Pilot Study

Immediate Placement and Stabilization of Dental Implants with Tetranite® Stabilization Material in Mandibular and Maxillary Tooth Extraction Sites that Fail to Provide Adequate Primary Stability

DVAL18041
Version 3.0

December 8th, 2020

Protocol Reviewed and Approved By:

Dr. David Cochran Study Monitor	Signature	Date
Dr. Ryushiro Sugita Principal Investigator	Signature	Date
Dr. Michael Pikos Principal Investigator	Signature	Date
Dr. George Kay Chief Science Officer	Signature	Date
Dr. Alan Pollack Chairman of Clinical Advisory Board	Signature	Date

Contact Information

Study Monitor:	David L. Cochran, DDS, PhD, MMSci University of Texas Health Science Center San Antonio Department of Periodontics, MSC 7894 7703 Floyd Curl Drive San Antonio, TX 78229 (210) 567-3604 – Phone (210) 567-3643 – Fax cochran@uthscsa.edu
Principal Investigator:	Ryushiro Sugita, DDS University of Texas Health Science Center San Antonio Department of Periodontics, MSC 7894 7703 Floyd Curl Drive San Antonio, TX 78229 (210) 567-0416 – Phone (210) 567-3761 – Fax sugita@uthscsa.edu
Principal Investigator:	Michael Pikos, DDS Pikos Institute 8740 Mitchell Blvd, New Port Richey, FL 34655 (727) 781-0491 – Phone (727) 807-6033 – Fax mapikos@gmail.com

Sponsor:	RevBio (F/K/A Launchpad Medical) 600 Suffolk Street Suite 250 Lowell, MA 01854
Sponsor Representatives: Study Manager:	Grayson Allen Clinical Study Director 600 Suffolk Street Suite 250 Lowell, MA 01854 617-947-6246 – Phone gallen@launchpadmedical.com

Abbreviations

Ø	Diameter
ADA	American Dental Association
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BLT	Bone Level Tapered
BOP	Bleeding on Probing
CBCT	Cone Beam Computed Tomography
CFR	Code of Federal Regulations
CRF	Case Report Form
DD	Device Deficiencies
ECRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GBR	Guided Bone Regeneration
GCP	Good Clinical Practice
GTR	Guided Tissue Regeneration
HDD	Horizontal Dimension of Defect
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISQ	Implant Stability Quotient
ITT	Intention To Treat population
mITT	Modified Intention to Treat
mGI	Modified Gingival Index
mm	Millimeter
mSBI	modified Sulcus Bleeding Index

Ncm	Newton Centimeter
PII	Plaque Index
PP	Per Protocol population
PPD	Probing Pocket Depth
PSP	Photostimulable Phosphor
RFA	Resonance Frequency Analysis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety Population
TN-SM	Tetranite® - Stabilization Material
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale

Synopsis

Study Title:	Immediate Placement and Stabilization of Dental Implants with Tetranite® Stabilization Material in Mandibular and Maxillary Tooth Extraction Sites that Fail to Provide Adequate Primary Stability – A Pilot Study
Study Protocol Number:	DVAL18041
Study Registration:	This protocol will be registered at www.clinicaltrials.gov before enrollment begins.
Aim:	The aim of this Pilot Study is to demonstrate the safety and efficacy of the use of Tetranite-Stabilization Material (TN-SM) to allow clinical study of the TN-SM device in a greater number of patients.

Primary Endpoint:	The primary endpoint is a composite measure of implant success (after criteria of Buser, et. al.[1]) at six-month post-functional loading consisting of:
	• Presence of the implant at its site of implantation; and,
	• Absence of a recurrent peri-implant infection with suppuration; and,
	• Absence of mobility, defined as:
	  ○ Lack of implant rotation subjected to 20 Ncm of clockwise torque applied 15 minutes after implant placement; and.
	  ○ Lack of implant rotation subjected to 35 Ncm of clockwise torque applied 13 weeks after implant placement; and,
	  ○ No construct mobility upon palpation at 6 months post-functional loading; and,
	• Absence of encapsulation defined as continuous radiolucency around the implant in a periapical radiograph.

Secondary Endpoints:	Incidence, severity and duration of device-related adverse events throughout the 12-month post-functional loading term; Implant success (after criteria of Buser, et. al.[1], see primary endpoint) after implants are stabilized with the TN-SM device throughout the 12-month post-functional loading term; Crestal bone level maintenance assessed by analysis of two-dimensional periapical radiographic records showing no more than a 2mm loss of height at the 12-month post-functional loading term; Dimensional changes in bone volume and changes in bone density will be tracked and qualitatively compared at the following time points: before tooth extraction, at follow-up to the implant placement, six months after functional loading of the implant, and at twelve months after functional loading of the implant. CBCT data will be used to perform these assessments; Periodontal and peri-implant tissue health satisfaction demonstrated throughout the 12-month post-functional loading as compared to existing conditions in the oral cavity near adjacent teeth to the implant site and to baseline around the implant at definitive restoration; Subject satisfaction after TN-SM device placement and implant uncovering (i.e., level of pain) as well as throughout the 12-month post-functional loading term

	(i.e., function, level of pain, esthetics).
Primary Analysis:	The primary analysis will be conducted after each subject completes six months of TN-SM device functional loading after crown placement.
Study Design:	Prospective, multi-center, single arm, clinical pilot study.
Number of Subjects:	20 subjects total, 10 subjects at each of two Research Centers
Subject Population:	Male or female subjects 21 years of age or older who require a tooth extraction and desire a replacement with a dental implant and crown reconstruction, and who meet all the Inclusion/Exclusion criteria listed below. The implant site anatomical location may be maxillary or mandibular, anterior or posterior; however, the residual alveolar defect must meet stability and size criteria.
Inclusion Criteria:	**Screening Inclusion Criteria** • Subjects must have voluntarily signed the informed consent form before any study related procedures; • Subjects must be males or females who are a minimum of 21 years of age, • Subjects who require a single tooth extraction and desire a replacement with a dental implant. Candidate subjects may require more than one extraction, but only one site will be considered for inclusion in the study. • Subjects must have opposing dentition (natural teeth, fixed or removable restorations); • Subjects must be committed to the study and the required follow-up visits; • Subjects must be ASA I or ASA II; • Planned site for implant must have at least one adjacent tooth; • There must be sufficient bone height crestal to critical anatomical structures, i.e., the inferior alveolar canal, maxillary sinus or piriform foramen, to safely place a dental implant within the bone contours; • Anatomical conditions that, in the opinion of the investigator, allow an implant crown restoration to be placed at the candidate site, e.g., sufficient interocclusal space, appropriate angulation of the ridge, etc. **Extraction Site Enrollment Inclusion Criteria** • There is at least 2mm of apical bone for positive seating of the implant; • Any implant site in which placement of the selected implant leaves an HDD greater than 2mm in at least two directions, (i.e., mesially, distally, buccally, or lingually) between the implant surface and the most coronal aspect of the osteotomy.

Exclusion Criteria:	**Screening Exclusion Criteria** • Subjects with a systemic disease or condition affecting a major organ system that would preclude dental implant surgery (e.g., malignant neoplasm or chemotherapy in the past 6 months, uncontrolled diabetes, major infection, Cushing's syndrome, metabolic bone disease, immunosuppression, blood dyscrasias, healing bone fracture, myocardial infarction or cerebrovascular accident within the last six months, etc.); • Subjects with any contraindications for oral surgical procedures (e.g. scleroderma, etc.); • Subjects with mucosal diseases (e.g. erosive lichen planus, mucous membrane pemphigoid, erythema multiforme, etc.) in the localized area around the study implant site; • Subjects with bone diseases or conditions (e.g. Paget's disease, fibrous dysplasia, history of osteomyelitis, etc.) in the region of the potential study implant site; • Subjects with a history of local radiation therapy in the head/neck area or osteonecrosis of the jaws; • Subjects with any acute and untreated endodontic lesions or periodontal disease; • Subjects receiving, or having a recent or long-term history of receiving, oral or parenteral anti-osteoclastic agents [e.g., bisphosphonates, Xgeva® and Prolia® (denosumab); Forteo® (teriparatide), strontium ranelate, etc.], or anti-angiogenesis factors; • Subjects who have major active substance abuse problems (e.g., alcoholism, opiate addiction, methamphetamine abuse, etc.); • Subjects who are pregnant or intending to become pregnant during the duration of the study; • Subjects who are heavy smokers (defined as >10 cigarettes per day or >1 cigar per day or equivalent of electronic cigarette vaping) or chew tobacco; • Subjects with inadequate oral hygiene or who are unmotivated for adequate home care; • Subjects who have physical or mental handicaps that would interfere with the ability to perform adequate oral hygiene; • Subjects who have undergone administration of any investigational device within 30 days of enrollment in the study; • Subjects who are allergic or otherwise sensitive to any materials likely encountered during the course of the study (e.g. titanium, suture materials, local anesthetics); • Subjects with conditions or circumstances, which, in the opinion of the Investigator, would prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance or unreliability **Extraction Site Enrollment Exclusion Criteria** • Any site into which the implant is not or cannot be placed during the same visit as the extraction. • Any implant site where there is a dehiscence or fenestration of buccal or lingual plates of bone greater than 5mm in any direction;

	• Any implant site in which placement of the selected implant leaves an HDD greater than 5mm in any direction between the implant surface and the most coronal aspect of the osteotomy; • Any site which provides primary implant stability after seating as demonstrated by insertion torque of greater than or equal to 15 Ncm; • Any site into which the implant is not or cannot be placed during the same visit as the extraction.

Treatment Plan for the Study Subjects:

Visit	#	Procedures	Schedule
Screening	1	Informed Consent, Screening, Demographics, Pregnancy Test, Periodontal Measurements	
Qualifying Examination	2	History, Baseline Clinical Examination, Baseline Radiographs and Holder Fabrication, Photographs	
Surgery	3	Tooth Extraction, Enrollment, TN-SM Placement, Implant Placement and Stability Test, Health Check, Radiographs, Photographs	< 45 days from screening
Postoperative Follow-up	4	Suture Removal, Health Check, Radiographs, Photographs	2-weeks post TN-SM device and implant placement
Implant Uncovering	5	Uncover Implant, Health Check, Stability Test, Radiographs, Photographs, Periodontal Measurements	13-weeks post TN-SM device and implant placement
Restorative Records	6	Health Check, Records for Fabrication of Definitive Restoration (Impressions or scans, shade, jaw relation, etc.), Photographs	3-weeks post implant uncovering
Insertion of Definitive Restoration **(Baseline)**	7	Insertion of Definitive Restoration, Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs	4 - 6 months post TN-SM device and implant placement
3-month Follow-up	8	Health check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	3-months post-functional loading
6-month Follow-up – **Primary Endpoint**	9	Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	6-months post-functional loading
9-month Follow-up	9.5	Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	9-months post-functional loading

	12-Month Follow-up	10	Health check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	12-months post-functional loading
	15-month Follow-up	11	Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	15-month post-functional loading
	18-month Follow-up	12	Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	18-month post-functional loading
	21-month Follow-up	13	Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	21-month post-functional loading
	24-month Follow-up	14	Health Check, Satisfaction Survey, Periodontal & Peri-Implant Measurements, Radiographs, Photographs, Implant Success	24-month post-functional loading

Study Products:	Tetranite Stabilization Material, TN-SM Commercially available endosseous dental implants Manufacturer's recommended prosthetic components for the implant systems
Registration Status:	TN-SM is the experimental device under study.
Safety:	Study subjects will be monitored for device-attributable adverse effects during the scheduled examinations and at any examinations resulting from study subjects' self-reported concerns. A licensed physician will evaluate any evidence of systemic adverse effects.
Countries in which the Study will be Conducted:	United States
Number of Participating Centers:	2 centers
Study Monitor:	David L. Cochran, DDS, MS, PhD
Principal Investigators at Centers:	Michael Pikos, DDS, Pikos Institute, 8740 Mitchell Blvd, New Port Richey, FL 34655 Ryushiro Sugita, DDS, University of Texas Health Science Center, San Antonio, TX 78229
Estimated Date of Study Initiation:	Q1 2019

Estimated Date of Study Completion:	Q2 2020 for all subjects to reach the primary endpoint; Q4 2021 for all subjects to complete the follow-up phase.
Sponsor:	RevBio
Compliance:	This study and any amendments will be performed according to ISO 14155:2011, ICH E6(R1) Guideline on Good Clinical Practice (GCP) 1996 and conformed to the Declaration of Helsinki (last revised Fortaleza 2013). Local legal and regulatory requirements include compliance with 21 CFR 50, 21 CFR 54, and 21 CFR 56.

Schedule of Procedures / Assessments

Procedures:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 9.5	Visit 10	Visit 11-14
	Screening Visit[1]	Qualifying Exam	Surgery	Post-Op Follow-up	Implant Uncovering	Restorative Records	Insertion of Definitive Restoration **(Baseline)**	Follow-up	Follow-up **(Primary)**	Follow-up	Follow-up	Follow-ups every 3 months
			< 45 days after Screening	2 weeks post-implant placement	13 weeks post- implant placement	3 weeks post-implant uncovering	4-6 months post-implant placement	3-months post-loading	6-months post-loading	9-months post-loading	12-months post-loading	15-24 month post loading
Informed Consent			X									
Screening Criteria (Inclusion/Exclusion)	X	X										
Demographics	X											
Full Mouth CBCT or Panoramic Radiograph	X											
Radiographic Media Holder Fabrication		X										
Tooth Extraction			X									
Extraction Site Enrollment Criteria (Inclusion/Exclusion)			X									
TN-SM Device and Implant Placement			X									
Suture Removal				X								
Implant Uncovering					X							
Restoration Records						X						
Insertion of Definitive Restoration							X					

Assessments:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 9.5	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
	Screening Visit[1]	Qualifying Exam	Surgery	Post-Op Follow-up	Implant Uncovering	Restorative Records	Insertion of Definitive Restoration **(Baseline)**	Follow-up	Follow-up **(Primary)**	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
			< 45 days after Screening	2 weeks post-implant placement	13 weeks post-implant placement	3 weeks post-implant uncovering	4-6 months post-implant placement	3-months post-loading	6-months post-loading	9-months post-loading	12-months post-loading	15-months post-loading	18-months post-loading	21-months post-loading	24-months post-loading
Pregnancy Test	X[2]														
Med & Dental History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Check			X	X	X	X	X	X	X	X	X	X	X	X	X
Periapical radiographs			X		X	X	X	X	X		X		X		X
CBCT – localized		X[3]		X			X	X	X		X				X
Intra-oral photographs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Implant stabilization (torque check)			X		X										
Implant success (Buser et al.,[Error! Bookmark not defined.])								X	X	X	X	X	X	X	X
Oral Hygiene Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Periodontal Measurements	X	X			X		X	X	X	X	X	X	X	X	X
Peri-Implant Measurements							X	X	X	X	X	X	X	X	X
Subject satisfaction evaluation							X	X	X	X	X	X	X	X	X

[1] The screening assessments can be taken at several visits as long as they are performed within 45 days of the surgery.

[2] The pregnancy test must be administered before taking study required radiographs.

[3] A localized CBCT is required at screening if a full mouth panoramic radiograph is used at screening instead of the full mouth CBCT.

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1 Background and Rationale

Every year, millions of procedures involving fixation of metal objects and bone fragments to bone are performed worldwide.[2-5] An assortment of autografts, allografts, xenografts, alloplasts, hardware fixation devices, as well as growth factors are currently being used to improve the outcomes of these procedures by aiding in immobilization, fixation, providing scaffolds, stimulating bone ingrowth and healing, or increasing bone volume.[6] The ideal material or device, or combination, used in many of these procedures must be biocompatible, at least osteoconductive, preferably biodegradable and replaced by native bone, able to withstand loads (strong) and absorb shocks (tough), produce predictable results, be easy to use, and be relatively inexpensive.[7] The list of desirable characteristics should also include the capacity to resist migration (cohesiveness), be used in minimally invasive procedure (injectability), adhere to living bone (wet field adherence), adhere to the hardware materials, accept direct bone deposition (ability to osseointegrate), and maintain the desirable mechanical properties throughout the useful life of the product. To date, such an ideal material has not been found.

In addition to allograft products, many semi-synthetic, synthetic, and xenograft bone graft substitute particulate materials have entered the market. The most successful of these are calcium phosphate salts, e.g., hydroxyapatite and β-tricalcium phosphate because of their biocompatibility and similarity to the natural bone mineral. These materials are osteoconductive, inexpensive and can be successfully used to expand the volume of autogenous grafts.[8] The physical characteristics of these materials, however, do not allow them to be weight bearing and many are not significantly biodegradable. Furthermore, particulate materials, such as bone chips and xenograft granules, often need to be contained by membranes or meshes to prevent migration from the application site and to maintain shape of the graft mass.

Hard-setting polymeric cements were developed to retain load-bearing implantable hardware such as prosthetic joints.[9-10] These synthetic materials have seen extensive use in orthopedics because they can uniquely and immediately provide load-bearing strength and toughness.[7, 11] However, their use is controversial in some applications as they can pose several serious problems as biomaterials. For instance, a class of bone cement based on polymethylmethacrylate (PMMA) resin is a legacy material that has no chemical adherence to bone, is not resorbable, and its monomer has been characterized as a toxic material particularly when used in bulk.[12] PMMA has also been known to cause serious complications related to its exothermic setting reaction,[13] its effect on the pulmonary and circulatory system,[14] and its lack of long-term hard tissue integration,

biodegradation and vascular penetration.[15-16] Inclusion of various additives such as fibers, nanotubes, beads, flakes, antibiotics, barium salts, magnesium salts, hydroxyapatite, bioglass, silica, chitosan, and others, has been investigated with the goal of improving the mechanical and biochemical properties of the PMMA bone cements to produce mixed incremental improvements.[17-20]

The use of synthetics has increased in the past several decades after the development of calcium phosphate cements (CPCs) in the mid 1980's.[21] This class of water-based self-setting cements composed of various calcium phosphate salts has been described and studied as potential synthetic bone grafting materials. CPCs are usually composed of two calcium phosphate salts, one more alkaline, e.g., α-tricalcium phosphate or tetracalcium phosphate (TTCP), and the other more acidic, e.g., dicalcium phosphate anhydrate or monocalcium phosphate,[22] which when mixed in an aqueous environment react with one another and precipitate as one of several intermediate pH calcium salts, often hydroxyapatite.[23] The newer CPC formulations often add a non-calcium-phosphate compound acidic component, e.g., polymethyl-vinyl ether-maleic acid or citric acid, etc. in order to improve properties of the biomaterial.[24-25,]

Even though many of the non-metallic materials and devices available are osteoconductive, resorbable, injectable, capable of osteointegration and increasingly tougher and stronger, most are brittle and not strong enough for load bearing applications required for the skeleton.[26-28]

On the other hand, metallic implantable fixation devices, which do have the load bearing intrinsic strength, are not biodegradable,[29] nor do they conform to the defect shape or size. Both metal and resorbable (e.g. collagen) hardware, such as screws, plates, and buttons, require a significant, often unavailable, bone quantity and quality for successful application, thereby presenting technical challenges or leading to compromised results.[30]

A material combining load bearing, resorbable, osteoconductive, and injectable characteristics has been elusive, yet another highly desirable characteristic, that of robust adherence to bone in a biocompatible and biodegradable material has not been described in spite of much effort expended and some promising results. One direction to follow is the synthetic path with known adhesives being applied to the biological system. A variety of cyanoacrylates,[31-32] polyurethanes,[33] PMMAs,[34] glass ionomers,[35] as well as calcium and magnesium phosphates[36] and others have been investigated without resulting in a broadly used clinical product for a variety of reasons spanning from cytotoxicity, insufficient strength of bonds formed with bone, method of use incompatible with osseous tissue survival, to brittleness of the material itself.[7]

Another direction followed was to adapt a naturally-occurring adhesive to bone applications. Fibrin clot based[37] and aldehyde cross-linked collagen derivatives based[38] systems have been successful as soft tissue adhesives but lack strength for bone applications. Attempts to directly use proteins involved in adhesion in nature resulted in unacceptable immune responses in vivo; however, biomimetic polymers based on marine organisms such as the mussel Mytilus californianus[39-40] and the sandcastle worm Phragmatopoma californica[41] have produced more promising results. The continuing work by Messersmith and by Lee with the mussel-inspired materials related to dihydroxyphenylalanine (DOPA), such as 3,4-dihydroxyhydrocinnamic acid (DOHA), dopamine, and nitrodopamine has led to reports of implantable soft tissue adhesive,[42] underwater bonding and debonding by exposure to ultraviolet irradiation,[43] underwater adhesion with post-translationally modified, bioengineered proteins, and a functional osteoinductive binder for grafting of bone substitute particles,[44] among others.

RevBio (RB) seeks to obtain marketing approval for Tetranite™ Stabilization Material Device (TN-SM), a calcium phosphate-based synthetic material with adhesive properties that make it suitable to bond metal implants to bone. The adhesive contains O-phospho-L-serine (OPLS), which is essential to the adhesive properties. Tetranite® is a synthetic, osteoconductive, biodegradable bone-adherent biomaterial. It is injectable, mildly exothermic during cure, bonds to most high surface energy materials, including living bone and metals such as titanium and its alloys, and is capable of forming durable and stable bonds in a wet environment. The components of Tetranite are substances that occur naturally in the human body. Tetranite technology is partly built on Chow's work with calcium phosphates but is also partly inspired by a glue protein found in the sea-dwelling sandcastle worm. The results show a robust ability to bond both metals and bone in a wet-field environment combined with injectability, biocompatibility, biodegradability and osteoconduction.

The stability in bone of a newly placed dental implant is critical to its success.[45] Frequently, the conditions at presentation do not predictably guarantee that the new implant will be stable on placement and require reconstructive procedures aimed at rebuilding the bone through grafting.[46] This additional sequence of procedures, with an additional healing period to follow, delays the completion of treatment by four to six months. It also adds increased risk for post-surgical complications including inadequate healing and infection, as well as greater morbidity for the patient. Additionally, implants placed in grafted bone have a higher risk of failure to osseointegrate.[47] The purpose of the present study is to evaluate the safety and efficacy of a single stage approach using Tetranite® Stabilization Material (TN-SM). The purpose of the efficacy

component of this study is a composite comprising: (1) First – To demonstrate and evaluate the ability of TN-SM to achieve immediate implant stabilization in sites otherwise unable to provide primary stability without requiring the delay in treatment imposed by the current multi-staged standard-of-care method; (2) Second - To demonstrate and evaluate the ability of TN-SM to achieve short-term stabilization of implants as the device undergoes initial resorption and replacement with new bone; and (3) Third - To demonstrate and evaluate the ability of a TN-SM stabilized implant to achieve implant success (after criteria of Buser, et. al.1) after 6 months of functional-loading while the device undergoes significant resorption, facilitates osteoconduction, and replacement with new bone. In addition to the Primary Endpoints of establishing the Safety and Efficacy of Implant Stabilization and Implant Success throughout the initial 6 months of post-functional loading, the study also assesses several secondary endpoints over the course of the study and one-year follow-up, as outlined in the sections below. These include assessment of incidence, duration, and severity of adverse effects and events; assessment of implant success; assessment of bone level, volume and density changes; patient satisfaction surveys, and assessment of periodontal and peri-implant health integral to implant success.

There are currently many alternatives for clinicians and patients to choose for use as bone graft materials. While safety and efficacy have been well established for the majority of them, success rates vary both in their ability to allow bone replacement and their ability to maintain volume of bony architecture once placed, and as healing and bone replacement occur over time. Additionally, where bony walls are absent, guided bone regeneration (GBR) procedures are indicated. While also highly successful, these GBR procedures introduce additional risk of treatment failure, post-surgical infection and other complications, as well as increased cost and treatment time for the patient. While not a primary outcome of this proposed study, animal data to date have demonstrated soft tissue exclusion with Tetranite and, therefore, no need for barrier membranes to be used. Additionally, the TN-SM is dimensionally stable as it is replaced by the patient's bone, thereby limiting the need for overfill or secondary grafting procedures.

The goal of implant therapy is to provide support for a functional and esthetic restoration with a low-risk of complication to the patient. Clinicians have many treatment decisions that impact the successful delivery of functional and esthetic restorations, including timing of implant placement and type of implant. This study will consider the clinical outcomes of using TN-SM to establish adequate stability for immediate implantation following extraction of natural teeth for successful osseointegration. The study treatments have been developed in the course of exploratory and pivotal preclinical large animal studies using the TN-SM device in unstable implant sites.

2 Study Endpoints

The aim of this study is to demonstrate, at a pilot level, the Safety and Efficacy of TN-SM for its stated indications for use to allow clinical study in a greater number of patients. It is also an aim of this study to test performance characteristics and capabilities of study designs, measures, procedures, recruitment criteria, and operational strategies that are under consideration for use in a larger subsequent study.

2.1 Primary Endpoint (Composite)

The **primary endpoint** is implant success through six-months of post-functional loading. The implant success criteria will be collected on a per patient level and are a composite of implant survival, health and efficacy measures, based after criteria of Buser, et. al. [1], including:

- Presence of the implant at its site of implantation; and,
- Absence of a recurrent peri-implant infection with suppuration; and,
- Absence of mobility, which will be assessed at multiple timepoints. Specifically,
    - Immediate stabilization (implant placement, Visit 3) is assessed by applying a torque of 20 Ncm applied directly to the implant 15 minutes after implantation.
    - Short-term stabilization (implant uncovering, Visit 5) is assessed by applying a torque of 35 Ncm 13 weeks after implant insertion.
    - Continued stabilization is assessed at 6-months post-functional loading (Primary Follow-up, Visit 9) by applying manual palpation.
- Absence of encapsulation determined by a continuous radiolucency around the implant assessed via periapical image.

2.2 Secondary Endpoints

2.2.1 Incidence and Severity of Device Attributed Adverse Effects and Events

The **first secondary endpoint** will be to demonstrate low incidence and severity as well as short duration of adverse device-attributed systemic effects and events as reported by study subjects and/or investigator/monitors throughout the 12-month post-functional loading term.

2.2.2 Long Term Implant Success

The **second secondary endpoint** will be to demonstrate long-term implant success after implants are stabilized with the TN-SM device throughout the 12-month post-functional loading term. The implant success criteria will be collected on a per patient level at each timepoint and are a composite of implant survival, health and efficacy measures, based after criteria of Buser, et. al.[1], including:

- Presence of the implant at its site of implantation; and,
- Absence of a recurrent peri-implant infection with suppuration; and,
- Absence of mobility, which will be assessed by applying manual palpation; and,
- Absence of encapsulation determined by a continuous radiolucency around the implant assessed via periapical image.

2.2.3 Crestal Bone Level Maintenance

The **third secondary endpoint** will be to demonstrate crestal bone level maintenance measured directly by two-dimensional periapical radiographic methods showing no more than a 2mm loss of height at the 12-month post-functional loading term.

2.2.4 Peri-Implant Bone Stability

The **fourth** secondary endpoint will be to determine if there are any dimensional changes in bone volume and changes in bone density which will be tracked and qualitatively compared at the following time points: before tooth extraction, at follow-up to the implant placement, six months after functional loading of the implant, and at twelve months after functional loading of the implant. CBCT data will be used to perform these assessments.

2.2.5 Periodontal and Peri-Implant Health

The **fifth secondary endpoint** will be to demonstrate satisfactory periodontal and peri-implant health throughout the 12-month post-functional loading term compared to existing conditions in the oral cavity near adjacent teeth and to baseline around the implant at definitive restoration;

2.2.6 Patient Satisfaction

The **sixth secondary endpoint** will be to demonstrate acceptable level of subject satisfaction after TN-SM device placement and implant uncovering (i.e., level of pain) as well as throughout the 12-month post-functional loading term (i.e., function, level of pain, esthetics). Patient Satisfaction scores will be determined by analysis of patient reports using a Visual Analog Scale.

3 Study Design

3.1 Overview

This is a prospective, multi-center, single arm, pilot clinical study evaluating the use of TN-SM for implant stabilization immediately after tooth extraction. The purpose of this pilot study is to test performance characteristics and capabilities of study design, recruitment criteria, procedures, measures, and operational strategies that are under consideration for use in a subsequent, larger clinical pivotal study. The purpose of the subsequent study will be to provide data demonstrating the safety and efficacy for the use of TN-SM to provide immediate and continued stabilization of implants placed into otherwise unstable sites. Use of TN-SM eliminates the need for the standard practice of bone grafting after tooth extraction and staged implant placement, significantly shortening the overall length of this treatment.

3.2 Intended Use

Tetranite® Stabilization Material bonds dental implants to bone in applications where additional mechanical stabilization is required at the time of placement. Its purpose is to augment primary stability of dental endosseous implants inserted into sites that lack adequate primary stability. Tetranite is resorbed over several months while being replaced with new bone without compromising implant stabilization.

3.3 Indications for Use

Tetranite Stabilization Material is indicated to stabilize a dental implant in a compromised implantation site which requires an adjunct to hardware fixation between the implant surface and the bone recipient site. These sites are sockets after the recent extraction of a tooth, that include a surgically created osteotomy within the extraction site made in preparation for dental implant placement in which primary stability is unable to be achieved through conventional means. The adhesive is intended only as an adjunct to hardware fixation and is not intended for stand-alone use.

3.4 Study Population

The study population will consist of male and female subjects at least 21 years of age. The

demographic data will be recorded in the study logs. Subjects will be recruited through the clinics where the investigators are practicing and possibly through referring dentists. There will be a stratified examination of inclusion/exclusion criteria applied during the patient evaluation process to make the process less burdensome to both the potential study subjects and the investigators: the first is the screening criteria of the patient overall, which will consider whole-patient and oral factors, while the second is the extraction site enrollment criteria, which is a more detailed assessment of the candidate study subject and of the specific potential study site which will be determined at the time of the tooth extraction and implant placement. All of the inclusion criteria must be met to receive the study implant. If any of the exclusion criteria are met, the potential study subject must be excluded from the study.

3.5 Study Sample Size

This study size will enroll 20 subjects, 10 at each of the two Research Centers. The enrollment will be capped at 20 subjects total and will not include control subjects.

3.6 Study Duration

The study is expected to enroll 20 subjects over a 6-month period. Study subjects will participate for 30 months (up to 6 months to reach implant loading, then 6 months to reach the primary endpoint, followed by another 18 months to reach 24-months follow-up). The total duration of the study is expected to span 36 months.

3.7 Screening Criteria

Those potential subjects who appear eligible according to the Screening Inclusion and Exclusion Criteria will be asked to provide informed consent in writing prior to any study related procedures and will be considered “consented” in the study and logged in as “consented” candidates. Potential subjects will be evaluated based on the Screening Inclusion Criteria (Section 5.2.2) and Screening Exclusion Criteria (Section 5.2.3) for initial eligibility during the Screening and Examination visits. Subjects must fulfill all of the inclusion criteria and not meet any of the exclusion criteria to be eligible for the study. If the “consented” study candidate meets all the Criteria he/she will be scheduled for the Surgical Visit. If a “consented” study candidate does not meet all the Inclusion/Exclusion Criteria, his/her name will be logged in as a “screen failure”. Subject demographics, including age, gender, race, and ethnicity, will be documented at the Examination visit.

3.8 Extraction Site Enrollment Criteria

Potential subjects are permitted to have multiple teeth extractions and/or receive multiple implants during the surgical procedure, however only one of the sites will be enrolled as the study site. The study subject candidate site tooth will be extracted during the Surgical Visit, and the extraction site will be immediately prepared with an implant osteotomy and next evaluated for enrollment by application of the Enrollment Inclusion Criteria (Section 5.3.2) and Enrollment Exclusion Criteria (Section 5.3.3). In the case of multiple potential candidate sites, the study site will be selected by the investigator prior to the TN-SM device and implant placement based on which site meets the Extraction Site Enrollment Criteria. If multiple sites meet the criteria, the least stable qualifying site will be selected and enrolled as the study site.

Once the subject meets all the Extraction Site Enrollment Criteria, he/she is considered "enrolled" in the study, and the status will be documented in the Enrollment Log. Any "consented" potential subject who at the end of the Surgical Visit does not have a single "enrolled" site, will be considered an "enrollment failure" and his/her name will be logged in as such. Once the number of enrolled subjects at a Research Center reaches ten, no further subjects will be considered or enrolled.

Once the planned number of subjects at the study center is reached (10), no more potential subjects will be considered or enrolled in the study.

3.9 Study Treatment Plan

Subjects enrolled in the study will have had, during the Surgical Visit, a test site which met the criteria of an initially placed implant demonstrating inadequate stability. After implant removal, the TN-SM is applied to the site and the implant is reinserted per the Tetranite IFU – Document # 50001-00 (Appendix 1). Immediate stabilization is assessed by applying a torque of 20 Ncm applied directly to the implant 15 minutes after implantation. This level is a clinically relevant indicator of stability and is expected to be a sub-threshold and nondestructive test.[48] After successful completion of the torque test, all implants will be closed with a cover screw and soft tissues left to granulate over the socket crests. Monofilament sutures will be used at the discretion of the clinician to approximate soft tissue margins, as needed. Photographic records will be captured of the study site before and after soft tissue adaptation. A standardized periapical image will be captured for documentation of the crestal bone level pre-extraction and after TN-SM device and implant placement.

Two weeks following placement of the TN-SM device and the implant, all subjects will return for evaluation of the study site for healing and possible suture removal. A localized CBCT scan of the region of the study site will be performed and will serve as baseline.

All subjects will return at 13 weeks following the TN-SM device implantation to uncover the implant. At this point, short-term stabilization will be assessed by applying a torque of 35 Ncm to the implant. The test is performed at a clinically relevant torque level to demonstrate readiness for restoration of an implant supported prosthesis.[49] A healing or standard abutment will be placed during the visit. A standardized periapical image for documentation of crestal bone level and for evaluation of indicators of encapsulation will be captured. Photographic records of the study site will be captured before uncovering surgery and following abutment placement and soft tissue adaptation.

Following a three to four-week healing period, records will be obtained for fabrication of a crown restoration. These records will consist of the following: final impression or scan of the test site dental arch, an impression or scan of the opposing dental arch, a jaw relation record and a shade registration of the dentition. Photographic records will also be captured at this time.

Contingent upon satisfactory stabilization, the implant will be loaded by the implant crown in appropriate occlusion with an abutment and crown prosthesis no sooner than four months and no later than six months after TN-SM device placement. A baseline standardized periapical image for documentation of crestal bone level and for evaluation of indicators of encapsulation will be captured. Photographic records will be captured of the study site before and after the crown is inserted from lingual (or palatal) and from buccal aspects. If the definitive restoration is inserted provisionally at this time, the provisional insertion date will be treated as the baseline loading date for the purposes of the study and the definitive insertion visit will be recorded as a separate visit.

Any loosened implants that are identified during the course of the study will be considered a failure and will be removed. The remaining Tetranite material will be removed by curetting or drilling the osteotomy until a bleeding bone surface is obtained. The clinician may place a wider or longer implant as appropriate for the tooth position. Otherwise the site will be grafted as per a conventional staged approach.

3.10 Post-Loading Follow-up Visits

Following crown placement, all subjects will return for routine evaluation of the study site and for evaluation of the TN-SM device function at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-months of post-functional loading. In addition to the routine elements of the site evaluation, the following assessments will be performed: Photographic records will be captured of the study site from lingual (or palatal) and buccal aspects, and the subject will also answer a satisfaction survey (pain, function, and esthetics) at every post-loading follow-up. A standardized periapical image for documentation of crestal bone level and for evaluation of encapsulation of the study will be captured

at 3 months and 6 months post-loading, and every 6 months thereafter (3, 6, 12, 18, and 24 months). A CBCT scan of the region of the study site will be performed at the 3-, 6-, 12-, and 24-month post-loading follow-up visits.

3.11 Study Assessments

3.11.1 Implant Success

Implant success will be assessed at post-functional loading follow-ups. A successful implant will meet all of the following criteria according to Buser et al.[1]; including,

- Presence of the implant at its site of implantation;
- Absence of a recurrent peri-implant infection with suppuration;
- Absence of mobility, which will be assessed at several timepoints. Specifically,
    - Immediate stabilization (implant placement, Visit 3) is assessed by applying a torque of 20 Ncm applied directly to the implant 15 minutes after implantation.
    - Short-term stabilization (implant uncovering, Visit 5) is assessed by applying a torque of 35 Ncm 13 weeks after implant insertion.
    - Long term stabilization is assessed every 3 months post-functional loading until 24-months post-functional loading by manual palpation.
- Absence of encapsulation determined by a continuous radiolucency around the implant recorded in a periapical image.

Any dental implant showing excessive bone loss, radiolucency, or infection shall be treated in the manner best suited to the well-being of the subject, including treatment to save the dental implant. Continuous radiolucency, implant loss, recurrent peri-implant infection with suppuration, or implant mobility shall be considered a failure for the purposes of the study.

3.11.2 Medical and Dental History

The medical and dental history will be obtained at the screening visit and updated at each visit in the study. The dental history should include dental status information including a description of the opposing and adjacent dentition. Relevant medical history (e.g., systemic diseases, medications, etc.) and current medical conditions will be recorded by the investigator. The information may be obtained from the subject's general physician or from oral communication with the subject.

Any study subject who develops a medical condition during the course of the study which would have been considered an exclusion criterion will not be exited from the study. Patients will continue

in the study and will continue to be followed except as required to ensure appropriate medical care for their specific conditions. For example, patients who become pregnant during the study would be unable to undergo the required imaging but would be followed clinically. Patients who develop cancer and require systemic chemotherapy or radiation would also continue to be followed except if deemed necessary to exit the study by their clinician.

3.11.3 Concomitant Medication

Concomitant medication, procedures, and supportive therapies will be recorded at the screening visit. Any changes in the concomitant medications, procedures, and supportive therapies must be documented at each study visit until the end of the study. All prophylactic antibiotics and anesthesia given must be recorded on the Concomitant Medication Form. This includes the pre-rinse with chlorhexidine mouthwash 0.12% for 30 seconds immediately prior to the surgery.

3.11.4 Adverse Event Check

Following surgery and at each visit until the end of the study, the Investigator will determine if any adverse events occurred since the last study visit by speaking with the subject and reviewing any dental and medical records. These Adverse Events (AEs), along with any adverse events from the current study visit, should be documented and reported as described in Section 6.3 of the protocol. In addition, the Investigator will evaluate the status of any ongoing adverse events throughout the study as specified in Section 6.4.

3.11.5 Subject Satisfaction

Subject satisfaction will be assessed utilizing Visual Analog Scales (VAS) at insertion of definitive restoration, as well as at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-months post-functional loading for the following parameters related to the implant and restoration:

- Level of pain associated with the implant and crown

  □ Painful □ No pain

- Level of satisfaction with the function of the implant supported crown

  □ Not satisfied at all □ Highly satisfied

- Level of satisfaction with the esthetics of the implant supported crown

  □ Not satisfied at all □ Highly satisfied

Each subject will be asked to complete a VAS for each of the above parameters by the Investigator. The subject will be given a paper questionnaire to mark their responses on the VAS (Appendix 3). The subject will mark a 100 mm scale with a vertical line. A measurement will be made from the

left on the scale to the point of the first marking from the subject. This measurement will be recorded on a case report form.

3.11.6 Oral Hygiene Evaluation

The subject's overall oral hygiene will be evaluated at each study visit starting with the screening visit by choosing one of the following: "excellent", "good", "fair" or "poor".

3.11.7 Periodontal and Peri-Implant Measurements

Periodontal and peri-implant measurements will include the modified sulcus bleeding index (mSBI) and the pocket probing depth (PPD), as detailed below. All periodontal measurements will be performed using a manual, millimeter calibrated periodontal probe (UNC 15, Hu-Friedy, Chicago, IL, USA). The periodontal measurements will be used to assess the periodontal health of the region. These measurements will be made on the teeth adjacent to the study site during screening, at surgery, at implant uncovering, at definitive crown insertion, and at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-months post-functional loading. These measurements will also be made around the study site implant at definitive crown insertion, and at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-months post-functional loading.

- Modified Sulcus Bleeding Index (mSBI):

  It will be documented if bleeding is induced at the marginal gingival tissue by running a blunt periodontal probe along the soft tissue wall at the orifice of the pocket. The bleeding tendency will be evaluated on the two adjacent teeth at 6 locations (distofacial, facial, mesiofacial, distolingual, lingual, mesiolingual) and assessed using the mSBI by Mombelli et al.[2] If only one adjacent tooth is present only that tooth will be evaluated.

  - Score 0: No bleeding when a periodontal probe is passed along the gingival margin
  - Score 1: Isolated bleeding spots visible
  - Score 2: Blood forms a confluent red line on margin
  - Score 3: Heavy or profuse bleeding

- Probing Pocket Depth (PPD):

  The PPD will be measured at the two adjacent teeth by recording the distance from the gingival margin to the bottom of the probeable pocket at six locations (distofacial, facial, mesiofacial, distolingual, lingual, mesiolingual). If only one adjacent tooth is present only that tooth will be evaluated.

3.11.8 Periapical Radiographs

Standardized peri-apical radiographs of the area being treated will be recorded pre-operatively, at surgery after device placement, during implant uncovering, at the prosthetic records visit, at insertion of the definitive restoration, and 3, 6, 12, 18, and 24 months post-functional loading. The radiographs must be of high quality and definition, so as to identify the bone contours in question. Ideally the entire implant should be visible on the radiograph. However, it is not essential that the apical end of the implant is contained within the radiograph; in case it is not, at least three threads from the top of the implant showing first bone-implant contact must be visible in the image. These radiographs will be used for crestal bone level assessment and evaluation of implant success (e.g., presence of encapsulation as determined by a continuous radiolucency around the implant).

Radiographs will be digital, using either a direct sensor system or an indirect system with Photostimulable Phosphor (PSP) plate. The patient-specific, custom stent fabricated during the Qualifying Exam must be used. All settings must be noted and consistently used on subsequent visits. To standardize the series of periapical radiographs, the same customized sensor/phosphor plate holder and beam aiming device will be used throughout the study for each study implant site. The radiographs will be captured with the sensor/phosphor plate placed parallel to the implants and the X-ray beam directed perpendicular to the implants. The digital image should will be saved and the file name will be formatted as follows: Subject number (XX-XX), Subject initials (XXX)_Image date (DD MMM YYYY), i.e., 01- 01_ABC_04 Nov 2019. The files will be uploaded as a DICOM file into the Electronic Data Capture system. The records will contain the kV, mA, and exposure time settings.

3.11.9 Cone Beam Computed Tomography (CBCT)

CBCT scans will be performed during initial diagnostic exam, during the post-operative follow-up, at the definitive crown insertion visit (approximately 4-6 months after implant placement), and at the 3-, 6-, 12-, 18-, and 24-months post functional loading follow-up visits. A diagnostic quality, collimated view of the region of interest, showing the entire study site as well as all tissues within 12 to 15 mm distant will be considered acceptable. The CBCT digital records will be saved and the file name will be formatted as follows: Subject number (XX-XX), Subject initials (XXX)_Image date (DD MMM YYYY), i.e., 01- 01_ABC_04 Nov 2019. The files will be uploaded as a DICOM file into the Electronic Data Capture system. The records will contain the kV, mA, and collimation settings.

3.11.10 Intra-oral Photographs

Standardized intra-oral photographs of the area being treated will be taken throughout the study

for documentation of procedures as well as results. The following standard field of view scales will be used:

- Complete dental arch - a view including the entire alveolar ridge and all teeth in the arch
- Segment of the region of interest - a view centered on the implant site and including between 12 and 15 mm view of surrounding tissues, the long axis of the image will coincide with the mesio-distal direction.

The following aspects of view will be used:

- Occlusal view – a view nearly perpendicular to the occlusal plane, a mirror may be used to capture the image
- Facial view – a view nearly perpendicular to the facial surfaces of the teeth in the area of interest, a mirror may be used to capture the image
- Occluso-facial view – a view nearly perpendicular to the mesio-distal direction in the area of interest and approximately 45 degrees from the occlusal plane and the facial surface of the teeth
- Occluso-lingual view – a view nearly perpendicular to the mesio-distal direction in the area of interest and approximately 45 degrees from the occlusal plane and the lingual surface of the teeth, a mirror may be used to capture the image

Ideally the following clinical photographic images will be captured during the study visits as a matter of routine. Additional images of other significant findings will also be recorded.

Preoperative Baseline, Visits 1, 2, or 3:

- Facial view of the segment
- Occlusal view of the segment
- Occlusal view of the entire dental arch where implant will be placed
- Occlusal view of the entire opposing dental arch

Surgical, Visit 3:

- Occlusal view of the segment after extraction
- Occlusal view of the segment after trial implant placement
- Occlusal view of the segment after definitive implant placement and TN-SM trim
- Facial view of the segment after definitive implant placement and TN-SM trim

- Occlusal view of the segment after closure

Post-Surgical Follow-up, Visit 4:

- Occlusal view of the segment as the patient arrives
- Occlusal view of the segment at end of visit

Implant Uncovering, Visit 5:

- Occlusal view of the segment as the patient arrives
- Occluso-facial view of the segment with torque test hardware in place
- Occluso-buccal view of the segment with the abutment in place at the end of visit

Prosthetic Records, Visit 6:

- Occlusal view of the segment as the patient arrives
- Occlusal view of the segment immediately after removal of the healing abutment, if used
- Facial view of the segment in full occlusion
- Occluso-facial view of the segment with scan body or impression pickup hardware
- Occlusal view of the segment at the end of the visit

Crown Insertion, Visit 7:

- Occlusal view of the segment as the patient arrives
- Occlusal view of the segment immediately after removal of the healing abutment, if used
- Facial view of the segment in full occlusion showing the definitive abutment in place, if used
- Facial view of the segment in full occlusion after definitive restoration seated and adjusted
- Occluso-lingual view of the segment after definitive restoration seated and adjusted
- Occlusal view of the entire arch with occlusal markings displayed after definitive crown seated and adjusted

Post-Loading Follow-up, Visits 8 - 14:

- Occlusal view of the segment as the patient arrives
- Occluso-lingual view of the segment as the patient arrives
- Facial view of the segment as the patient arrives
- Occlusal view of the entire arch with occlusal markings displayed

The photographs must be of high quality and definition, so as to identify the tissue condition and contours in question. These photographs will be used for evaluation of implant success (e.g., presence of peri-implant infection). The photographs will be saved as a .jpeg file (or equivalent) and the file name will be formatted as follows: Subject number (XX-XX), Subject initials (XXX)_Image date (DD MMM YYYY)_Image Number, i.e., 01- 01_ABC_04 Nov 2019_01. The files will be uploaded into the Electronic Data Capture system.

4 Device Description

4.1 Study Product

4.1.1 General Description of the Study Device

Tetranite Stabilization Material Device (TN-SM) is a synthetic, osteoconductive, biodegradable bone-adherent biomaterial. It is injectable, mildly exothermic during cure, bonds to most high surface energy materials, including living bone and metals such as titanium and its alloys, and is capable of forming stable bonds in a wet environment.

Each capsule of TN-SM contains two pre-dosed and pre-mixed, powdered reactants, TTCP and OPLS, which are packaged together with a pre-dosed amount of pure water in a separate compartment. These capsules are packaged in a pouch which preserves its sterility, protects it from environmental contaminants, and allows inspection for damage through a clear panel. The packaging is designed to allow activation of the capsule contents, i.e., combining of the components and mixing of the material, without breaching the protective pouch. The mixing is accomplished utilizing an automatic, factory-set, dedicated triturator capable of holding the capsule in its sterile pouch. The packaging method allows for aseptic placement of the capsule containing mixed adhesive within the clinical sterile field for aseptic attachment of the capsule to a dedicated hand-held applicator and for application to the implantation site. After mixing, the TN-SM material, as extruded from capsule for use, is a viscous, tacky, white liquid approximately the consistency of honey.

4.1.2 Dental Implants and Restorative Components

The study clinician may select the appropriate dental implants, abutments and other restorative components from any legally marketed components that are labeled as compatible. The prostheses fabricated for the study subjects will be single crowns.

4.2 Instructions for Use, Handling, and Labeling

RevBio will provide the study Research Centers with the necessary amount of product for the study. The product delivered for the study is to be used only for the subjects enrolled in the study and according to the clinical investigation plan. The study product will be used as described in the Tetranite IFU – Document # 50001-00 (Appendix 1). The Tetranite Stabilization Material Device (TN-SM) is a device designed and intended to provide immediate stabilization to dental implants. All device deficiencies shall be reported by the investigator to RevBio as described under section 6.3.3.

4.3 Storage

The study product will be stored in its original container until used and its access shall be controlled. The study product shall be stored in a dry environment within the temperature range 15-25°C.

4.4 Device Accountability

The Investigator must maintain an accurate and up-to-date accountability record of all study products received, used, discarded (opened, but non-used) and returned during the course of the study. This information shall be recorded in the Device Accountability Record Log. At each monitoring visit, the monitor will check the investigational device accountability for accuracy and completeness. At the end of the study, the monitor or RevBio's delegate conducting the closeout visit will perform a final reconciliation of the device accountability (cross check between the Device Record Accountability Log, the shipments delivery notes and the acknowledgement of device receipts).

4.5 Return of Study Device

After treatment of the last subject, any remaining unopened study product at site must be returned to RevBio and acknowledged for receipt. A copy of the acknowledgement of receipt must be filed in the Investigator File.

4.6 Risk Analysis, Risk/ Benefits

The device risk analysis and risk assessment for the TN-SM device was conducted according to EN ISO 14971. Full results are included in the Risk Management Hazards Analysis (91048-00) dated 28 November 2018. Refer to **Table 3** of this protocol for a list of anticipated adverse device effects (ADE) following the placement of TN-SM and insertion of dental implants. Read carefully the risks associated with the TN-SM device and the procedures involved in its use listed in the Instructions for Use 50001-00 (Appendix 1) as well as the Warning and Cautions/Precautions in Section 4.7.

4.7 General Precautions:

4.7.1 Warnings:

- Avoid approaching the proximity of the inferior alveolar nerve canal during implant bed preparation, adhesive injection, and implant insertion. If the integrity of the canal is violated nerve damage may result in anesthesia, paresthesia and/or dysesthesia.
- Avoid approaching the proximity of the maxillary sinus during implant bed preparation, adhesive

injection, and implant insertion. Placement of the Implant and/or TN-SM, or any other object, into the lumen of the sinus on indwelling basis could potentially result in a foreign body reaction, sinusitis, or a chronic infection in the sinus.

- TN-SM warnings are listed in the Instructions for Use (Appendix 1).

4.7.2 Cautions/Precautions:

- Particular care should be taken to assure proper implant alignment when comparatively high loads are expected.
- A careful clinical and radiological examination of the patient should be performed prior to surgery to determine the psychological and physical status of the patient. Special attention should be given to patients who have local or systemic factors that could interfere with the healing process of either bone or soft tissue or the osseointegration process (e.g. bone metabolism disturbances, previously irradiated bone in the head or neck area, diabetes mellitus, anticoagulation drugs/hemorrhagic diatheses, untreated bruxism or other parafunctional habits, unfavorable anatomic bone conditions, tobacco abuse, untreated periodontal disease, acute infection of implant site, temporomandibular joint disorders, treatable pathologic diseases of the jaw and changes in the oral mucosa, pregnancy, and inadequate oral hygiene).
- Sterile handling is essential. Never use potentially contaminated components. Contamination may lead to infections.
- TN-SM precautions are listed in the Instructions for Use (Appendix 1)

5 Study Procedures

5.1 Schedule of Procedures and Assessments

The schedule of administrative, treatment and evaluation visits will follow the matrix detailed in Table 1. The timing of the scheduled events listed in the table will be acceptable if it is within the tolerances listed. Except for the First Surgical Visit, i.e., the extraction, test device and implant placement visit, it is permissible for portions of the procedures to be completed on separate visits provided they are within the allowable schedule windows. A record of procedure and evaluation dates will be maintained.

Table 1: Schedule of Procedures and Assessments

Visit #	Visit Name	Visit Window

Visit 1	Screening	
Visit 2	Qualifying Examination	
Visit 3	First Surgical	< 45 days from screening
Visit 4	Post-Operative Follow-up	2 weeks ± 3 days after implant surgery
Visit 5	Implant Uncovering	13 weeks ± 1 week after implant surgery
Visit 6	Restorative Records	3 weeks ± 1 week post-uncovering
Visit 7	Definitive Restoration (Loading)	4 - 6 months from implant insertion
Visit 8	3-month follow-up	3 months ± 2 weeks post-functional loading
Visit 9	6-month follow-up – Primary Endpoint	6 months ± 1 month post-functional loading
Visit 9.5	9-month follow-up	9 months ± 1 month post-functional loading
Visit 10	12-months follow-up	12 months ± 2 month post-functional loading
Visit 11	15-months follow-up	15 months ± 2 month post-functional loading
Visit 12	18-months follow-up	18 months ± 2 month post-functional loading
Visit 13	21-months follow-up	21 months ± 2 month post-functional loading
Visit 14	24-months follow-up	24 months ± 2 month post-functional loading

5.2 Subject Screening and Qualifying Evaluation (Visits 1 and 2)

An initial evaluation will be conducted to determine whether the subject meets the Screening Inclusion/Exclusion criteria and for collection of baseline data. This evaluation will include an appropriate medical and dental history, a clinical examination, and a radiographic evaluation. The screening evaluations and data collection can take place at several office visits as long as the visits are all within 45 days of the surgery.

If the screening evaluations are not conducted within 45 days of the surgery, then the subject may be asked to re-consent and re-screen, as long as enrollment is still open.

In particular, the subject will have the following procedures and/or evaluations performed and documented at this visit:

- Screening Inclusion/Exclusion criteria applied
- Demographics
- Pregnancy test (administered before taking study required radiographs or CBCT scans)
- Medical and dental history
- Full mouth CBCT, or panoramic radiograph with a localized CBCT scan
- Oral Hygiene Evaluation
- Concomitant medications
- Radiographic stent fabrication

- Intra-oral photographs

5.2.1 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations) to obtain informed consent in writing from each subject participating in this study prior to any study related procedures. As part of the informed consent discussion with a potential subject, the investigator must provide an adequate explanation of the overall requirements/procedures of the study, purpose of the study, the nature of the planned treatment, any alternative procedures, and possible risks, complications, or benefits of the study. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from the study at any time for any reason without prejudice.

The informed consent must be approved by an Institutional Review Board (IRB) before consenting can begin. The informed consent form must be available in the primary language of the subject. It is written in accordance with the "Declaration of Helsinki" (as adopted by the 18th World Medical Assembly, 1964, and as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008), and Fortaleza (2013) (Appendix 2)) and applicable local regulations.

This IRB approved consent form must be personally signed and dated by the subject and the person obtaining consent with a witness present for the signature. Investigators should keep the original signed informed consent document in a secure location. A copy of the signed consent form should be given to the subject. The Case Report Forms (CRFs) for this study contain a section for documenting informed consent, and this must be completed appropriately.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All consented and enrolled subjects should be informed of the new information, given a copy of the revised form and give their consent to continue the study, unless the subject signed consent and was considered a screen failure.

5.2.2 Screening Inclusion Criteria:

- Subjects must have voluntarily signed the informed consent form before any study related procedures;
- Subjects must be males or females who are a minimum of 21 years of age,
- Subjects who require a single tooth extraction and desire a replacement with a dental implant. Candidate subjects may require more than one extraction, but only one site will be considered

for inclusion in the study.

- Subjects must have opposing dentition (natural teeth, fixed or removable restorations);
- Subjects must be committed to the study and the required follow-up visits;
- Subjects must be ASA I or ASA II;
- Planned site for implant must have at least one adjacent tooth;
- There must be sufficient bone height crestal to critical anatomical structures, i.e., the inferior alveolar canal, piriform foramen, and maxillary sinus, to safely place a dental implant within the bone contours;
- Anatomical conditions must be present to allow an implant crown restoration to be placed at the candidate site, e.g., sufficient interocclusal space, appropriate angulation of the ridge, etc.

5.2.3 Screening Exclusion Criteria:

- Subjects with a systemic disease or condition affecting a major organ system that would preclude dental implant surgery (e.g., malignant neoplasm or chemotherapy in the past 6 months, uncontrolled diabetes, major infection, Cushing's syndrome, metabolic bone disease, immunosuppression, blood dyscrasias, healing bone fracture, myocardial infarction or cerebrovascular accident within the last six months, etc.);
- Subjects with any contraindications for oral surgical procedures (e.g. scleroderma, etc.);
- Subjects with mucosal diseases (e.g. erosive lichen planus, mucous membrane pemphigoid, erythema multiforme, etc.) in the localized area around the study implant site;
- Subjects with bone diseases or conditions (e.g. Paget's disease, fibrous dysplasia, history of osteomyelitis, etc.) in the region of the potential study implant site;
- Subjects with a history of local radiation therapy in the head/neck area or osteonecrosis of the jaws;
- Subjects with any acute and untreated endodontic lesions or periodontal disease;
- Subjects receiving, or having a recent or long-term history of receiving oral or parenteral anti-osteoclastic agents [e.g., bisphosphonates, Xgeva® and Prolia® (denosumab); Forteo® (teriparatide), strontium ranelate, etc.], or anti-angiogenesis factors;
- Subjects who have major active substance abuse problems (e.g., alcoholism, opiate addiction, methamphetamine abuse, etc.);

- Subjects who are pregnant or intending to become pregnant during the duration of the study;
- Subjects who are heavy smokers (defined as >10 cigarettes per day or >1 cigar per day or equivalent of electronic cigarette vaping) or chew tobacco;
- Subjects with inadequate oral hygiene or who are unmotivated for adequate home care;
- Subjects who have physical or mental handicaps that would interfere with the ability to perform adequate oral hygiene;
- Subjects who have undergone administration of any investigational device within 30 days of enrollment in the study;
- Subjects who are allergic or otherwise sensitive to any materials likely encountered during the course of the study (e.g. titanium, suture materials, local anesthetics);
- Subjects with conditions or circumstances, which, in the opinion of the Investigator, would prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance or unreliability.

5.2.4 Pregnancy Test

Women of child-bearing potential (women who are not surgically sterile or postmenopausal (defined as amenorrhea for >12 months) must perform a pregnancy test (validated over-the-counter test) at Visit 1, before taking study required radiographs or CBCT scans to confirm that they are not pregnant. The test result must be documented in the source data. A woman who is pregnant or planning to become pregnant at any point during the study duration cannot be enrolled in this study and will be considered a screening failure.

If a woman becomes pregnant during the study, a protocol deviation form should be completed. The woman should be followed for the duration of the pregnancy, without the study required projected radiographs or CBCT until term, and the outcome of the pregnancy should be documented.

5.2.5 Full Mouth CBCT or Panoramic Radiograph + Local CBCT

A panoramic radiograph or full mouth CBCT scan must be available during screening to assess the complete dentition and for use in surgical planning. The screening panoramic radiograph or full mouth CBCT scan can be taken during the screening visit or be available from a previous date within 6 months of the implant surgery. If a panoramic radiograph is used for screening, then a localized CBCT scan is also required as a baseline.

5.2.6 Fabrication of Radiographic Media Holder

A radiographic media holder used to capture periapical (PA) radiographs throughout the study will be fabricated at screening. The device will be fabricated according to the instructions provided by Larheim and Eggen.[3]

5.3 Surgical Procedure (Visit 3)

This visit should be completed within 45 days of screening. In particular, the subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral hygiene
- Informed consent
- Tooth extraction
- Enrollment Inclusion/Exclusion criteria
- TN-SM device and implant placement
- Implant stability by clockwise torque with maximum at 20 Ncm to confirm stabilization
- Standardized periapical radiographs
- Intra-oral photographs

5.3.1 Tooth Extraction

Each potential subject will have the candidate site tooth extracted using standard procedures in an outpatient environment under local anesthesia. Curettage of the extraction socket will be performed to remove soft tissue remnants, including the periodontal ligament, granulation tissue, etc. Intra-oral photographs will be captured. Subjects will pre-rinse with chlorhexidine mouthwash 0.12% for 30 seconds immediately prior to the surgery.

5.3.2 Extraction Site Enrollment Inclusion Criteria

- Approximately 2mm of apical bone is available for positive seating of the implant;
- Placement of the selected implant leaves an HDD greater than 2mm in at least two directions, (i.e., mesially, distally, buccally, or lingually) between the implant surface and the most coronal aspect of the osteotomy. (For the purpose of clarity, HDD is measured from the outer surface

of the implant to the inner aspect at the crest of the socket walls.)

5.3.3 Extraction Site Enrollment Exclusion Criteria

- Any implant site where there is a dehiscence or fenestration of buccal or lingual plates of bone greater than 5mm in in any direction;
- Any implant site in which placement of the selected implant leaves an HDD greater than 5mm in any direction between the implant surface and the most coronal aspect of the osteotomy;
- Any site which provides primary implant stability after seating, as demonstrated by insertion torque of greater than or equal to 15 Ncm;
- Any site into which the implant is not or cannot be placed during the same visit as the extraction.

5.3.4 Surgery – TN-SM Device and Implant Placement

Each study subject will receive the TN-SM device to stabilize an implant in an outpatient environment. The procedure will be performed under local anesthesia following standard surgical and sterile techniques. After initial evaluation, surgical guides may be prepared in accordance with the surgeon's preference and standard practices. All implants will be placed in accordance with the IFU of the respective implant manufacturer, with possible departure related to the placement of the TN-SM. Prophylactic antibiotic treatment will be given according to the investigator's standard practice and shall be recorded. All prophylactic antibiotics and anesthesia given must be recorded on the Concomitant Medication Form. Prior to surgery, subjects should have teeth cleaned, if required, as per standard of care at the practice. Guided Bone/Tissue Regeneration (GBR/GTR) procedures will not be employed in this study as bone volume insufficiency and a large dehiscence are among Site Enrollment Exclusion Criteria.

The following is a detailed list of the procedures and measurements to be performed during the implant placement surgery visit:

- Following tooth extraction curette the socket;
- Prepare the implant bed according to the standard drilling sequence recommended by the implant manufacturer;
- Place the implant into the site according to standard procedures and apply the Extraction Site Enrollment Criteria to qualify the site.
- Assuming the implant has insufficient insertion torque, remove the implant. Prepare and apply the TN-SM device to the site according to the IFU - Document 50001-00 (Appendix 1). Re-insert the implant to its preplanned seating position into apical bone. Consistent with the IFU,

additional TN-SM may be applied, if necessary, to fill any residual space between the implant surface and surrounding bone, up to the height of crestal bone. Care must be taken to ensure proper final position of the implant by use of standard measures that may include manual control or use of a prefabricated surgical guide.

- After the TN-SM device cures around the implant for 15 minutes, implant stabilization will be tested by applying a clockwise torque of 20 Ncm. If the implant does not rotate with torque application, stabilization will be considered a success of the device and the event will be logged as a "success of immediate stabilization" with time since mixing noted. Should the implant rotate with torque application, the implant will be removed, the osteotomy refreshed with the last drill used prior to implant placement, and a second application of TN-SM will be prepared per the IFU and injected into the site along with a new implant. After the TN-SM device cures for 20 minutes around the implant, implant stabilization will be tested a second time by applying a clockwise torque of 20 Ncm. If the implant does not rotate with torque application, stabilization will be considered a success of the device and the event will be logged as a "success of immediate stabilization" with time since mixing noted. Should the implant rotate with torque application again after the second application, stabilization will be considered a failure of the device and the event will be logged as a "failure of immediate stabilization" with time since mixing noted. The loosened implant will be removed. The remaining Tetranite will be removed by curetting or drilling the osteotomy until a bleeding bone surface is obtained. The clinician may place a wider or longer implant as appropriate for the tooth position. Otherwise the site will be grafted as per a conventional staged approach.
- The implant platform will be covered by seating a cover screw and the soft tissue will be reapproximated with monofilament sutures, as needed.

The Investigator will prescribe Chlorhexidine rinse in addition to medications for infection control and post-operative pain control according to his/her standard practice. Standard post-operative instructions will be provided, including the use of Chlorexidine and antibiotics These instructions will also include a description of dietary restrictions to only soft foods for a period of up to two weeks following surgery.

5.4 Post-Operative Follow-up (Visit 4)

The subject will return for a post-operative visit at 14 days (± 5 days) following implant placement for a general assessment of wound healing and to remove sutures, if applicable. In particular, the subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral hygiene evaluation
- CBCT - Localized
- Intra-oral photographs
- Suture removal, if necessary

5.5 Implant Uncovering (Visit 5)

At 13 weeks (± 1 week) following implant surgery, the implant will be uncovered, the short-term implant stabilization will be checked, a healing or standard abutment will be placed, and the soft tissue adapted around the abutment. Short-term implant stabilization will be tested by applying a clockwise torque of 35 Ncm to the implant. If the implant does not rotate with torque application, stabilization will be considered a success of the device and the event will be logged as a "success of short-term stabilization". Should the implant rotate with torque application, the abutment will be removed, and the implant will be left and allowed to heal for an additional month and re-evaluated for successful integration. Lack of stabilization will be considered a failure of the device and the event will be logged as a "failure of short-term stabilization". In particular, the subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral hygiene evaluation
- Uncover implant, place healing abutment
- Implant stability by clockwise torque with maximum of 35 Ncm to confirm stabilization
- Standardized periapical radiograph
- Intra-oral photographs

5.6 Restorative Records (Visit 6)

At 3 weeks (+/- 2 weeks) following uncovering impressions/records will be taken for fabrication of a definitive crown restoration. In particular, the subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene Evaluation
- Restorative Records
- Standardized periapical radiograph
- Intra-oral photographs

5.7 Insertion of Definitive Restoration (Functional Loading) (Visit 7, Baseline)

At 4 - 6 months after implant surgery, and contingent upon good stability, the study implant will be loaded with an abutment and crown restoration in appropriate occlusion. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral hygiene evaluation
- Periodontal measurements
- Insertion of definitive restoration
- Standardized periapical radiograph
- CBCT - localized
- Intra-oral photographs
- Subject satisfaction

5.8 3-Month Follow-up (Visit 8)

Subjects will return at 3 months (± 2 weeks) post-loading for brief evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the

following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Standardized periapical radiograph
- CBCT - localized
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.9 6-Month Follow-Up (Visit 9, Primary Endpoint)

Subjects will return at 6 months (± 1 month) post-loading for an evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Standardized periapical radiograph
- CBCT - Localized
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.10 9-Month Follow-Up (Visit 9.5)

Subjects will return at 9 months (± 1 month) post-loading for an evaluation of the implant supported

definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.11 12-Month Follow-Up (Visit 10)

Subjects will return at 12 months (± 2 month) post-loading for an evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Standardized periapical radiograph
- CBCT - Localized
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.12 15-Month Follow-Up (Visit 11)

Subjects will return at 15 months (± 2 month) post-loading for an evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.13 18-Month Follow-Up (Visit 12)

Subjects will return at 18 months (± 2 month) post-loading for an evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Standardized periapical radiograph
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.14 21-Month Follow-Up (Visit 13)

Subjects will return at 21 months (± 2 month) post-loading for an evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check

- Oral Hygiene evaluation
- Periodontal measurements
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.15 24-Month Follow-Up (Visit 14)

Subjects will return at 24 months (± 2 month) post-loading for an evaluation of the implant supported definitive restoration and check possible adverse events. The subject will have the following procedures and/or evaluations performed and documented at this visit:

- Dental and medical history
- Concomitant medication
- Adverse event check
- Oral Hygiene evaluation
- Periodontal measurements
- Standardized periapical radiograph
- CBCT - Localized
- Intra-oral photographs
- Implant success
- Subject satisfaction

5.16 Protocol Related Procedures

5.16.1 Early Withdrawal

Any subject may withdraw from the study at any time without prejudice and will be offered an alternative treatment for his/her dental condition. Subjects will be advised of the need for the prescribed follow-up visits for their ongoing care, well-being, and collection of any safety data.

The Investigator may withdraw any subject from the study in the case of:

- Non-compliance with the protocol
- Failure to attend the follow-up visits
- Serious Adverse Event (SAE) or adverse event, which in the opinion of the Investigator prevents

the subject's further participation in the study.

The subject withdrawal will be documented on a study termination form and must include the reason for the subject withdrawal. Efforts should be made to capture the primary study endpoint for each subject prior to withdrawal, if possible.

5.16.2 End of Study

Once the subject is seen for the final visit at 24-months post-functional loading, the subject will have completed the study. This will be documented on a study completion form.

5.16.3 Subject Replacement Policy

Subjects withdrawn from the study after enrollment will not be replaced.

5.16.4 Protocol Deviations

Deviations from the procedures established in the protocol are not permitted. If a deviation occurs, the study center must record the deviation on the appropriate CRF. The sponsor shall be notified immediately of any deviations in informed consent or Inclusion/Exclusion criteria. The IRB should be notified according to the requirements of the local IRB.

Any deviation from the protocol (including deviations from the expected study visit windows) may jeopardize the study outcome. Non-compliance of the subjects, as well as of the Investigators, may lead to the closure of the respective study center.

6 Evaluation of Adverse Events

For the avoidance of doubt, all AE/SAEs as defined below should be collected, fully investigated and documented in the source document and appropriate case report form for all subjects from the time of the signing of the informed consent until the last protocol-specific procedure. Documentation includes dates of event, treatment, outcome, assessment of seriousness and causal relationship to the device and/or study procedure (rationale to be provided).

6.1 Definitions

6.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or surgical procedure. This definition includes events related to the investigational medical device or events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

6.1.2 Serious Adverse Event (SAE)

Any adverse event that:

- led to a death
- led to a serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- led to fetal distress, fetal death, or a congenital abnormality or birth defect

NOTE: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered to be a serious adverse event.

NOTE: Implant failures requiring the removal of the implant are to be considered a serious adverse event.

6.1.3 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. ***Any adverse event which the clinical investigator believes has even a possible relationship to the device will be classified as an ADE.***

6.1.4 Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

6.1.5 Unanticipated Serious Adverse Device Effect (USADE)

An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

6.1.6 Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is a serious adverse device effect which by its nature, incidence, severity or outcome

has been identified in the risk analysis report.

Table 2: *Summary of the classification for adverse events*

<table>
<tr><th>Adverse Events</th><th>Non-Device Related</th><th colspan="2">Device Related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

6.2 Assessment of Adverse Events

In the event of an adverse event, the investigator or another suitably qualified clinician who is trained in recording and reporting AEs and have been delegated to this role (such delegation must be captured in the study site delegation log) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event. Each adverse event should be assessed for seriousness, relationship to the study device or the procedure, severity, outcome, and expectedness, as described below, by the Investigator.

6.2.1 Seriousness

An adverse event will be described as serious if it meets the definition in Section 6.1.2. The rationale for the assessment shall be provided in a short narrative.

6.2.2 Relationship to the Study Device

The investigator should assess the relationship of the adverse event to the implanted product (e.g., TN-SM device and dental implant) and provide the rationale in a short narrative. The relationship should be assessed using the following categories:

- Definitely related – There is a reasonable causal and temporal relationship between the treatment with the study device and the adverse event.
- Possibly related – The causal and temporal relationship between the treatment with the study

device and the adverse event is less likely; however, the determination that there is no relationship cannot be made.

- Not related – A causal relationship with device application can be definitely excluded. By definition, all AEs/ADEs, with a start date before the surgery procedure at Visit 2 must be assigned a “not related” relationship with study device.

NOTE: Device deficiencies that might have led to an SAE are always related to the medical device.

6.2.3 Relationship to the Procedure

The investigator should assess the relationship of the adverse event to the implant procedure (e.g. placement of TN-SM device and the dental implant) and provide the rationale in a short narrative. The relationship should be assessed using the categories described in Section 6.2.2.

6.2.4 Severity

Each adverse event should be assessed by the investigator for its severity, or the intensity of an event experienced by a subject, using the following:

- Mild – discomfort noticed, but no disruption in daily activities; the event is easily tolerated by the subject
- Moderate – discomfort severe enough to reduce or affect normal daily activity
- Severe – Inability to work or perform normal daily activity and/or the subject’s life is at risk from the adverse event

The maximum severity observed is to be recorded, except if there is a significant worsening in an AE/ADE severity after device intake, then the change will be tracked as a new AE/ADE record as follows:

- The same wording describing the original AE/ADE must be used.
- Outcome of the initial entry should be designated as 'worsened'.
- The end date of the previous AE/ADE must equal the start date of the new AE/ADE.

6.2.5 Outcome

The outcome should reflect the status of the adverse event at the time of recording.

- Resolved - The subject fully recovered from the event without any sequelae. This option also applies when it is unknown whether there are sequelae.
- Resolved with sequelae - The subject’s condition stabilized despite the persistence of sequelae (e.g., lesion or medical condition which is a consequence of the event). This option does not

apply to irreversible congenital anomalies (see under “ongoing”).

- Ongoing - The subject has not yet recovered from the event. By convention, in the case of an irreversible congenital anomaly, the “Ongoing” option should be chosen and understood as “Not recovered/Not resolved“. The same applies to conditions that are not yet resolved, but are controlled by medication (e.g., diabetes, epilepsy) and therefore may not have any symptoms.
- Worsened - The severity of the AE/ADE increased.
- Fatal - The event is related to a death; whether it caused death or contributed to it. If the subject died of a different cause, prior to resolution of the AE/ADE, the outcome of this AE/ADE should be designated “Ongoing”, and not “Fatal”, and an end date should not be specified.
- Unknown - Knowledge of the current status of the AE/ADE is truly not available to the investigator (i.e. event was ongoing at last observation, but no further contact with the subject could be established). However, all efforts should be made to determine the outcome of any AE, especially that of an SAE/SADE.

6.2.6 Expectedness

If the adverse event is judged to be related to the device, the investigator will make an assessment of expectedness based on knowledge of the reaction and any relevant product information as documented in the IFU and current protocol. The event will be classed as either;

- Expected - the reaction is consistent with the effects of the device listed in the IFU and protocol;
- Unexpected - the reaction is not consistent with the effects listed in the IFU and protocol.

The table below presents the potential expected adverse device effects following the placement of TN-SM and insertion of dental implants.

Table 3: *List of expected ADEs following the placement of TN-SM and insertion of dental implants*

Biological complications		
Nature of effect	**Severity** *(mild, moderate, severe)*	**Frequency** *(very rare, rare, probable, frequent)*
• **Peri-implant mucositis**		
Bleeding (BOP Bleeding On Probing)	Mild	Probable
Bruising	Mild	Frequent
Delayed healing of the gum	Mild	Rare
Inflammatory papillary hyperplasia	Mild	Probable

Gingival/mucosal hyperplasia	Mild	Probable
Pain	Mild to Moderate	Probable
Recession/dehiscence of the gum	Moderate	Rare
Redness	Mild	Probable
Suppuration	Moderate	Rare
Swelling/gingival inflammation	Mild	Probable
• **Peri-implantitis**		
Bleeding (BOP Bleeding On Probing)	Mild	Probable
Bone loss around implant	Moderate	Probable
Bruising	Mild	Frequent
Infection at implant site without suppuration (not recurrent)	Mild to Moderate	Rare
Infection at implant site with suppuration (not recurrent)	Moderate	Rare
Recurrent infection at implant site without suppuration	Moderate to Severe	Rare
Recurrent infection at implant site with suppuration	Moderate to Severe	Rare
Systemic infection	Severe	very rare
Pain	Mild to Moderate	Probable
Swelling	Mild	Probable
• **Bone integration deficiency**		
Early loss/exfoliation (within 2 weeks after surgery)	Moderate	Rare
Late loss/exfoliation (after prosthetic restoration)	Moderate	Rare
Implant mobility (tactile horizontal or vertical)	Moderate	Rare to Probable
Crestal ridge height bone loss	Mild to Moderate	Rare
Fibrous tissue around implant	Moderate	Rare
Ectopic bone growth	Moderate	very rare
• **Non-plaque related**		
Chronic pain in connection with the dental implant	mild to moderate	Rare
Foreign body sensation	Mild	Rare
Material allergy	Moderate	very rare
Oro-sinus or oro-nasal intrusion/fistula	Severe	Rare

Permanent paresthesia, dysesthesia	Severe	very rare
Temporary or permanent paresthesia in the jaw	Severe	Rare
Mechanical complications		
Loosening of dental implant	Mild	Probable
Loss of dental implant	Mild	Probable
Migration of TN-SM	Mild	Probable
Fracture of TN-SN	Moderate	Rare
Other complications		
Aspiration of implant	Severe	Very Rare
Swallowing of implant	Severe	Very Rare
Aesthetic problem	Mild	Probable
Aspiration of component(s) (other than implant)	Severe	Rare
Jaw, bone fracture	moderate to severe	very rare
Phonetic difficulties	mild to moderate	Rare
Swallowing of component(s) (other than implant)	Severe	very rare
Hypersensitivity (adjacent teeth)	Mild	Rare

6.3 Procedure for Reporting Adverse Events

Adverse event reporting will begin at the time a subject provides written informed consent and ends after a subject withdraws from the study or completes the final study visit. For screen failure subjects, any AEs, ADEs, and DDs that occur from the time of informed consent up until the date on which the subject is deemed ineligible for the study will be recorded on a case report form. Only one AE/SAE case report form should be completed per event. To ensure patient confidentiality, the following reports will include the patient number only.

6.3.1 AE Reporting

In the occurrence of an AE, data should be entered into the AE case report form in the EDC system within five working days of awareness of the event. Safety reporting to the IRB should occur according to the requirements of the local IRB.

6.3.2 SAE Reporting

In the occurrence of a serious adverse event (SAE), expedited reporting requirements are followed.

The SAE case report form should be completed in the EDC within 24 hours of awareness of the event. RevBio will receive an automated notification generated by the EDC system. Safety reporting to the IRB should occur according to the requirements of the local IRB. It is recognized that in many cases SAEs will be treated in a medical rather than a dental environment and the investigator may not have immediate knowledge of the event. The investigator should report an SAE as soon as he/she has knowledge of the event within the above time frame irrespective of when the actual event occurred.

6.3.3 DD Reporting

The Investigator should report all device deficiencies to RevBio by submitting a description to the following email address: reg_complaints@launchpadmedical.com

If appropriate, the product shall be returned in appropriate packaging by courier (trackable method) directly to:

Regulatory Affairs
RevBio
600 Suffolk Street, Suite 250
Lowell, MA 01854

When a device deficiency leads to a potential AE (e.g. bleeding, pain, swelling, infection, peri-implantitis) the AE case report form in the database needs to be completed in a timely manner. Moreover, **device deficiencies with SADE potential** (e.g. nerve encroachment, sinus perforation, etc.) must be recorded in the SAE case report form and follow the expedited reporting requirements (**within 24 hours**).

6.3.4 ADE Reporting

Adverse device effects must be recorded and submitted to RevBio by completing the AE case report form in the EDC system within five working days of awareness of the event. Safety reporting to the Institutional Review Board (IRB) should occur according to the requirements of the local IRB.

Bone loss reporting: Continuous substantial reduction of the peri-implant bone level is a sign of failure of the implant system. The first European Workshop on Periodontology specified an average marginal bone loss of less than 1.5 mm bone loss within the first year after the insertion of the prosthesis, and thereafter less than 0.2mm annual bone loss as criteria for measuring success.[50] This has been a standard and a basis for success criteria since it was defined in 1993. A more recent systematic review article in 2012 reported 2 mm of bone loss being universally acceptable

at one year.[51] Based on this information and since this is a pilot study, the central radiologist will flag any bone level changes that are greater than 2 mm in the first year post-functional loading. The study manager will review the flagged values and discuss with the principal investigator whether the bone level change will be reported as an ADE.

6.3.5 SADE Reporting

In the occurrence of a serious adverse device effect, expedited reporting requirements are followed. The SAE case report form should be completed within 24 hours of awareness of the event in the EDC system. RevBio will receive an automated notification generated by the EDC system.

The product safety officer at RevBio will work with the Investigator to determine whether the event is anticipated (ASADE) or unanticipated (USADE). In case of USADE, the investigator must promptly notify its reviewing IRB as soon as possible, but no later than ten (10) working days after first learning of the event.

Since this is a multi-center study, RevBio will inform investigators at all participating centers of any reported USADEs related to this protocol and the study device. Copies of such external USADE reports should be forwarded to the IRB for review and a copy must be kept in the investigator site files.

6.3.6 Additional Safety Reporting

RevBio will report additional safety information to the centers that is relevant to the protocol or study device and may affect the risk/benefit ratio, the rights, safety or welfare of subjects, or the integrity of the study. Such reports may include notification of any changes to the instructions for use, any publications or interim reports, or any product recalls.

6.4 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of this study must be monitored and followed-up by the investigator until one or more of the following have occurred:

- The AE is resolved,
- Pathological laboratory findings have returned to normal,
- Steady state has been achieved, or
- It has been shown to be unrelated to the study products.

The outcome of an event will be pursued until resolution or until the last data queries are issued following the subject's last study visit. For screen failure subjects, ongoing AEs, ADEs, and DDs

must be followed and updated until the date the subject is deemed a screen failure. For subjects documented as lost to follow-up, ongoing AEs, ADEs, and DDs will not be followed. It is the responsibility of the sponsor to cooperate with the investigator to assure that any necessary additional therapeutic measures and follow-up procedures are performed.

The Clinical Events Committee (CEC) will be an independent board who will not be participating in the study and will adjudicate SAEs reported in the study.

7 Analysis of Endpoints

7.1 Analysis of Primary Endpoints

The primary endpoint in this pilot study will be summarized descriptively and no hypothesis tests are planned.

7.2 Analysis of Secondary Endpoints

All secondary endpoints will be summarized descriptively, and no hypothesis tests are planned. Secondary endpoints include implant success, dimensional changes of bone around the localized region of the implant as determined from radiographic data (periapical and CBCT), qualitative bone density changes in the localized region of the implant as determined from CBCT data, changes in periodontal health measurements, and subject satisfaction (esthetics, function, and level of pain). The radiographic data will be sent to a centralized location to be evaluated by a single reader using a calibrated measuring tool. The images will be provided to the evaluator individually coded and randomized by a third party to make the identity of the subject and the time point of image capture not identifiable by the evaluator, rendering the evaluator blinded. A central radiologist will assess evidence of encapsulation, bone dimensional changes and density values from the radiographs.

7.3 Analysis of Safety Endpoints

For analysis of safety endpoints, summary tables and/or listings will be provided for all adverse events by event category. Adverse events will also be summarized by relationship to the study device, implant procedure, by seriousness, severity and by outcome. Adverse events leading to discontinuation from the study will be tabulated. Except where indicated, a subject reporting the same adverse event more than once will be counted once when calculating the number and percentage of subjects with that particular event. Except where indicated, if a subject reports the same adverse event more than once, the strongest relationship to the procedure and/or device recorded for the event will be presented.

Adverse events that occurred in screen failure subjects will be presented separately.

7.4 General Statistical Methods

Only descriptive statistics will be used, including mean, standard deviation, and range.

7.4.1 Surgery and Supporting Procedures

Detailed information regarding the surgical procedure will be presented in listings. This will include information on crestal bone measurements, bone quality, evaluation of primary stability, and soft tissue procedures.

Details regarding other supportive procedures in the study will be presented in listings, including suture removal, second stage surgery, soft tissue procedures, impressions, temporary prosthesis placement, and definitive prosthesis placement.

7.4.2 Other Data Summaries

Concomitant medications will be presented in listings and also summarized by drug category. Protocol deviations will be summarized by deviation type and study center.

7.4.3 Subject Disposition

A detailed description of subject disposition will be provided using a CONSORT diagram and summaries of subjects falling in various subgroups of interest, such as enrolled but did not receive study treatment and early withdrawals. All enrolled subjects entered in the study will be accounted for in the summary.

7.4.4 Missing Data

Every effort will be made to minimize the amount of missing data. If a subject drops out of the study prior to completing their primary endpoint assessment, every effort will be made to measure their primary endpoint immediately prior to discontinuation if possible. No missing data will be imputed.

8 Data Management

The general data management procedures are described below, details can be found in the Data Management Plan. Required clinical data for this study will be collected and recorded in the clinical database using an electronic case report form for all study subjects from whom informed consent is obtained. Research Center numbers and subject numbers will be used to track subject information throughout the registry. The Principal Investigator or authorized designee is responsible for the timely completion and electronic signature of all electronic case report forms. The information entered into the database will be checked systematically by the data management for inconsistent, illogical and/or missing data using electronic and manual validation checks defined

in the Data Validation Plan. If validation of data leads to discrepancies, data management will generate electronic queries. The timely resolution of the queries is under the responsibility of the monitor and the investigators at the Research Center. The query process is an ongoing process starting with the first data entered into the database. The electronic clinical data system used for this study has a security system that prevents unauthorized access to the data and any deletion of data (audit and edit trail).

9 Study Management

9.1 Regulatory and Ethical Requirements

9.1.1 Informed Consent

Informed consent will be obtained from all subjects prior to study participation as described in Section 5.2.1.

9.1.2 Institutional Review Board

Prior to initiation of any study procedures, the protocol and informed consent will be submitted to an IRB for review and approval. In addition, any amendments to the protocol or informed consent will be reviewed and approved (if necessary) by the IRB. The sponsor must receive a letter documenting the IRB approval at the center prior to the initiation of the study at the center.

The investigator is responsible for providing the appropriate reports to the IRB during the course of the clinical study. This will include the following:

- Informing the IRB of the study progress periodically as required, but at a minimum annually
- Reporting any unanticipated serious adverse device effects within 10 working days of becoming aware of the event
- Reporting any deviations from the protocol that adversely affect the risk/benefit ratio, the rights, safety, or welfare of the participants, or integrity of the study
- Providing any other reports requested by the IRB

9.2 Reports and Record Management

9.2.1 Investigator Records

The following will be required from the investigator prior to the initiation of the study:

- A signed confidentiality agreement
- Signed and dated curriculum vitae of the investigator(s) and a copy of his/her dental license
- Signed financial disclosure

- A signed copy of the final protocol and any amendments
- A signed copy of the clinical study agreement with the sponsor
- IRB approval letter and IRB approved informed consent document

9.2.2 Case Report Forms

The investigator will be responsible for the accuracy of the data entered on the Electronic Case Report Forms (eCRFs). The investigator will also allow a RevBio representative and/or regulatory bodies to review the data reported on the case report form with the source documents as far as is permitted by local regulations.

9.2.3 Source Documents

Source documents are defined as the original point of entry of a specific data point. Source documents will include, but are not limited to, progress notes, electronic data, computer printouts, radiographs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigator and made available for inspection by authorized persons.

9.2.4 Records/Data Retention

Original radiographs, photographs, and study documents will be maintained at the research center in a file established for this study. All study documentation needs to be stored at the research center for at least fifteen (15) years following the completion of the study, as specified by the sponsor. The investigator should have access to the study documents in order to answer any queries associated with the study. All other study records will be kept by RevBio once the study has been completed. These records will be maintained at RevBio according to RevBio's standard operating procedures.

9.3 Monitoring

RevBio will assign a qualified individual to monitor the study. The general monitoring procedures for this study are described below, details can be found in the Monitoring Plan.

9.3.1 Study Initiation Visit

Once a Research Center receives IRB approval, the monitor will schedule a site initiation visit in order to make sure all study documents are in place and that all the site personnel that will participate in the study are trained on the study procedures. The monitor will ensure during the study initiation that the investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study:

- Understands the clinical protocol and relevant items outlined in the protocol (including

Inclusion/Exclusion criteria, AE and SAE reporting requirements);

- Understands and accepts the obligations to obtain informed consent;
- Understands how to document study data (especially the importance of having supporting documentation for AE assessment);
- Understands the information outlined in the investigator's brochure, including proper device usage
- Understands aspects of study device accountability (i.e. how to obtain the device, how to store the device, how to document device receipt, usage and return);
- Understands and accepts the obligation to obtain IRB review and approval of the protocol and informed consent, and to ensure continuing review of the study by the IRB;
- Has adequate facilities and access to an adequate number of suitable subjects to conduct the study

9.3.2 Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically, but at a minimum annually to review the following:

- The study is in compliance with the currently approved protocol/ amendment(s); deviations will be discussed with the responsible investigator, documented, and reported to the sponsor and IRB (according to the IRB policy);
- The study is in compliance with Good Clinical Practice (GCP) and with the applicable regulatory requirements;
- Only authorized investigators/ clinical personnel are participating in the clinical investigation;
- Device accountability including adequate supply at center, proper storage, and documentation of device traceability;
- The reported study data entered on CRFs are accurate, complete, and verifiable from source documents
- All adverse events and serious adverse events are reported correctly. In cases where there is missing information about an adverse event or missing evidence to support the investigator's assessment, a monitor will review and discuss the adverse event with the responsible investigator;
- The reason for a subject's withdrawal has been documented

The investigator will allow RevBio to have access to all study documents during each monitoring visit for a thorough review of the study's progress.

9.3.3 Study Closeout Visit

After the last subject has completed the study and the database has been cleaned, the closeout visit will be conducted at the center. The following tasks should be completed by RevBio or the monitor:

- Review any outstanding questions from the Clinical Investigation Report and organize the signature process;
- Ensure that the documentation and clinical investigation requirements were met;
- Collect outstanding documents;
- Ensure that adverse events were reported to the IRB according to the IRB's policy;
- Ensure that device accountability is complete;
- Organize the archiving of all study-related documents and remind the investigator of the obligation to retain the records

9.4 Study Termination

At study termination, a Clinical Investigation Report will be prepared by the sponsor, even if the study was terminated prematurely.

The study can be terminated early at the discretion of the investigator or the sponsor in the case of any of the following:

- Occurrence of adverse device effects unknown at the start of the study with respect to their nature, severity, and duration, or the unexpected excessive incidence of known adverse device effects;
- New scientific knowledge obtained after the start of the study showing the ethical claim of the study is no longer valid

9.4.1 Center Discontinuation

The study Center will be closed and the study terminated under the following circumstances:

- The Center is not recruiting a sufficient number of subjects or is unlikely to recruit a sufficient number of subjects;
- The Center does not respond to study management requests;

- Repeated protocol violations have been discovered that effect the integrity of the study or the study data

9.5 Protocol Amendments

Once the first subject has entered the study, any part of this study plan can be amended upon agreement of the sponsor and the participating principal investigators throughout the clinical investigation. Protocol changes will be kept to a minimum. Only those changes that are deemed essential to the successful completion of the protocol will be considered.

The reasons and justifications for the amendment will be included with each amended section of the document, and the amendment will include a version number and date. Once the investigator and the sponsor have accepted the changes, a written amendment to the protocol will be sent to the investigator for signature.

All significant protocol changes affecting the scientific soundness of the study or the rights, safety, or welfare of subjects which occur after the initial IRB approval, must be submitted for approval by each center to the IRB as an amendment to the original protocol before the changes can be implemented by the Investigator. Each investigational center will send a copy of the IRB approval letter for the amendment to RevBio.

Requests for clarifications to the protocol shall be discussed with the study monitor. The clarification statements will be sent to each investigator and will be kept in the appropriate file.

9.6 Publications

Analysis of data will be conducted by RevBio and the final report will be prepared by RevBio with input from the investigators. Any publications or presentations utilizing the data from this study must be reviewed by RevBio prior to submission according to the time frame specified in the clinical study agreement.

10 Protocol Signature Page

Protocol: DVAL18041

Title: Immediate Placement and Stabilization of Dental Implants with Tetranite® Stabilization Material in Mandibular and Maxillary Tooth Extraction Sites that Fail to Provide Adequate Primary Stability

Version: 3.0

I have read the foregoing protocol and agree to conduct the study as outlined. I agree that the examinations and follow-up visits required by the study protocol are in accordance with the standard treatment plan for dental implant subjects.

Signature:

Dr. Ryushiro Sugita UT Health Science Center – San Antonio	Date

Signature:

Dr. Michael Pikos Pikos Institute	Date

Received by Sponsor:

Printed Name of Study Director	Signature of Study Director	Date

References

1. Buser, D.; Weber, H. P.; Bragger, U.; Balsiger, C., Tissue integration of one-stage ITI implants: 3-year results of a longitudinal study with Hollow-Cylinder and Hollow-Screw implants. *Int J Oral Maxillofac Implants* **1991,** *6* (4), 405-12.
2. Ray, N. F.; Chan, J. K.; Thamer, M.; Melton, L. J., 3rd, Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res* **1997,** *12* (1), 24-35.
3. Baldwin, K.; Morrison, M. J., 3rd; Tomlinson, L. A.; Ramirez, R.; Flynn, J. M., Both bone forearm fractures in children and adolescents, which fixation strategy is superior - plates or nails? A systematic review and meta-analysis of observational studies. *J Orthop Trauma* **2014,** *28* (1), e8-e14.
4. Murray, C. M., Thomson, W.M., Leichter, J.W., Dental implant use in New Zealand: A 10-year update. *New Zealand Dental Journal* **2016**, 49-54.
5. McAnany, S. J.; Baird, E. O.; Qureshi, S. A.; Hecht, A. C.; Heller, J. G.; Anderson, P. A., Posterolateral Fusion Versus Interbody Fusion for Degenerative Spondylolisthesis: A Systematic Review and Meta-Analysis. *Spine (Phila Pa 1976)* **2016,** *41* (23), E1408-E1414.
6. Sarkar, S. K.; Lee, B. T., Hard tissue regeneration using bone substitutes: an update on innovations in materials. *Korean J Intern Med* **2015,** *30* (3), 279-93.
7. Farrar, D. F., Bone adhesives for trauma surgery: A review of challenges and developments. *International Journal of Adhesion and Adhesives* **2012,** *33*, 89-97.
8. Jensen, S. S.; Chen, B.; Bornstein, M. M.; Bosshardt, D. D.; Buser, D., Effect of enamel matrix derivative and parathyroid hormone on bone formation in standardized osseous defects: an experimental study in minipigs. *J Periodontol* **2011,** *82* (8), 1197-205.
9. Tsukeoka, T.; Suzuki, M.; Ohtsuki, C.; Sugino, A.; Tsuneizumi, Y.; Miyagi, J.; Kuramoto, K.; Moriya, H., Mechanical and histological evaluation of a PMMA-based bone cement modified with gamma-methacryloxypropyltrimethoxysilane and calcium acetate. *Biomaterials* **2006,** *27* (21), 3897-903.
10. Mousa, W. F.; Kobayashi, M.; Shinzato, S.; Kamimura, M.; Neo, M.; Yoshihara, S.; Nakamura, T., Biological and mechanical properties of PMMA-based bioactive bone cements. *Biomaterials* **2000,** *21* (21), 2137-46.
11. Heini, P. F.; Berlemann, U.; Kaufmann, M.; Lippuner, K.; Fankhauser, C.; van Landuyt, P., Augmentation of mechanical properties in osteoporotic vertebral bones--a biomechanical investigation of vertebroplasty efficacy with different bone cements. *Eur Spine J* **2001,** *10* (2), 164-71.
12. Leggat, P. A., Smith, D.R., Kedjarune, U., Surgical Applications of Methyl Methacrylate: A Review of Toxicity. *Archives of Environmental & Occupational Health* **2009,** *63* (3), 207-212.
13. Serbetci, K., Korkusuz, F., Hasirci, N., Thermal and mechanical properties of hydroxyapatite impregnated acrylic bone cements. *Polymer Testing* **2004,** *23* (2), 145-155.
14. Donaldson, A. J.; Thomson, H. E.; Harper, N. J.; Kenny, N. W., Bone cement implantation syndrome. *Br J Anaesth* **2009,** *102* (1), 12-22.
15. Tsukimura, N.; Yamada, M.; Aita, H.; Hori, N.; Yoshino, F.; Chang-Il Lee, M.; Kimoto, K.; Jewett, A.; Ogawa, T., N-acetyl cysteine (NAC)-mediated detoxification and functionalization of poly(methyl methacrylate) bone cement. *Biomaterials* **2009,** *30* (20), 3378-89.
16. Provenzano, M. J., Murphy, K.P., Riley III, L.H., Bone Cements: Review of Their Physiochemical and Biochemical Properties in Percutaneous Vertebroplasty. *AJNR Am J Neuroradiol* **2004,** *25*, 1286-1290.
17. Ormsby, R.; McNally, T.; O'Hare, P.; Burke, G.; Mitchell, C.; Dunne, N., Fatigue and biocompatibility properties of a poly(methyl methacrylate) bone cement with multi-walled carbon nanotubes. *Acta Biomater* **2012,** *8* (3), 1201-12.
18. Khandaker, M.; Vaughan, M. B.; Morris, T. L.; White, J. J.; Meng, Z., Effect of additive particles on mechanical, thermal, and cell functioning properties of poly(methyl methacrylate) cement. *Int J Nanomedicine* **2014,** *9*, 2699-712.

19. Topoleski, L. D.; Ducheyne, P.; Cuckler, J. M., Flow intrusion characteristics and fracture properties of titanium-fibre-reinforced bone cement. *Biomaterials* **1998,** *19* (17), 1569-77.
20. Serbetci, K., Hasirci, N., Recent Developments in Bone Cements. In *Biomaterials in Orthopedics*, Yaszemski, M. J., Trantolo D.J., Lewandrowski, K.U., Hasirci, V., Altobello, D.E., Wise, D.L., Ed. Marcel Dekker, Inc: 2004; pp 241-280.
21. Brown, W. E., Chow, L.C., A new calcium phosphate water-setting cement. *Cements Research Progress* **1986**, 352-379.
22. Bohner, M.; Lemaitre, J.; Ring, T. A., Effects of Sulfate, Pyrophosphate, and Citrate Ions on the Physicochemical Properties of Cements Made of β-Tricalcium Phosphate-Phosphoric Acid-Water Mixtures. *Journal of the American Ceramic Society* **1996,** *79* (6), 1427-1434.
23. Gruniger, S. E., Evaluation of the biocompatibility of a new calcium phosphate setting cement. *J Dent Res* **1984,** *63*, 200.
24. Khashaba, R. M.; Moussa, M. M.; Mettenburg, D. J.; Rueggeberg, F. A.; Chutkan, N. B.; Borke, J. L., Polymeric-calcium phosphate cement composites-material properties: in vitro and in vivo investigations. *Int J Biomater* **2010,** *2010*.
25. Yokoyama, A.; Yamamoto, S.; Kawasaki, T.; Kohgo, T.; Nakasu, M., Development of calcium phosphate cement using chitosan and citric acid for bone substitute materials. *Biomaterials* **2002,** *23* (4), 1091-101.
26. Bercier, A.; Goncalves, S.; Lignon, O.; Fitremann, J., Calcium Phosphate Bone Cements Including Sugar Surfactants: Part One-Porosity, Setting Times and Compressive Strength. *Materials (Basel)* **2010,** *3* (10), 4695-4709.
27. Zakaria, S. M.; Sharif Zein, S. H.; Othman, M. R.; Yang, F.; Jansen, J. A., Nanophase hydroxyapatite as a biomaterial in advanced hard tissue engineering: a review. *Tissue Eng Part B Rev* **2013,** *19* (5), 431-41.
28. Zhang, J.; Liu, W.; Schnitzler, V.; Tancret, F.; Bouler, J. M., Calcium phosphate cements for bone substitution: chemistry, handling and mechanical properties. *Acta Biomater* **2014,** *10* (3), 1035-49.
29. Kraus, T.; Moszner, F.; Fischerauer, S.; Fiedler, M.; Martinelli, E.; Eichler, J.; Witte, F.; Willbold, E.; Schinhammer, M.; Meischel, M.; Uggowitzer, P. J.; Loffler, J. F.; Weinberg, A., Biodegradable Fe-based alloys for use in osteosynthesis: outcome of an in vivo study after 52 weeks. *Acta Biomater* **2014,** *10* (7), 3346-53.
30. Kim, Y. H.; Park, J. W.; Kim, J. S., Is diaphyseal stem fixation necessary for primary total hip arthroplasty in patients with osteoporotic bone (Class C bone)? *J Arthroplasty* **2013,** *28* (1), 139-46 e1.
31. Kilpikari, J.; Lapinsuo, M.; Tormala, P.; Patiala, H.; Rokkanen, P., Bonding strength of alkyl-2-cyanoacrylates to bone in vitro. *J Biomed Mater Res* **1986,** *20* (8), 1095-102.
32. Maurer, P.; Bekes, K.; Gernhardt, C. R.; Schaller, H. G.; Schubert, J., Tensile bond strength of different adhesive systems between bone and composite compared: an in vitro study. *J Craniomaxillofac Surg* **2004,** *32* (2), 85-9.
33. Fedak, P. W.; Kieser, T. M.; Maitland, A. M.; Holland, M.; Kasatkin, A.; Leblanc, P.; Kim, J. K.; King, K. M., Adhesive-enhanced sternal closure to improve postoperative functional recovery: a pilot, randomized controlled trial. *Ann Thorac Surg* **2011,** *92* (4), 1444-50.
34. Smeets, N. M.; Bakaic, E.; Patenaude, M.; Hoare, T., Injectable poly(oligoethylene glycol methacrylate)-based hydrogels with tunable phase transition behaviours: physicochemical and biological responses. *Acta Biomater* **2014,** *10* (10), 4143-55.
35. Hatton, P. V.; Hurrell-Gillingham, K.; Brook, I. M., Biocompatibility of glass-ionomer bone cements. *J Dent* **2006,** *34* (8), 598-601.
36. Sehlke, B. M.; Wilson, T. G.; Jones, A. A.; Yamashita, M.; Cochran, D. L., The use of a magnesium-based bone cement to secure immediate dental implants. *Int J Oral Maxillofac Implants* **2013,** *28* (6), e357-67.
37. Chivers, R. A., Wolowacz, R.G.,, The strength of adhesive-bonded tissue joints. *International Journal of Adhesion and Adhesives* **1997,** *17* (2), 127-132.

38. Heiss, C.; Kraus, R.; Schluckebier, D.; Stiller, A.-C.; Wenisch, S.; Schnettler, R., Bone Adhesives in Trauma and Orthopedic Surgery. *European Journal of Trauma* **2006,** *32* (2), 141-148.
39. Guvendiren, M.; Messersmith, P. B.; Shull, K. R., Self-assembly and adhesion of DOPA-modified methacrylic triblock hydrogels. *Biomacromolecules* **2008,** *9* (1), 122-8.
40. Jo, S. H.; Sohn, J. S., Biomimetic adhesive materials containing cyanoacryl group for medical application. *Molecules* **2014,** *19* (10), 16779-93.
41. Shao, H.; Bachus, K. N.; Stewart, R. J., A water-borne adhesive modeled after the sandcastle glue of P. californica. *Macromol Biosci* **2009,** *9* (5), 464-71.
42. Murphy, J. L.; Vollenweider, L.; Xu, F.; Lee, B. P., Adhesive performance of biomimetic adhesive-coated biologic scaffolds. *Biomacromolecules* **2010,** *11* (11), 2976-84.
43. Shafiq, Z.; Cui, J.; Pastor-Perez, L.; San Miguel, V.; Gropeanu, R. A.; Serrano, C.; del Campo, A., Bioinspired underwater bonding and debonding on demand. *Angew Chem Int Ed Engl* **2012,** *51* (18), 4332-5.
44. Choi, J. W.; Kim, N., Clinical application of three-dimensional printing technology in craniofacial plastic surgery. *Arch Plast Surg* **2015,** *42* (3), 267-77.
45. Nedir, R.; Bischof, M.; Szmukler-Moncler, S.; Bernard, J. P.; Samson, J., Predicting osseointegration by means of implant primary stability. *Clin Oral Implants Res* **2004,** *15* (5), 520-8.
46. Mesa, F.; Munoz, R.; Noguerol, B.; de Dios Luna, J.; Galindo, P.; O'Valle, F., Multivariate study of factors influencing primary dental implant stability. *Clin Oral Implants Res* **2008,** *19* (2), 196-200.
47. Elakkiya, S.; Ramesh, A. S.; Prabhu, K., Systematic analysis on the efficacy of bone enhancement methods used for success in dental implants. *J Indian Prosthodont Soc* **2017,** *17* (3), 219-225.
48. Mombelli, A.; van Oosten, M. A.; Schurch, E., Jr.; Land, N. P., The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol Immunol* **1987,** *2* (4), 145-51.
49. Larheim, T. A.; Eggen, S., Measurements of alveolar bone height at tooth and implant abutments on intraoral radiographs. A comparison of reproducibility of Eggen technique utilized with and without a bite impression. *J Clin Periodontol* **1982,** *9* (3), 184-92.
50. Albrektsson, T., Isidor, F. In *Consensus Report of Session IV.*, Proceedings of the First European Workshop on Periodontology, , Quintessence Publishing: 1994; pp 365-369.
51. Papaspyridakos, P.; Chen, C. J.; Singh, M.; Weber, H. P.; Gallucci, G. O., Success criteria in implant dentistry: a systematic review. *J Dent Res* **2012,** *91* (3), 242-8.

1 Appendix 1 – Instructions for Use

2 Appendix 2 – Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty. Medical progress is based on research that ultimately must include studies involving human subjects.

The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

Medical research should be conducted in a manner that minimizes possible harm to the environment.

Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the Endpoint outweighs the risks and burdens to the research subjects.

All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non- vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non- written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

When a potential research subject who is deemed incapable of giving informed consent is able to

give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

3 Appendix 3 – Visual Analog Scale

	Subject Initials:		Visit 9 12 Month Follow-Up
	Subject ID:	-	
	Date:	/ / d d m m m y y	

To be completed by the patient - comment on the implant and supported crown

Pain associated with the implant and crown

Please mark your pain level be drawing one vertical mark | through the line below.

Painful _____ **No pain**

Satisfaction with the function

Please mark your pain level be drawing one vertical mark | through the line below.

Not Satisfied _____ **Highly Satisfied**

Satisfaction with the esthetics

Please mark your pain level be drawing one vertical mark | through the line below.

Not Satisfied _____ **Highly Satisfied**

Patient's Signature: _____ *Date:* / /
 d d / m m m / y y