 6.2 Method of statistical analysis

---

### 6.2.1 Primary objective

The primary objective is to compare dimensional bone changes from baseline (Visit 2) to 4 months (Visit 8) occurring in a single tooth extraction socket following ridge preservation using three different techniques.

Assume the change (in the mid-buccal horizontal bone dimensions from baseline to five months) is denoted  $C_A$  and  $C_B$ , for group A and B. The null-hypotheses (two) is then to test if:

$$H_0 C_A = C_B$$

can be rejected and hence

$$H_1 C_A \neq C_B$$

accepted.

$H_0$  will be tested by means of the Wilcoxon rank sum test. A p-value less than 5% will be regarded statistically significant.

### 6.2.2 Secondary objectives

The data collected in the study were expressed as mean  $\pm$  standard deviation (SD). The Wilcoxon rank sum test will be used for statistical analysis.

## 6.3 Determination of sample size

---

A sample size of 22 participants per treatment group was selected following power calculations and allowing for 10% patient dropout. A sample size of 20 patients was calculated for the primary outcome variable (horizontal bone changes) with the assumption that the detectable difference would amount to 0.7 mm with a standard deviation of 0.8. The type I error probability was set at 0.05 and the statistical power was set at 80%.

---

## 7 STUDY MANAGEMENT

---

### 7.1 Monitoring

---

Before first subject into the study, a representative of Sponsor will visit the investigational study site to:

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

During the study, a monitor from Sponsor or a company representing sponsor will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (e.g., clinic charts).

The monitor or another Sponsor representative will be available between visits if the investigator(s) or other staff at the center needs information and advice.

### 7.2 Audits and inspections

---

Authorized representatives of Sponsor, and an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ISO 14155, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

### 7.3 Training of staff

---

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

### 7.4 Changes to the protocol

---

Study procedures will not be changed without the mutual agreement of the principal investigators and Sponsor.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to or approved by each IRB, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular center's Informed Consent Form, then Sponsor and the center's Ethics Committee must be notified. Approval of the revised Informed Consent Form by Sponsor and by the IRB is required before the revised form is used.

Sponsor will distribute administrative changes, amendments and new versions of the protocol to each principal investigator.

## 7.5 Study agreements

---

The principal investigator at each center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

## 7.6 Study timetable

---

Before a subject's enrollment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between Sponsor and the Principal Investigator/Study Site
- Approval of the study by the IRB

## 8 PROCEDURES IN CASE OF EMERGENCY

### 8.1 Medical emergency

In the case of a medical emergency you may contact the Clinical Study Team Leader. If the Clinical Study Team Leader is not available, contact the Senior Manager at SUNSTAR, see below:

Role in the study	Name	Address & telephone number
Scientific advisor	Akane Takemura, PhD  Senior Manager Technology & New Product Development	SUNSTAR Americas, Inc. 301 E. Central Rd. Schaumburg, IL 60195  [REDACTED]
Principal Investigator	Dr. Hanae Saito, DDS, MS, CCRC  Assistant Professor, Department of Periodontics  Dr. Gustavo Avila-Ortiz, DDS, MS, PhD  Associate Professor Department of Periodontics	University of Maryland School of Dentistry 650 W. Baltimore Street Rm 4201 Baltimore, MD 21201 [REDACTED]  The University of Iowa College of Dentistry Dental Science Building - Room S462, 801 Newton Rd. Iowa City, IA 52242-1001 [REDACTED]
Study Coordinator	Dr. Hanae Saito  Amber Marolf, BA Clinical Research Coordinator	University of Maryland School of Dentistry  Dows Institute for Dental Research The University of Iowa College of Dentistry & Clinics Iowa City, IA 52242 [REDACTED]
Medical Research Manager (CRO)	[REDACTED]  [REDACTED]	[REDACTED] [REDACTED] [REDACTED]

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such.**

## 8.2 Pregnancy

---

Many physiologic changes can be observed in the pregnant patient and should be considered when planning dental treatment. It has been suggested to avoid elective dental procedures in the 1<sup>st</sup> and 3<sup>rd</sup> trimesters due to risk of spontaneous abortions, pre-term births, increased patient discomfort, and increased likelihood of intraoperative complications. The ultimate goal in dental therapy during pregnancy should be to educate the patient on the importance of oral hygiene and plaque control, perform periodontal maintenance therapy and treat emergency situations. All women except for postmenopausal women will require a negative urine human chorionic gonadotropin (HCG) test result prior to inclusion in the study to rule out pregnancy. Postmenopausal is considered when the patient has not had her period for an entire year.

Pregnancy itself is not regarded as an AE/ADE unless there is a suspicion that the medical device under study may have interfered with the effectiveness of a contraceptive medication.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported as SAEs. Elective abortions without complications should not be handled as AEs/ADEs.



---

## 9 REFERENCES

---

1. Tan WL, Wong TL, Wong MC, Lang NP. A systematic review of post-extraction alveolar hard and soft tissue dimensional changes in humans. *Clinical oral implants research* 2012;23 Suppl 5:1-21.
2. Araujo MG, Liljenberg B, Lindhe J. beta-Tricalcium phosphate in the early phase of socket healing: an experimental study in the dog. *Clinical oral implants research* 2010;21:445-454.
3. Araujo MG, Lindhe J. Dimensional ridge alterations following tooth extraction. An experimental study in the dog. *Journal of clinical periodontology* 2005;32:212-218.
4. Vignoletti F, Matesanz P, Rodrigo D, Figuero E, Martin C, Sanz M. Surgical protocols for ridge preservation after tooth extraction. A systematic review. *Clinical oral implants research* 2012;23 Suppl 5:22-38.
5. Chan HL, Lin GH, Fu JH, Wang HL. Alterations in bone quality after socket preservation with grafting materials: a systematic review. *The International journal of oral & maxillofacial implants* 2013;28:710-720.
6. Hammerle CH, Araujo MG, Simion M. Evidence-based knowledge on the biology and treatment of extraction sockets. *Clinical oral implants research* 2012;23 Suppl 5:80-82.
7. Kakar A. Indirect Sinus Elevation And Implant Placement Using A Modified Crestal Approach - A Case report. *The Journal of Academy of Oral Implantology* 2011;3:37-40.
8. Horowitz RA, Mazor Z, Miller RJ, Krauser J, Prasad HS, Rohrer MD. Clinical evaluation alveolar ridge preservation with a beta-tricalcium phosphate socket graft. *The Compendium of continuing education in dentistry* 2009;30:588-590, 592, 594 passim; quiz 604, 606.
9. Leventis M, Fairbairn P and Horowitz R A: Extraction site preservation using an in-situ hardening alloplastic bone graft substitute. *Compend Contin Educ Dent* 2014;35(4): 11-13.
10. Misch CE. Bone density: A key determinant for treatment planning. In: *Contemporary Implant Dent*. 3rd ed. St Louis, MO: Mosby Elsevier; 2008;130–146.