A Prospective, Randomized-Controlled Evaluation of Biomet*3i´s* T3-Surface Configuration on the Certain Implant System for Implant Survival and the Preservation of Crestal Bone.

Protocol 3023

"OAK"

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Study Sponsor:
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ARTICLE I.

BACKGROUND

Since their introduction to dental therapeutics in the 1970's, root-form dental implants have evolved in function to address the needs of clinicians. Originally the mechanism for connecting abutments was an external-hex system with later versions having an internal connection mechanism. The internal connection systems themselves have seen numerous design changes all in the pursuit of providing a reliable support of abutments and also to promote better healing of the surrounding tissues. Both types of connection systems, however, are associated with the loss of some crestal bone after placement of a transmucosal abutment. The specific cause of this bone regression is unclear but has been associated with movement of the abutment, loading forces, and most recently there has been a focus on the microbiology of the region.

The placement of an implant-abutment interface at the level of alveolar bone is associated with a zone of inflammatory cells at this microgap junction (Gross 1999, Jansen 1997). There is greater bone loss for two-stage implants as compared with transmucosal implants that do not have a microgap interface (Broggini *et al.*, 2003). These observations suggest that an inflammatory stimulus originates at the implant-abutment interface, and there is a relationship between the extent of peri-implant inflammation and the magnitude of alveolar bone loss.

The source and nature of this stimulus remains unclear but likely reflects the presence of microbes within the implant-abutment and the crown interface, as reported in clinical studies (Quirynen and van Steenberghe, 1993; Persson *et al.*, 1996). The presence of microbes may be due from either contamination during implant placement or also at abutment connection. It is possible that microorganisms transit from the oral environment into the implant-abutment interface at prosthetic installation (Persson *et al.*, 1996). The phenomenon of microleakage has been described for most implant systems tested (Quirynen *et al.*, 1994; Jansen *et al.*, 1997; Guindy *et al.*, 1998; Gross *et al.*, 1999). Microbial access through the microgap has been reduced by use of washers between components, cement *vs.* screw-retained restorations, or inter-component varnish application (Besimo *et al.*, 1999; Piattelli *et al.*, 2001; Rimondini *et al.*, 2001). Additional evidence that the persistent inflammatory stimulus originates at the microgap interface is supported by data generated that show that when the interface is removed, only small amount of peri-implant inflammatory cells are found (Broggini *et al.*, 2003).

The amount of crestal bone lost after placement of a transmucosal abutment is usually less than 2 mm and unless there is chronic mucosal inflammation it is self-limiting. Nevertheless, crestal bone regression has clinical relevance because esthetic and restorative demands encourage the placement of implants in a more apical position. Relative to the original alveolar crest, crestal and subcrestal implants have demonstrated greater bone loss than have implants placed supracrestally (Todescan *et al.*, 2002; Piattelli *et al.*, 2003). Additionally, differences in response may exist for implants (Abrahamsson *et al.*, 1997) whose abutments have not been manipulated during healing (Todescan *et al.*, 2002).

Biomet***3i*** with over 20 years of dental implant design and commercialization has developed a new implant surface. The new T3 implant will combine a roughened surface in conjunction with the design features of the current Certain™ Tapered Implant System. This study will evaluate the T3 system for the preservation of alveolar crestal bone that is lost after the placement of a

transmucosal abutment. In this manner the new system may contribute to improved soft and hard tissue healing and affect in a positive manner the establishment of initial osseous fixation. This latter benefit is of specific interest for early- or immediate-loading cases where implant healing takes place while the implant is supporting a prosthesis.

Until recently, the drill unit's torque limiting feature was used to help establish the final or peak torque used to seat the implant. The implant drill unit, however, is neither accurate nor precise. The new procedures for inserting study implants will not use the drill unit and handpiece (an exception is made for very soft bone). The implant will instead be picked-up using a ratchet extension and the initial insertion is done by hand to establish proper alignment and to obtain initial fixation. The Torque indicating ratchet wrenches are then used to both drive the implant and assess the force resistance at each 1 mm of descent.

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OBJECTIVES

General Objective

This prospective, multicenter, randomized-controlled clinical study will evaluate the safety and performance of the T3 implants with a modified implant surface and make comparisons against the legacy Nanotite Certain Tapered Implant System for the amount of alveolar crestal bone loss after the placement of a transmucosal abutment.

Specific objectives include:

1. To document the integration success of all study implants by measuring and documenting implant immobility and resonance frequency assessment for up to 5 years.
2. To assess duration of failure-free performance while supporting restorations for five years
3. To measure and document the radiological changes in peri-implant crestal bone levels.
4. To measure and document insertional torque forces using torque-indicating ratchet wrenches.
5. The enrollment of at least 100 patients (up to 200 implants) within three months.

STUDY DESIGN

This will be a prospective, randomized-controlled study in which qualified patients with partial edentulism will be treated with at least two dental implants. Implant sites will be randomly assigned to receive either a test (T3 Nanotite Certain Tapered Prevail - BNPT) or control (Nanotite Certain Tapered - NINTxx) implant (80:20 – test – control randomization ratio). All implants will be placed in a single-stage manner using torque-indicating instruments to document the torque-insertion profile. At implant placement surgery test implants will receive Encode healing abutments whereas control implants will be provisionalised with prefabricated or standard abutments. For the test group an Encode Level Impression will take place at 10 weeks and individual final abutments and prosthesis placement at 3 months following implant placement surgery. A fixture level impression will be taken for control implants at week 10, followed by final restorations at month 3. All implants will be allowed to integrate without occluding forces and all restorations will be cemented. Resonance frequency assessment procedures will be done at implant placement surgery and at prosthesis insertion. Cumulative success rate and crestal bone regression will be the primary study endpoint. Enrollment will continue until 100 patients have completed final prosthetic treatment at the participating study centers. Additional control cases will be derived from on-going clinical trials of the NINT implants matched with the prospective study control group for baseline variables, restorative type (STR, fixed bridges), and implant dimensions. The additional control cases will bring the test and control groups to a 1:1 ratio and allow for more powerful analyses.

Study (null) hypothesis:

The functional success (survival and success rate) of the T3 implant to maintain integration and support of prostheses in this study will be no different than of the control implant. Moreover there crestal bone changes that take place after placement and loading of the T3 Certain Tapered Prevail (BNPTxxx – test implant) and Certain Tapered (NINTxx - control implant) will be the same.

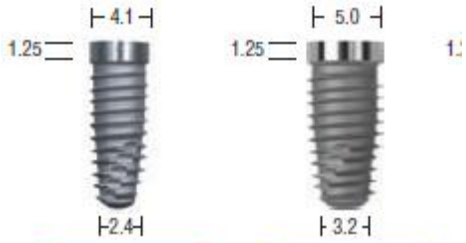
MATERIALS AND METHODS

Implants with similar geometry but with different surface roughness will be evaluated. All implants are titanium root-form dental implants. The test implant has an integrated platform switch feature, whereas the restorative components of the control implant will be matched.

The **test implant** surface is fashioned using calcium phosphate grit blasting and then etched using the Osseotite© dual acid-etching (DAE) process that establishes a surface roughness (Sa of about 1.2). The blasted and etched surface is present from the implant apex to 1.5 m from the implant collar above this is the original Osseotite surface (Sa 0.6) to the abutment seating surface. The entire length of the test implant has a discrete crystalline deposition of Calcium Phosphate nanoparticles (DCD). Implant length and diameter will be up to the discretion of the investigator within the limits of the following configurations.

4.0mm (D) x 3.4mm (P)	5.0mm (D) x 4.1mm (P)
BNPT4385	BNPT5485
BNPT4310	BNPT5410
BNPT4311	BNPT5411
BNPT4313	BNPT5413

Like the test implants the **control implants** consist of the same internal connection. The NanoTite Tapered implant (Biomet3*i*) is a threaded titanium alloy (Ti6Al4V) root-form dental implant featuring an internal connection system and associated restorative components. The Osseotite acid-etched surface is present from the apex to the bottom of the machined collar. To the acid-etched surface is added the NanoTite surface treatment of discrete crystalline depositions of calcium phosphate. These crystals range in length from 20 to about 100 nanometers. Restorations will be constructed using Biomet 3i components.



4.0mm (D)	5.0mm (D)
NINT485	NINT585
NINT410	NINT510
NINT411	NINT511
NINT413	NINT513

All implants will be available in diameters of 4 and 5 mm and lengths of 8.5, 10, 11.5, and 13 mm.

Patient Sample

A total of 100 patients will be enrolled in the study. Each qualified study patient will provide at least two implants to the data set. Enrollment will continue for three months or until 100 qualified patients (contributing at least 200 implants) have completed final prosthetic treatment. A qualified patient is one who meets admission criteria and has provided informed consent. Each patient will receive **either** test or control implants. Each patient will be randomly assigned to receive either Test or Control implants.

Patient Numbering

Only those patients found eligible for the study will be assigned a patient number. Those enrolled patients will receive a unique study identification consisting of a study number (3023), a center number (assigned number by the sponsor), a patient number (a sequential number beginning with #1), and a case number (a sequential number beginning with #1). For example, in patient number 3023-1-4-1, 3023 is the study number, 1 is the center number, 4 is the fourth patient enrolled in the study, and 1 is the first case.

Randomization

Randomization assignments will be included with the study materials provided by Biomet*3i*. Only those patients found eligible for the study will be assigned a patient number. Randomization cards will be supplied for each study patient number (80:20 – test – control randomization ratio). Each patient will either receive test OR control implants. Prior to implant placement surgery, the randomization assignment will be revealed on the card enclosed in the envelope. At the completion of the surgery, the randomization card will be adhered to the appropriate Case Report Form. The corresponding randomization code (Test or Control) will be recorded on the appropriate Case Report Form.

Study Materials and Components

A consignment of implants and healing abutments will be provided prior to study initiation. An inventory record shall be maintained to indicate the quantity and description of all materials received and utilized during the course of the study. At the conclusion of the surgical phase of the study components will be returned to the study sponsor.

Admission Criteria

Inclusion Criteria

1. Patients of either sex and any race greater than 18 years of age
2. Patients for whom a decision has already been made to use dental implants for the restoration of existing edentulism in the mandible or maxilla.
3. Patients must be physically able to tolerate conventional surgical and restorative procedures.
4. Patients must agree to be evaluated for each study visit, especially the yearly follow-up visits.

Exclusion Criteria

1. Patients with active infection or severe inflammation in the areas intended for implant placement.
2. Patients with a > 10 cigarette per day smoking habit.
3. Patients with uncontrolled diabetes mellitus.
4. Patients with uncontrolled metabolic bone disease where there is a diagnosis of the following: Osteomalacia, primary or secondary hyperparathyroidism, renal osteodystrophy, or Paget's disease of bone.
5. Patients with a history of therapeutic radiation to the head
6. Patients in need of bone grafting at the site of the intended study implant for augmentation purposes.
7. Patients who are known to be pregnant at the screening visit.
8. Patients with evidence of severe para-functional habits such as bruxing or clenching.

Treatment Planning and Exclusions

The following are conditions and situations that must be considered before the patient is to be qualified for participation in the study.

1. All implants will be placed in sites with native bone, with at least three months of healing since tooth extraction or four months from bone augmentation grafting procedure.

2. Patients in need of bone augmentation grafting at the site of the intended study implant are not candidates for this study. If at the time of surgery some lateral voids need to be filled this is acceptable and does not exclude the patient from the analysis.

3. All implants will be placed using torque-indicating ratchets that will allow recording of applied torque force at various depths during implant placement.

4. Each implant must be associated with one crown – it is not possible to use two implants to support one crown.

5. Prosthesis have to be fabricated based on Biomet 3i original components. The choice of components is up to the discretion of the investigator but the restoration need to be cemented.

6. Epicrestal seating surface positioning: The test and control implants are to be placed in an epicrestal position with the top of the implant collar placed at the mesial-distal crestal bone level as best possible. We recognize that not all alveolar ridges are flat and for the requested posterior sites it may be necessary to place an implant such that the distal portion is subcrestal and the mesial portion of the collar is supracrestal. In these scenarios please place the implant so that the mesial and distal portions of the implant are equally epicrestal as possible.

   While all implants are to be placed epicrestal if the depth of the osteotomy is over-prepared (e.g., the depth indicator shows that the osteotomy is 1 mm too deep) the implant should always be fully inserted into the osteotomy. If this results in a subcrestal placement this is preferred to a partially-placed implant. Therefore do not reverse or back-out the implant to have the seating surface epicrestal. Do not reverse or back-out the implant for any reason! It is better to be fully-seated in the osteotomy than to be epicrestal.

7. Proximity to teeth: Do not place an implant any closer than 1.5 mm from the crestal emergence margin of a proximal tooth.

8. Proximity to an adjacent implant: Do not place an implant any closer than 3 mm from the collar margin of a proximal implant.

9. Intra-ridge implant positioning: Please be mindful of placing the implant in the buccal-lingual center of the ridge to prevent loss of wall integrity. Whenever possible, select osteotomy positions that are equally distributed mesial-distally in the treatment region.

10. Conforming to the protocol's osteotomy preparation procedures: The drill sequence that is described in the study protocol is to be followed without exception. Please see the drill sequence chart in the Special Procedures section of this protocol. Do not undersize the osteotomy in soft bone conditions.

11. A case comprises all implants covered with one prosthesis. A case will consist of at least one implant with a crown.

12. Restorative cases will consist of single tooth restorations or unilateral short-span fixed prosthesis (<4implants). A patient can receive the maximum of two cases or 8 implants.

13. Cantilevers and pontics are not allowed in any of the study prostheses.

14. Test and control implants have different provisionalization procedures. A detailed description of the prosthetic procedures is part of the chapter "Specific procedures".

15. Temporary prosthesis are limited to flippers or resin bonded bridges for both test and control implants.

Schedule

Follow-up Evaluations

Visit:	**1**	**2**	**3**	**4**	**5**	**6 - 11**
	Screening	Day 0	Day 7	Week 10	Month 3	Months 6, 12, 24; 36; 48; 60

Dental / Medical History	X					
Clinical Evaluations		X	X	X	X	X
Randomization		X				
Implant Surgery		**X**				
Healing Abutment Placement		X				
Healing Assessment			X			
Impressioning				X		
Final Prosthesis Insertion					X	
Implant Mobility Assessment					X	X
RFA Analysis		X			X	
Radiography	PN	PA			PA	PA

PN = Panoramic radiograph
PA = Periapical radiograph of case site

All patients must have all study implants contributing to the study dataset placed during the same visit (one surgery date).

STUDY PROCEDURES

Visit 1 - Baseline (pre-surgical assessment)

Patients will be seen initially for evaluation and for collection of demographics, medical and dental conditions. An informed consent must be signed by the patient prior to enrollment in the study. A patient study number will be assigned at this time.

Patient specific bite blocks for all periapical X-Rays are a prerequisite to ensure reproducibility. The bite block can either be prepared at Visit 1 or at Visit 2 (before implant surgery); details of this process are described in the Special Procedures section.

A Panoramic radiograph of the existing dentition will be obtained. Information will be recorded on the corresponding Case Report Form. Please make sure that all subsequent radiographs (visit 2 till11) are periapical radiographs.

Visit 2 (Day 0) - Implant Placement Surgery

All surgeries will be performed by no more than two clinicians per study center. For sites where teeth have recently been extracted, the time from extraction will be recorded. The minimum of elapsed time is 3 months. Temporary prosthesis are limited to flippers or resin bonded bridges for both test and control implants.

Clinical Evaluation

An evaluation of the patient's general oral health will be done using the Gingival and Plaque Indices as described in the Special Procedures section.

Randomization

The randomization assignment will then be revealed on the card enclosed in the supplied envelope. Each patient will be randomly assigned to either the test or the control group. Each patient must receive at least one case. At the completion of the surgery the randomization card will be attached to the Admission / Randomization Assessment Case Report Form.

Osteotomy preparation

The gingival biotype (morphotype) will be assessed prior to implant placement:
Procedure: Perform a midcrestal incision on the center of the edentulous ridge. Raise a buccal flap and measure the the mucosal thickness of the unseparated palatal-lingual flap with a periodontal probe at the bone crest at the center of the future implant site.

Implants will be inserted using the general placement instructions provided in the Biomet3i Surgical Manual for the Tapered implant system. All surgeries will be performed under clean conditions keeping the implant sterile throughout placement. To avoid unnecessary soft-tissue damage, surgical retractors should not be used. We recommend using split flaps to minimize bone influencing factors. Efforts will be made to avoid over-reduction of the alveolar bone recipient site. Bone cutting procedures will be performed with a high-speed copiously irrigated hand piece.

All study implants **must** be placed during the same surgical visit and in an **epicrestal position** (level with the adjacent mesial and distal crestal bone).

The initial drill sequence for all cases will begin with the Pointed Starter Drill to make a small impression in the bone where the twist drills will be centered. Next will be the **2.0 mm twist drill** and this will be taken to the appropriate depth mark for the intended implant length. During the use of this drill the operator will make an assessment of the **bone density** at that site, scoring the density of bone as: (Type I (dense), Types II and III (medium/ normal), or Type IV (soft). Next use the 3.25 mm quad shaping drill **(QSD32XX)**. For 4.0 mm diameter implants, the last drill used will be the 4**.0 mm** quad shaping drill **(QSD4XX).** For 5.0 mm diameter implants, the last implant used will be the **5.0 mm** quad shaping drill **(QSD5XX)** . For implant placement in dense bone (Type I), tapping is necessary using the corresponding sized bone tap for each of the implant diameters (3.25mm- NTAP32xx; 4.0mm- NTAP4xx; 5.0mm- NTAP53s). The recommended drill speed for all drills is 1200 – 1500 rpm. The quad shaping drills must be used without pumping actions. Undersizing the osteotomy by one shaping drill diameter is recommended for implant placement in soft bone (Type IV).
For more information please see the Special Procedure Section.

Implant Placement

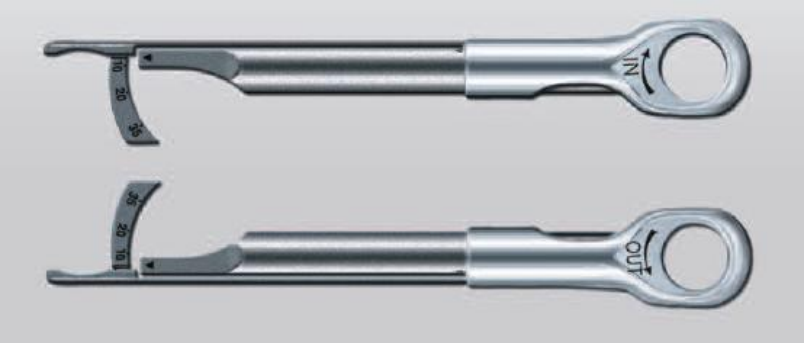
For all Biomet3i implant dental studies a specific effort will be made to record the torque force needed to drive the implant to its final position. These procedures describe how to use the required components and how to document the outcomes. All investigators participating in study implant placements should be trained in these procedures.

The procedures for inserting study implants will not use the drill unit and handpiece (an exception is made for very soft bone). The implant will instead be picked-up using a ratchet extension and the initial insertion is done by hand to establish proper alignment and to obtain initial fixation. The Torque indicating ratchet wrenches are then used to both drive the implant and assess the force resistance at each 1 mm of descent. A standard data form is used to collect these data as well as the RFA ISQ values (if obtained).

The sequence of procedures is as follows:

1) During osteotomy preparation the density of bone is determined. (If the density is very soft (Type IV) then the drill unit and handpiece may be used to initiate placement of the implant)
2) Insert the Certain Implant Ratchet Extension Driver (IMRExxx or IRExxx) into the adapter
3) Mount the H-TIRW onto the adapter
4) Position the implant into the osteotomy
5) A dental probe is used to measure the distance from the crestal bone (mesial-distal) to the implant seating surface and this value is recorded and used to determine the "Initial Drop" distance.
6) Hold the main body and torque arm together with the tumb and index finger.
7) Turn the wrench clockwise to insert the implant

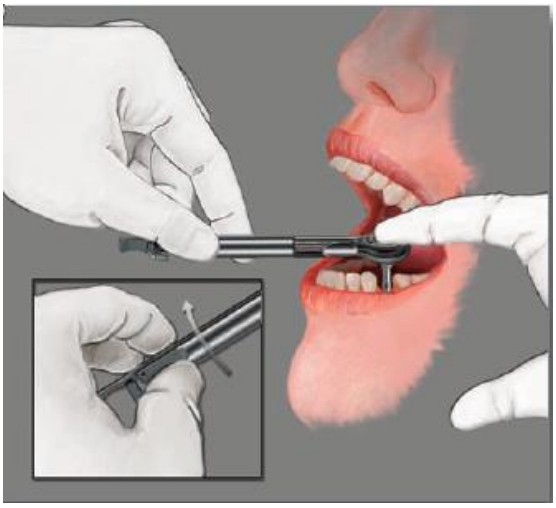
Note the proper side to use when inserting an implant.



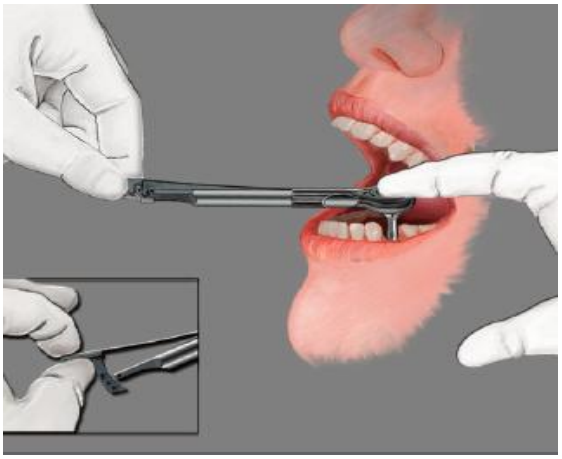
The Biomet3i High Torque Indicating Ratchet Wrench – H-TIRW

8) The implant is driven downwards while holding the mid-portion of the shaft. A torque measurement is made for each 1 mm descent into the osteotomy which is about 400 degrees of implant rotation.

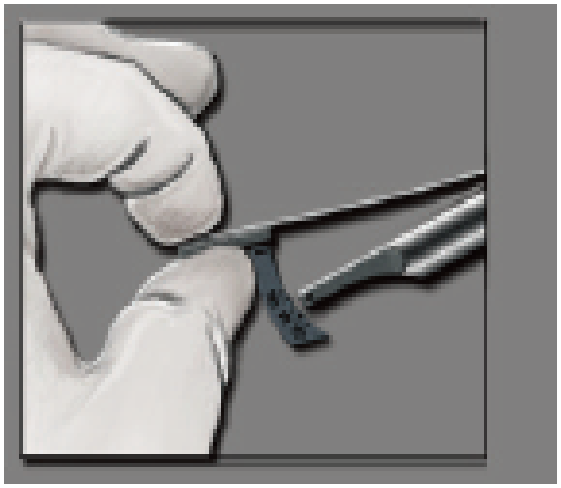
   For anterior sites each "swing" of the wrench may be about 160 degrees but for distal sites may be as low as 60°. Use as many wrench swings as needed to obtain 400° of implant rotation and then take a torque measurement using the torque measuring feature of the H-TIRW will be used to determine the amount of force that is being applied.



9) The H-TIRW has a second smaller "swing arm" that is used to measure the amount of force that is being applied. Holding only the curved handle (avoid touching the shaft of the wrench) apply torque and read the highest value on the indicator arm. Note that the wrench will continue to move as you apply force so you will be making a reading on a moving object.



10) This value will be document on the data collection form in Ncm. The data form has several possible entries for each of the force measurements during the implants descent.



[Note – for posterior maxillary sites where very soft bone is found the handpiece/drill unit may be used to initiate implant insertion until it is about 3 mm from its intended position at which time the L-TIRW is attached and used to drive the implant and measure the resistance force for the remaining 3 mm.]

Peak Torque - As the implant nears the intended ultimate vertical (seating) position use only the torque measuring feature to drive the implant to ensure that at the final implant positioning the peak amount of applied torque is measured and recorded.

General Instructions for the use of the H-TIRW are available on the Biomet 3i website at:
http://biomet3i.com/countries/en/directory/Pdf/ART1116_High_Torque_Indicating_Wrench.pdf
Please refer to the H-TIRW manual for an illustrated example of its use.

At the final seating of the implant record the operators subjective assessment of the final implant fit into the bone as either 1 = Tight, 2 = Firm, or 3 = Loose. Document if any **Dehiscences or Fenestrations** are observed during osteotomy preparation or implant placement. Record the final **Implant Placement** position relative to the mesial-distal crestal bone as supracrestal, epicrestal, or subcrestal.

Resonance Frequency Analysis

After removing the Torque Indicating Ratchet Wrench place a Type 15 Osstell Smartpeg into the implant and perform a **Resonance Frequency Analysis (RFA).** Obtain for each study implant an Implant Stability Quotient (ISQ) value. Care will be taken in cleaning and packaging the patient's Smartpegs to ensure they may be used for subsequent RFA measurements.

Healing Abutment Placement / Provisionalization

A single stage surgical protocol will be followed in which all study implants will have a healing abutment or a provisional abutment attached during study surgery. Test implants will be restored using one size-smaller healing abutments only (platform switch). For the control implants matched provisional abutments or healing abutments will be used. All provisional prosthesis for both test and control implants should be constructed to be flippers or raisin bonded bridges **out of occlusion.**
Tighten all healing abutments/provisional abutments with the Low Torque Indicating Ratchet Wrench to approximately 10-20 Ncm. The catalog number for the healing abutments will be recorded on the appropriate Case Report Form.

Radiography

Preparation of a bite block is essential to ensure proper radiographic alignment for subsequent periapical radiographs. Details of this process are described in the Special Procedures section.

A periapical radiograph after completion of the implant placement surgery will be obtained for each study implant site preferably in digital TIFF format. JPEGs will only be accepted above a size of 1MB per radio. The radiographs obtained after implant placement surgery will be considered baseline and used as reference for all subsequent radiographs.

Only periapical radiographs contain detailed information to assess crestal bone level changes, a panoramic scanning (orthomopantogram) does not fulfill the requested level of detail.

Failure to obtain a periapical radiograph at this and all subsequent study visits will disqualify the patient from the study.

For centers using digital radiography please name the file according to the following system: study number + center number + patient study identification number + date + tooth number. On conventional radiographs please write: study number + center number + patient study identification number + date + tooth number (for example, 3023-165-23-1, Oct-12-10, 23, 24, 25).
For centers using conventional radiographic films, only ***original radiographs*** can be used for evaluation and analysis. Be sure to use duplicate original film. *The radiograph must be examined by the investigator before the patient leaves the clinic to ensure that the radiographs are of sufficient quality so as to include the study implants and the crestal bone.*

Healing Period

A non-loaded healing period of three (3) months will be provided for all implants. Patients should be further instructed to:

1. rinse with 0.12% Clorhexidine solution twice per day for 7 days
2. avoid chewing at the treated sites,
3. avoid manipulating the sites with their tongue,
4. avoid probing the site with objects.
5. refrain from brushing the implant/surrounded tissues
6. gently brush the affected jaw with soft a soft brush only.

Visit 3 (Day 7) – Clinical Evaluations

Clinical Evaluation and Healing Assessment

During this visit patients will be interviewed to determine if any adverse events have taken place since the last visit. An evaluation of the patient's general oral health will be done using the **Gingival and Plaque Indices** as described in the Special Procedures section.

An evaluation of the status of the study implants will be done including signs or symptoms of implant failure, peri-implant suppuration and erythema. If they are observed the investigator may consider to take a periapical radiograph for inspection for signs of radiolucency. The investigator will make an assessment of implant status, and if a failure is determined, this will be recorded on the appropriate Case Report Form. In case of a spinning implant (not osseointegrated – but no signs of infection or radiolucency) the investigator may think about preparing a flap, close the site and have the implant heal in a two stage procedure. Those cases will be recorded as "Bail-Out" cases but included in the statistical analysis.

Visit 4 (Week 10) – Impressioning

Clinical Evaluation

During this visit patients will be interviewed to determine if any adverse events have taken place since the last visit. An evaluation of the patient's general oral health will be done using the Gingival and Plaque Indices as described in the Special Procedures section.

An evaluation of the status of the study implants will be done including signs or symptoms of implant failure, peri-implant suppuration and erythema. If they are observed the investigator may consider to take a periapical radiograph for inspection for signs of radiolucency. The investigator will make an assessment of implant status, and if a failure is determined, this will be recorded on the appropriate Case Report Form. In case of a spinning implant (not osseointegrated – but no signs of infection or radiolucency) the investigator may think about preparing a flap, close the site and have the implant heal in a two stage procedure. Those cases will be recorded as "Bail-Out" cases but included in the statistical analysis.

Encode Healing Abutment Impression – test implants only

Impressioning for the fabrication of the final abutments and prosthesis will take place no later than 10 weeks following implant placement. The Encode abutments will **not** be removed for the procedure – the impression will be taken of the entire ridge and the healing abutment in place. The impression tray will be sent to the dental laboratory, where the cast is poured and sent to Biomet 3i Valencia. Please see details of this procedure in the Special Procedures section of this protocol.

Conventional Impression – control implants only

An implant level impression will be made for all control implants using a standard pick-up impression coping.

Visit 5 (Month 3) – Final Prosthesis Insertion

Clinical Evaluation and Implant Mobility Assessment

An evaluation of the implants will be done prior to the placement of the prosthesis. Scores for gingival inflammation, plaque indices, implant mobility, peri-implant radiolucency, and suppuration will be recorded on the appropriate Case Report Form. Patients will be interviewed to determine if any adverse events have taken place since the last visit.

The evaluation of gingival inflammation as well as the scoring of the gingival and plaque indices have been described in the Special Procedures Section of this protocol. The scores will be recorded on the appropriate Case Report Form.

In case of a spinning implant (not osseointegrated – but no signs of infection or radiolucency) the investigator may think about preparing a flap, close the site and have the implant heal in a two stage procedure. Those cases will be recorded as "Bail-Out" cases but included in the statistical analysis.

For any implant associated with radiolucency, infection, pain, or neuropathy, a specific attempt will be made to determine implant mobility. Opposing force from two hand instruments (e.g. mirrors) will be applied to the abutment and any overt indication of mobility will be recorded as a failure. For all failed implants, a detailed report will be completed and provided to ***3i*** through the Case Report Form ADE (adverse Dental Event form) and Case Report Form ICF (Implant and Component Failure Form).

Resonance Frequency Analysis

After removing the healing abutment place a Type 15 Osstell Smartpeg into the implant and perform a Resonance Frequency Analysis (RFA). Obtain for each study implant an Implant Stability Quotient (ISQ) value. Care will be taken in cleaning and packaging the patient's Smartpegs to ensure they may be used for subsequent RFA measurements.

Final Abutment and permanent Prosthesis Attachment

Prosthetic parts must be of Biomet 3i origin. Prosthetic procedures will take place no later than three (3) months following implant placement. If a patient has more than one case contributing to the study dataset, all cases must be finished at the same time (during the same visit).

Test Implants: Due to the nature of the Encode Impression System only cement retained crowns/dentures are available. Restorations will be composed of milled patient specific abutments (3i Facility Valencia) and individual crowns/prosthesis (local lab) considering the platform-switch approach.

Control Implants: In order to minimize the variables between the two groups, control implants should as well be restored with cemented prosthesis. The prosthesis type, material and anchorage will be recorded on the appropriate Case Report Form.

Radiography

Periapical radiographs of all study implants will be obtained (be sure to use the fabricated bite block). Only original radiographs will be submitted to Biomet3i. For both, digital and conventional radiography, please name the x-rays as previously described (see visit 2).

Visit 6-11 (Month 6-60) – Follow up - Clincal Evaluation

Clinical Evaluation

An evaluation of the status of the study implants will be done according to the procedures described in the Special Procedures section.

Implant Mobility Assessment

For any implant associated with radiolucency, infection, pain, or neuropathy, a specific attempt will be made to determine implant mobility. The restauration will be removed and a post will be firmly attached to the implant to facilitate an evaluation. Opposing force from two hand instruments (e.g. mirrors) will be applied to the post. Any overt indication of mobility will be recorded as a failure. For all failed implants, a detailed report will be completed and provided to ***3i*** through the Case Report Form ADE (adverse Dental Event form) and Case Report Form ICF (Implant and Component Failure Form).

Radiography

Periapical radiographs of all study implants will be obtained (be sure to use the fabricated bite block). Only original radiographs will be submitted to Biomet3i. For both, digital and conventional radiography, please name the x-rays as previously described (please see visit 2).

SPECIAL PROCEDURES

Drilling sequence for TEST and CONTROL implants:

The BIOMET 3i Tapered Implant System

Why Tapered Implants Are Different

Due to the geometrical differences that exist between a tapered and a parallel walled implant, there are several important technique adjustments that are required.

In all tapered implant placement procedures, **the surgeon should determine the appropriate vertical position of the implant (supracrestal, crestal or subcrestal) at the time of osteotomy preparation.** The surgeon should prepare the tapered osteotomy so that when the implant is fully seated, the implant seating surface is at the desired position. The Tapered Implant Depth/Direction Indicator (NTDI) was designed to simulate the tapered implant position prior to placement. After preparation of the osteotomy with the final shaping drill, suction out the osteotomy to remove debris. Select the corresponding NTDI and place the tapered end into the osteotomy. Check the platform position (crestal or subcrestal) of the NTDI in relation to the adjacent bone. This position locates where the platform of the tapered implant will be positioned when properly placed. If during placement with the power drill, the tapered implant platform is higher in relation to the bone than was demonstrated with the NTDI platform, the clinician should consider using a hand ratchet to complete the implant placement so that the tapered portion of the implant body conforms correctly with the tapered portion of the osteotomy (Figure 1. Proper Subcrestal Placement).

Over Preparing the osteotomy depth and then placing the implant at a crestal level may result in a conical space around the apical and coronal aspects of the tapered implant with minimal thread engagement (Figure 2. Over Prepared Subcrestal Placement). This placement position may result in decreased implant to osteotomy contact, with contact occurring only along the parallel coronal portion of the implant, resulting in decreased stability of the implant.

Under Preparing the osteotomy depth and then placing the implant more apical relative to the prepared depth may result in increased pressure along the tapered portion of the osteotomy and on the collar contact areas of the implant profile (Figure 3. Under Prepared Subcrestal Placement). This may result in the implant spinning and losing rotational resistance.

The clinician may consider undersizing the osteotomy in soft bone (Type IV). For more detailed information on implant placement in soft bone, please refer to page 18 of this manual.

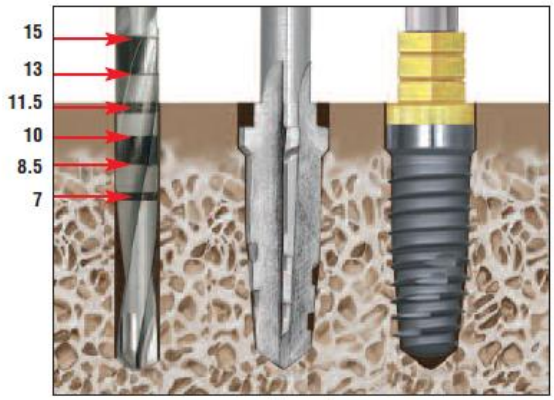


Figure 1
Proper Subcrestal Placement Of 11.5mm Implant

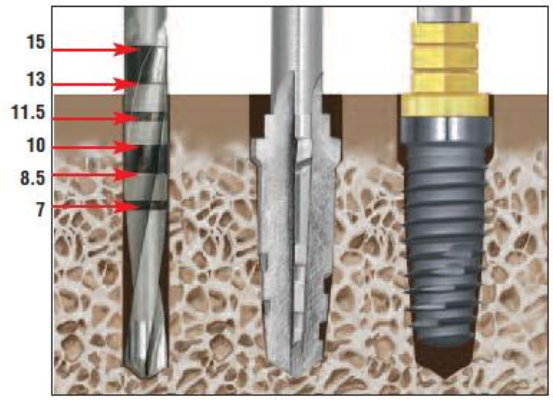


Figure 2
Over Prepared Subcrestal Placement Of 11.5mm Implant

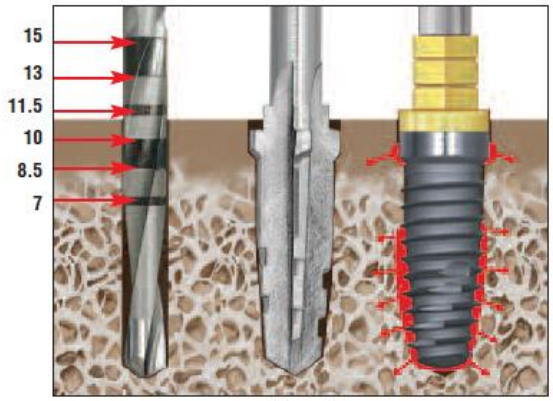
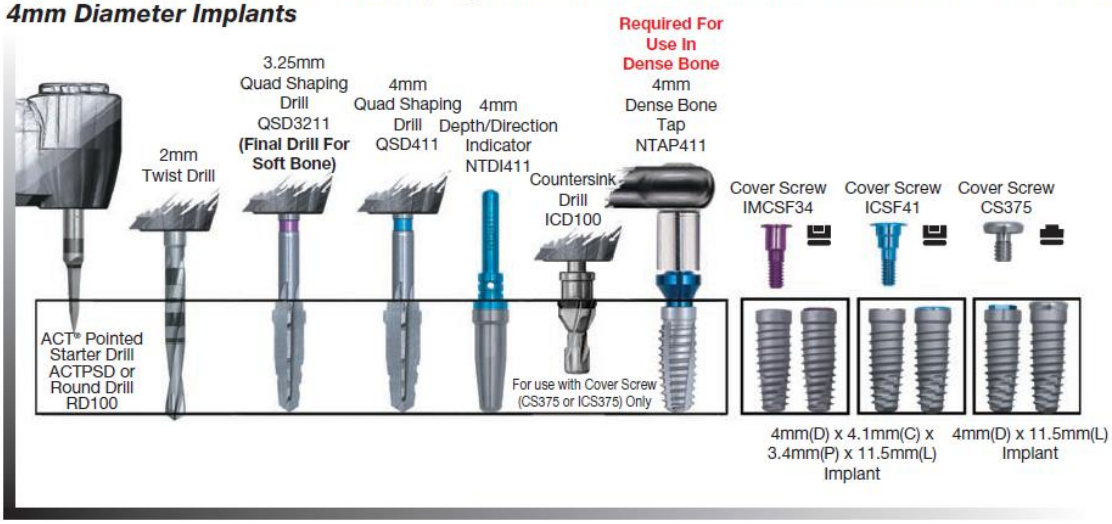
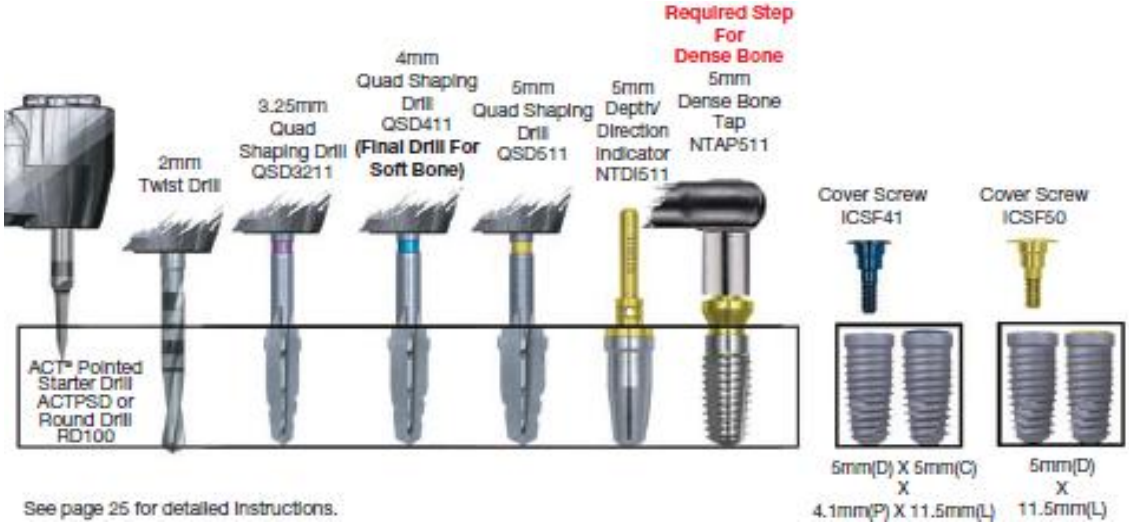


Figure 3
Under Prepared Subcrestal Placement Of 11.5mm Implant

Tapered Certain® PREVAIL® 4/3mm, Tapered Certain® Internal And External Hex Connection 4mm Diameter Implants



Tapered Certain Prevail 5/4 and Tapered Certain 5 mm implants:



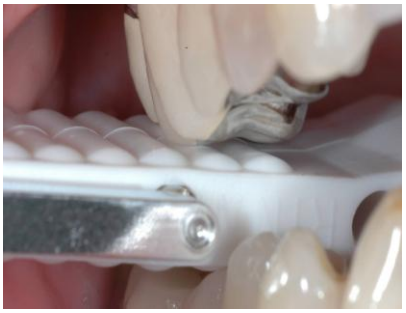
See page 25 for detailed instructions.

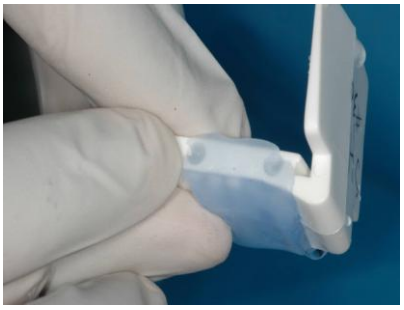
Clinical Evaluations

At various time points patients will be interviewed to determine if any pain or numbness has been experienced since the study surgery or the previous interview. The patient will be asked about their experience with the prosthesis to determine comfort, fit, retention, ability to chew, and ability to speak. The implant sites will then be examined for any evidence of implant failure including peri-implant suppuration and erythema. If signs or symptoms of implant failure are observed at any time during the course of the study, a periapical radiograph will be obtained and inspected for signs of radiolucency. The investigator will make an assessment of implant status, and if a failure is determined, this will be recorded on the appropriate Case Report Form.

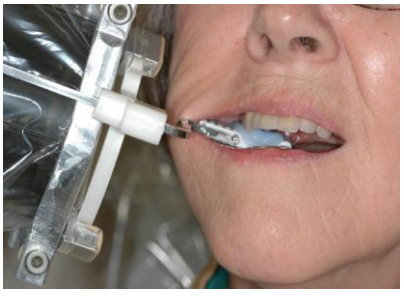
Radiographic Image Acquisitions

The investigator is responsible for obtaining radiographs for each patient case to determine the crestal bone levels, comparisons and analysis between visits, and accurate measurements of observed distances. Crestal bone analysis depends on good radiographs. Taking radiographs from the same exact position at each designated interval reduces the errors in measuring crestal bone levels. Ensuring parallelism and standardization of periapical radiographs for future comparison and analysis is best achieved using a paralleling technique. Repeatable positioning of periapical radiographs is made possible by modifying a plastic Rinn bite block with acrylic or impression material to register the incisal/occlusal position of the implant after placement. A bite block must be made from each of the patient's treated areas and stored for subsequent use.





Bite – Block Procedure (Example):
This procedure is an example of fabricating a re-usable device to use for standardized radiography. You may use your own method, but please do use one method for all radiographs of your study patients. For the following method you need a Rinn Film positioning device and thermoplastic impression material/light curing material.



1. Select the area of interest
2. Impress the occlusal surfaces of the opposing arch
3. Prepare the thermoplastic tabs/light curing material
4. Attach the tabs to the bite block
5. To stabilize the material, press a thin coating over the bite block, mold it to fill two of the holes on one side of the block

6. Position the bite block in the oral cavity
7. Instruct the patient to bite into the softened material and with your fingers, gently roll the material into the margins, creating an shallow impression of the occlusal surfaces opposing the area of interest

8. When the material is ready, try to re-engage the bite block again to ensure proper fit.
9. Slide the Rinn aligning ring as close the the face as possible and align the X-ray cone with the Rinn positioning ring in the usual way and expose the film
10. Label the assembled bite block with a patient ID and the selected area of interest by tooth number
11. Remove the positioning device from the mouth and develop the exposed film.
12. Disassemble the Rinn postioning apparatus and disinfect the molded bite block.
13. Store the molded bite block for subsequent radiographic exposures

Encode Procedure (for test implants only)

The Encode is a healing abutment system; it is composed of a titanium abutment and a screw (2 piece design). The abutment is intended to be installed immediately after implant placement, and left in place until installation of the final restoration. The Encode Impression System allows doctors to restore implants without the use of impression copings. Working above the gingiva without inserting and removing components spares the soft tissue from unnecessary trauma. As a result, soft tissue levels may be preserved and bone remodeling may be potentially minimized. The clinician simply makes a supragingival impression of the Encode Healing Abutment, sends it to the laboratory and in return, receives a patient specific abutment and crown ready for cementation.
Material, which has to be sent to your local lab:

- An impression of the Encode Healing Abutment and the opposing arch (please make sure that the height of the the abutment collar, not including the domed occlusal portion, should extend 2mm above the soft tissue (1mm minimum) on all sides).
- A Bite Registration
- Shade Selection

Special codes embedded on the occlusal surface of the Encode Healing Abutment are captured in the cast that is poured by your dental laboratory and sent to BIOMET 3i. These codes provide the essential information (implant depth, hex-orientation, platform diameter and Certain® Internal Connection interface) for placement of the implant analog in the master cast robotically (Robocast) and to design and mill the final abutment. Final abutments are available in zirconia and titanium. For more information please see detailed manuals in your investigator brochure.

Gingival Inflammation

An evaluation of gingival inflammation will be ranked under the following: (0) None, no sign of marginal red color around the gingival tissue; (1) Mild small color change of any portion of the gingival unit; (2) Mild color change of the entire gingival unit but with no edema; (3) Moderate has signs of glazing, redness, edema and/or hypertrophy; (4) Severe is characterized with marked redness, edema/hypertrophy, and spontaneous bleeding or ulceration.

Gingival and Plaque Indices

A global evaluation of the status of the area where the study implants were placed will be recorded using gingival and plaque indices. The **gingival index** will be ranked as follows: (0) Normal gingiva; (1) Mild inflammation, slight change in color, slight edema, no bleeding on probing; (2) Moderate inflammation, redness, edema and glazing, bleeding on probing; (3) Severe inflammation, marked redness and edema, ulcerations; tendency toward spontaneous bleeding.

The criteria for **plaque index** are as follows: (1) No plaque in gingival area; (2) No plaque visible by the unaided eye, but plaque is made visible on the point of the probe after it has been removed across surface at entrance of gingival crevice; (3) Marginal area is covered with a thin to moderately thick layer of plaque; deposit is visible to the naked eye; (4) Heavy accumulation of soft matter, the thickness of which fills out a niche produced by gingival margin and tooth surface; interdental area is stuffed with soft debris.

EVALUATION CRITERIA

Implant Integration Success

An implant will be considered successful if it is immobile at specific points in time. Additionally, long-term implant success will be achieved when tested with instrument pressure at follow-up evaluations with no evidence of persistent peri-implant radiolucency, no persistent or irreversible signs and symptoms of pain, infection, neuropathies, or paresthesia.

Additionally the correlation of initial stability (as reflected in the Insertion Torque Profile) and clinical success will be assessed. The individual implant will be considered the experimental unit. The Insertion Torque Profiles for failed implants will be compared with those from successful implant cases to determine if this baseline variable is predictive.

Radiological Crestal Bone Level Changes

Bone levels measured at three and six month, and all follow-up intervals from both treatment groups will be compared to those measurements observed at the time of implant placement surgery to derive *changes from baseline* values. Differences between groups will be calculated and used to determine if the crestal bone changes are different between groups. A difference of 5% will be considered relevant.

An impartial evaluator using standard operating procedures to ensure accuracy and precision will evaluate all radiographs. Radiographs will be examined under magnified field and electronic calipers will be used to make all measurements. The distance between the crestal bone level on the mesial and distal coronal aspects of each implant and the point where the bone attaches to the implant will be measured. To correct for any foreshortening that may occur due to minor angulation errors, this value will be expressed as an absolute value in millimeters and as a *normalized* value. The normalized value is determined by multiplying the absolute value by the difference between the observed length of the implant on the radiograph and the actual length of the implant.

Gingival Health

Gingival and plaque indices as well as gingival inflammation will be first recorded during the surgical assessment. They will then be collected at time of prosthesis insertion and at the follow-up evaluations. The first scores will serve as the baseline values for the subsequent evaluations.

ADVERSE DENTAL AND MEDICAL EVENTS

An adverse event is any event that threatens the success of an implant or the health of a patient.

Dental Adverse Events

Fracture of an implant, major infection at an implant site or any pathology that results or threatens to result in an implant's being non-usable is an adverse event and must be reported on the Dental Adverse Event form (ADE). If the implant fails, it must be reported on the Implant and Component Failure form (ICF). *Remaining implants which have survived are not considered implant failures but are included in the survival analysis as censored data.* Failure of an implant due to lack of osseointegration is considered an adverse event whether or not there is causative pathology, and is an implant failure for statistical purposes and must be reported on the Adverse Event (ADE) and Implant Failure (ICF) forms.

A dental adverse event will be assessed based on causality. Causality criteria are described as follows:

- Not related - an event for which sufficient information exists to indicate the etiology is unrelated to the test device.
- Possibly related - an event that follows a known or suspected response pattern, but could readily have been produced by a number of other factors.
- Probably related - an event that follows a known or suspected response pattern, is confirmed by improvement upon stopping or reducing treatment, and cannot be reasonably explained by the known characteristics of the patient's clinical state.
- Definitely related - an event that follows a known or suspected response pattern, is confirmed by improvement upon stopping or reducing treatment, and reappears upon repeated exposure.
- Unknown - relationships for which insufficient information exists.

Failure to use an implant due to improper placement is not an adverse event in the absence of pathology, but is censored data for the survival analysis and must be reported on the Implant Failure Form (ICF).

Medical Adverse Events

Death, serious illness or major trauma, whether implant success is affected or not, is an adverse event and must be reported on the Medical Event form (AME). A medical adverse event will be assessed based on causality (criteria described in dental adverse event section) and severity. Severity criteria are described as follows:

- Mild - the adverse reaction does not interfere in a significant manner with the patient's normal functioning level.
- Moderate - the adverse reaction produces some impairment of functioning but is not hazardous to health; may be uncomfortable.

- Severe - the adverse reaction produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health; this can lead to 1) death or decreased life expectancy, 2) an immediate life-threatening event, 3) inability to resume usual life pattern, 4) significant disability or incapacity.

STATISTICAL ANALYSES

The primary efficacy parameter will be the duration of implant survival (failure-free utilization or lack of mobility) from implant placement. The fraction of surviving implants and cases at the completion of 1, 2 and 5 years of function will be evaluated. Implant survival differences of >5 % will be considered clinically relevant. Clinical outcomes will be evaluated by clinical signs and symptoms of implant failure and dental and medical events.
Secondary efficacy parameters will be prosthesis survival and procedural success. For each patient, survival time after study surgery will be calculated by the duration of failure-free, intervention-free, duration of support of a prosthesis. Implant survival curves will be estimated for the Test and Control treatment group and these will be compared using the Log Rank or Wilcoxon tests. Survival rates at six months (Study Visit 6), one-year (Study Visit 7) and 5 years (visit 11) will be computed for each treatment group, and compared using chi-square. The sample size determinations were based upon survival to the five-year point as a measure of efficacy.

A secondary outcome question of this study is the equivalence in the changes in alveolar crestal bone between the modified implant (T3) and its predecessor the Certain™ implant. In previous studies of Biomet3i implants (Calvo-Guirado 2011, Zetterqvist 2009; Östman et al. 2010), crestal bone change-from-baseline values have ranged from a mean of 0.37 mm to 1.2 mm at the six month (Visit 6) time point. For purposes of this study there will be an assumption that the control implant will have a change-from-baseline mean value of 0.75 mm at the 6 month (Visit 6) time period. To declare equivalence the Test implant system will need to have a crestal bone change-from-baseline mean bone level regression of 0.75 $\pm$ 0.15 mm; or to declare superiority a mean value of 0.55 mm or lower. For the functional evaluation of crestal bone regression will be determined for each of the treatment groups at 3 months (Visit 5), six months (Visit 6) and at each of the annual study visits. The significance of these changes from baseline will be evaluated at each time point using a paired t-test or a Wilcoxon signed rank test. At each time point the treatment groups will be compared using the analysis of variance or the blocked Wilcoxon test, as appropriate. Analysis to determine association with other variables will use "exact" rather than "asymptomatic" methods where necessary.

The Test and the Control implants will be considered the experimental units. The influence of the length and diameter of the implants as a covariate on survival will be determined during the analysis. The comparability of the Test and Control treatment groups will be determined with regard to demographic

variables (including age, gender) and variables relating to the severity of disease (such as existing dental pathology and dental hygiene). For the continuous variables age and evaluations of oral hygiene and the gingival biotype, the groups will be compared using either analysis of variance or blocked Wilcoxon, as appropriate. For the qualitative variables, sex, smoking habit, existing dentition, concomitant conditions, a chi-square contingency table analysis will be used. Analysis to determine association with other variables will use "exact", rather than asymptotic methods where necessary.

All dental and medical events will be tabulated. Treatment groups will be compared using chi-square with regard to the number of patients in each group who experience those events most frequently and are assessed by the investigator as being probably or definitely related to the investigational treatment. Statistical significance will be declared if the two sided p-value is > 0.05.

Calvo-Guirado JL, Gómez-Moreno G , López-Marí L, Guardia J, Negri B, Martínez-González JM. Crestal bone loss evaluation in osseotite expanded platform implants: a 5-year study. Clin Oral Impl Res 2011 21 MAR 2011 DOI: 10.1111/j.1600-0501.2010.02130.x

Zetterqvist L, Feldman S, Rotter B, Vincenzi G, Wennström JL, Chierico A, Stach RM, Kenealy J N. A Prospective, Multicenter, Randomized-controlled Five-year Study of Hybrid and Fully-etched Implants for the Incidence of Peri-implantitis. J Periodontology 2009 Dec 23(14pp.)[Epub] 2010;81:493-501.

Östman PO, Wennerberg A, Albrektsson T. Immediate occlusal loading of NanoTite Prevail implants: a prospective 1-year clinical and radiographic study. Clin Implant Dent Relat Res. 2010 Mar;12(1):39-47.

Records / Data Retention

Case Report Forms (CRFs) will be prepared by 3i for the collection of data. These forms will be used for the entire duration of the study. The original of the completed CRF will continuously be collected by the study monitor for analysis and storage. Only original radiographs (or digital images saved on a disc) will be accepted and maintained by the study sponsor. Investigators will keep a copy of the CRFs and will maintain these records for at least three years.

CRFs are required for all individuals enrolled in the study. These should be filled out in ballpoint pen and be legible and complete. Errors should be lined out, such that the information being lined out can still be seen. Initial and date the correction. Do not use correction fluids. CRFs will be considered complete when all data queries have been fully addressed.

All original CRFs are the property of Biomet 3i. They may not be made available to a third party in any fashion, with the exception of authorized representatives of appropriate government agencies or business partners, who must accept the same level of confidentiality.

Protocol Amendments

Any proposed change to the protocol is to be discussed with the clinical monitor in a timely manner. Once both the investigator and the sponsor have accepted the changes, a written addendum to the protocol or a revised protocol will be sent to the investigator for signature. Copies of addenda and revised protocols will be kept by both parties in their respective files.

Protocol Deviations and Violations

Occasionally during the study, deviations from the procedures established in the protocol may occur. Any deviation from the protocol is reason to contact a clinical monitor without delay. The deviation will be documented on the appropriate data form. Enrollment and treatment of patients who do not meet Admission Criteria will be considered a protocol violation.

Data confidentiality, Verification and Monitoring

A Biomet 3i Study Monitor will be assigned to monitor the study. Before the start of the study, the monitor will contact the principal investigator to ensure that the protocol and study logistics are well-understood. Specific instructions as to the proper completion of the clinical data forms will be provided. The monitor may contact the investigator on a monthly basis for verbal updates.

At various time points in the study, a review of patient records may be needed to ensure accuracy of data. In this case study patient charts must be made available to the study monitors during site visits.

SIGNATURE PAGE

TITLE: A Prospective, Randomized-Controlled Evaluation of Biomet*3i´s* T3-Surface Configuration on the Certain Implant System for Implant Survival and the Preservation of Crestal Bone.

CODE NAME: OAK

PROTOCOL #: 3023

The signatures of the investigator and representative of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to Good Clinical Practices and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality.

It is agreed that the protocol contains all the necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the proper approvals (Institutional Review Board or Ethics Committee if required).

INVESTIGATOR:

_____
Print Name

_____ _____
Signature Date

SPONSOR:

_____
Print Name

_____ _____
Signature Date