Protocol 2406

A Prospective, Observational Multicenter Study of the Certain® PREVAIL™ Implant System in Maxillary and Mandibular Regions

"The PREVAIL Multicenter Study"

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Study Sponsor:
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BACKGROUND

Dental implants have enjoyed increasing success with the introduction of various design improvements. In 1995 3i introduced the incremental cutting edge (ICE), in 1996 the acid etched surface (Osseotite) feature was released, and in 2002 the internal connection system with a "click" feedback feature was introduced. These design components helped to ensure proper initial placement and long-term maintenance of implant function.

The remodeling of crestal bone that takes place after the installation of a transgingival abutment is one phenomenon that has been recently addressed by modification of the implant design. According to a biological-width hypothesis, a static colony of microbes exists in the implant-abutment microgap. The metabolic waste materials from these microbes pose an inflammatory barrier to osteogenic activity and within this inflammatory infiltrate zone the crestal bone recedes. At some distance from the microgap the concentration of inflammatory material decreases due to dilution in the interstitial fluids and reaches a threshold where osteogenic cellular activity can again take place. This is the point where no further loss of crestal bone is observed.

In support of this biologic-width hypothesis is the observation that by increasing the distance from the implant-abutment microgap to the crestal bone the amount of crestal remodeling is decreased. The assumption is that by moving the microgap the threshold of inflammatory material is moved proportionately.

Use of an abutment of a smaller diameter than the implant surface upon which it is placed serves this purpose of moving the microgap and manipulating the extent of crestal bone remodeling. This practice is referred to as platform switching and is actively being evaluated in clinical studies. Attention is also being focused on the changes in the soft tissues supported by the crestal bone.

The design of the Certain PREVAIL implant includes an integrated medialized seating platform that moves the microgap away from the crestal bone and may therefore help reduce the amount of soft and hard tissues changes observed with treatment using standard implant designs.

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OBJECTIVES

This prospective, multicenter, observational clinical study will evaluate the performance of the Certain® PREVAIL™ implant system.

Specific objectives include:

- To document the radiological changes in crestal bone level around the implants.
- To document the performance and safety characteristics of the Certain PREVAIL implants when used in mandibular and maxillary regions.
- The enrollment of 15 patients at each study center within twelve months.

STUDY DESIGN

This will be a prospective, observational study in which qualified patients with partial or complete edentulism will be treated with the Certain PREVAIL dental implant system and components. Restorations will consist of single tooth replacement, short-span fixed bridges, overdentures and full dentures. *Each patient may only have 1 case included in the study*. All implants will be placed in a single-stage manner with healing abutments placed at implant placement surgery and temporary provisionalization will take place after two months of healing. Enrollment will continue until 15 patients (15 cases) are treated at each study center.

Study (null) hypothesis:

The preservation of crestal bone for the Certain PREVAIL implants will be the same as that of standard non-platform switched implants from contemporaneous studies.

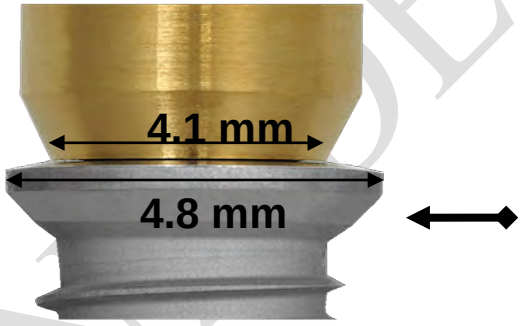
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MATERIALS AND METHODS

Test Device

The Certain PREVAIL implant system consists of an internal connection, threaded titanium alloy implant and associated restorative components. At the coronal portion, the implant diameter expands in a manner similar to the Osseotite XP implant design. The implant seating surface is medialized to move the implant-abutment interface away from the crestal bone. The implant is lateralized where the seating surface tapers at a 15º angle. The Osseotite acid-etched surface is present from the apex to the maximum diameter area where the platform tapers inward. The body of the implant is straight and the ICE incremental cutting feature is included at the apex.

For this study the Certain PREVAIL implants will be available in diameters of 3.25, 4, and 5 mm (these are the dimensions of the mid-portion of the implant body) and lengths of 8.5, 10, 11.5, and 13 mm. The largest coronal diameter is 4.8, and 5.8 mm respectively. Certain PREVAIL implants will be temporized with EP healing abutments.



The implants should be placed subcrestal to ensure engagement of the expanded platform with the bone crest.
(IIOS45XX shown)

Technical Dimensions – Certain® PREVAIL™ Implant System

Catalog No.	*Body Diameter*	*Max Dimension*	*Platform Dimension*	*Bevel Height*	*Medialization Factor*
IIOS34XX	3.25mm	4.1mm	3.4mm	0.1mm	0.35mm/side
IIOS45XX	4.0mm	4.8mm	4.1mm	0.1mm	0.35mm/side
IIOS56XX	5.0mm	5.8mm	5.0mm	0.1mm	0.40mm/side

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Patient Sample

Enrollment will continue at each of the participating study centers until 15 qualified patients have been enrolled. Each patient may only have one case contributing to the study database. Up to 120 implants may be placed at each participating center.

Patient Numbering

All enrolled patients will receive a unique study identification consisting of a study number (2406), a center number (assigned number by the sponsor), a patient number (a sequential number beginning with #1), and a case number (all patients will be assigned to case #1). For example, in patient number 2406-1-4-1, 2406 is the study number, 1 is the center number, 4 is the fourth patient enrolled in the study, and 1 is the case number.

Study Materials and Components

Study materials will be supplied by 3i. Study product will be kept in a locked and secure storage area, accessible only to those individuals authorized to dispense these materials. An inventory manifest will be maintained by the investigator or another nominated individual that includes details of materials received clear record of when they were dispensed, and to which patient. This inventory record shall indicate the quantity and description of all investigational materials on hand at any time during the course of the study. The sponsor has the right to ask for this manifest to qualify usage and quantity dispensed during a reasonable elapsed time of usage. At the conclusion of the surgical phase of the study, the investigator must provide an account of all used, partially used and unused investigational materials to the study monitor.

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 treating an existing dental condition specifically:

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- The dental implants will be restored as single tooth restorations, short-span fixed bridge, overdenture, or fixed full denture.
- A temporary healing abutment will be placed on the implant during the implant placement surgery (single stage procedure).

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 visit.

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 metabolic bone disease.
5. Patients who have had treatment with therapeutic radiation to the head within the past 12 months.
6. Patients in need of allogenic bone grafting at the site of the intended study implant for augmentation purposes. Grafting for treatment of dehiscence or fenestration must have occurred at least 8 weeks prior to implant placement surgery.
7. Patients who are pregnant at the screening visit.
8. Patients with evidence of severe para-functional habits such as bruxing or clenching.
9. Patients with less than 6 weeks healing time post tooth extraction at the intended treatment site.

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Schedule

Follow-up Evaluations [----------]

Visit:	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 9**
	Screening	Day 0	6 weeks	Month 2	Months 4 -6	Month 6	Months 14 to 38
Dental / Medical History	X						
Implant Surgery		**X**					
Healing Abutment Placement		X					
Click Assessment			X	X			
Impressioning for Temporary Prosthesis			X				
Temporary Prosthesis Attachment				X			
Impressioning for Permanent Prosthesis					X		
Permanent Prosthesis Attachment					X ◄——►	X	
Clinical Evaluations		X	X	X	X	X	X
Radiography	D/Pano	D/PA	D/PA	D/PA		D/PA	D/PA

Pano = Full mouth radiographs
PA = Periapical radiograph of case site
D = Digital

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. Radiographs of existing dentition will be obtained. Information will be recorded on Case Report Form 1-1.

Visit 2 (Week 0) - Implant Placement Surgery

All surgeries will be performed by no more than two clinicians per study center. Do not use two implants to support one crown. For sites where concomitant procedures such as recent tooth extractions, the details of the procedure will be recorded on Form 2-1.

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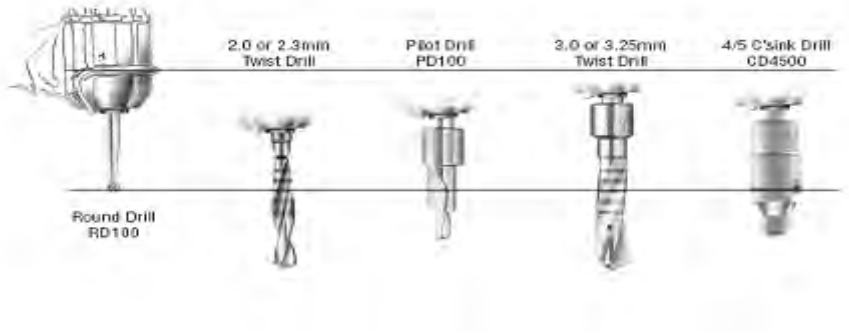
For implant placement the drill unit will be set at 50 rpm. The initial torque limit will be set at 20 Ncm and advanced by 10 Ncm increments until the implant is seated. If the required torque is above the unit's capability the ratchet may be used.

Drilling Protocol: Specific attention is required to perform the final countersink drilling procedure. The countersink drilling must be sufficient to enable a subcrestal implant placement. For example, the drilling protocol will be as follows:

For IIOS 45XX 4 / 5 mm implants:

- Round bur (RD100)
- 2.0 mm or 2.3 mm twist drill (ITD215) - use this to establish depth
- Pilot drill (PD100)
- 3 mm twist drill (ITD315)
- CD4500 – countersink drill

If needed, a bone profiler may first be used to condition the alveolar ridge to facilitate placement of abutments.



Bone Density Determination

During preparation of each implant site, the operator will score the density of bone as: 1 - dense (Type I), 2 - normal (Type II), 3 - soft (Type III).

Healing Abutment Placement

A single stage surgical protocol will be followed in which all study implants will have a healing abutment attached during study surgery. Study implants will be restored using EP healing abutments only. Tighten the healing abutment with a hex driver using hand tightening only (approximately 10-20 Ncm). The catalog numbers for the healing abutments will be recorded on Case Report Form 2-1.

Gingival and Plaque Indices

A global evaluation of the patient's oral health will be done by a scoring of the gingival and plaque indices as described in the Special Procedures section. The scores will be recorded on Case Report Form 2-1.

Healing Period

A non-loaded healing period of two (2) months (± 2 weeks) will be provided for all implants at which time a temporary prosthesis will be attached.

Radiography

Preparation of a bite block must be done 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 tooth site. The radiographs obtained after implant placement surgery will be considered baseline and used as reference for all subsequent radiographs. For centers using digital radiography please send a copy of the entire case as soon as possible by email. Please provide the radiographic files with the patient study identification, the date, and the tooth number (for example, 2406-165-23-1, Oct-12-04, 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.

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Visit 3 (Weeks 6 - 8) – Temporary Prosthesis Impressioning

Impressioning for the fabrication of a temporary prosthesis will take place no later than eight (8) weeks following implant placement. During this visit patients will be interviewed to determine if any adverse events have taken place since the last visit.

Click Assessment

An impression coping will be placed and a click assessment will be performed. The operator will place the impression coping while standing or seated in their normal operating position. They will listen and feel for any sensation emanating from the impression coping. Their observations will be documented on Case Report Form 3-1. Scoring and interpretation of this assessment is described in the Special Procedures section.

Radiography

Periapical radiographs of all study implants will be obtained at this visit for click-assessment and crestal bone analysis purposes. Please use the patient's bite block to assure good radiographic orientation. Only original radiographs will be submitted to 3i. For digital radiography, please provide 3i with the saved files containing the radiographic images with the file name as previously described.

Visit 4 (Month 2) - Temporary Prosthesis Loading

Prosthetic procedures will take place no later than two (2) months *(± 2 weeks)* following implant placement.

An evaluation of the implants will be done prior to the placement of the temporary prosthesis. Scores for gingival inflammation, implant mobility, peri-implant radiolucency, and suppuration will be recorded on Case Report Form 3-2. Patients will be interviewed to determine if any adverse events have taken place since the last visit.

All centers will standardize on a provisional prosthetic approach. Final restorations may be screw or cement retained.

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Clinical Examination

An evaluation of the patient's oral health will be done by a scoring of the gingival inflammation, and gingival and plaque indices as 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 bridge 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 7-1 (Implant Failure Form).

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 gingiva but with no edema; (3) Moderate contains glazing, redness, edema and/or hypertrophy; (4) Severe is characterized with marked redness, edema/hypertrophy, and spontaneous bleeding or ulceration. The scores will be recorded on Case Report Form 3-2.

Click Assessment

A final abutment (i.e.: GingiHue post) will be inserted and a click assessment will be performed. The operator will place the impression coping while standing or seated in their normal operating position. They will listen and feel (audible and tactile test) for any sensation emanating from the impression coping. This step is done the same way as for Visit 3. Scoring and interpretation of this assessment is described in the Special Procedures section. The abutment will then be torqued to 20 Ncm. All observations will be documented on Case Report Form 3-3.

Radiography

Periapical radiographs of all study implants will be obtained (if a bite block was fabricated during implant placement, please use it for this and subsequent radiographs). The radiograph of the

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implant/abutment interface will be assessed by the operator and the overall impression will be recorded on Case Report Form 3-3. ***Original radiographs*** *will be submitted to 3i. For digital radiography, please provide 3i with the saved files containing the radiographic images with the file name as previously described.*

Visit 5 (Months 4 – 6) - Permanent Prosthesis Impression

Impression(s) for the fabrication of a permanent prosthesis will take place no later than six (6) months following implant placement.

All centers will standardize on a provisional prosthetic approach. Restoration will utilize the full range of the Certain PREVAIL prosthetic components.

Visit 6 (Month 6) - Permanent Prosthesis Insertion

Permanent Prosthesis Insertion

Placement of a permanent prosthesis will take place no later than six (6) months following implant placement. The prosthesis type, anchorage, and overall dental conditions will be recorded on Case Report Form 4-1.

Clinical Evaluation

An evaluation of the status of the study implants will be done according to the procedures described in the Special Procedures section. Scores for Gingival Inflammation, Gingival and Plaque Indices, Implant Mobility, Peri-implant Radiolucency, and Suppuration will be recorded on Case Report Form 4-2.

Implant Mobility Assessment

For any implant associated with radiolucency, infection, pain, or neuropathy, a specific attempt will be made to determine implant mobility. The bridge 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.

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For all failed implants, a detailed report will be completed and provided to ***3i*** through the Case Report Form 7-1 (Implant Failure Form).

Radiography

A periapical radiograph will be obtained and evaluated for crestal bone levels. *Only **original radiographs** will be submitted to 3i. For digital radiography, please provide 3i with the saved files containing the radiographic images with the file name as previously described.*

Visits 7, 8, and 9 (1, 2 and 3-year) - Annual Follow-up Evaluations

Follow-up evaluations will be carried out annually based on the temporary prosthesis date for three years.

Clinical Examination

An evaluation of the status of the study implants will be done according the procedures described in the Special Procedures section. Scores for gingival inflammation, implant mobility, peri-implant radiolucency, and suppuration will be recorded on Case Report Form 5-1. An evaluation of the patient's oral health will be done by scoring gingival and plaque indices as 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 bridge 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 7-1 (Implant Failure Form).

Radiography

A periapical radiograph will be obtained and inspected to determine the bone level changes from baseline. *Only **original radiographs** will be submitted to 3i. For digital radiography, please provide*

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3i with the saved files containing the radiographic images with the file name as previously described.

SPECIAL PROCEDURES

Clinical Examination

The evaluation of implant function will be determined based on an interview with the patient, an examination of the implant sites, and a radiographic analysis.

Implant Survival Determination

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 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 prosthesis after placement of the initial prosthesis (temporary prosthesis). These bite blocks will be stored for subsequent use.

At the designated intervals radiographs of study implants will be obtained and the crestal bone level on the mesial and distal coronal aspects of each implant will be measured. The distance between the crestal bone level 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

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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.

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 observed dimensions will be compared against known dimensions (length/diameter) and the percent difference will be calculated and used to "normalize" the observed dimensions. These normalized values from the radiograph obtained at the immediate post-placement surgery date will be considered baseline against which all subsequent values will be compared. Periapical radiographs will also be examined for evidence of peri-implant radiolucency and to assess crestal bone level changes.

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

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Radiological Crestal Bone Level Changes

Bone levels measured at the one, two, and three year follow-up intervals will be compared to those measurements observed at the time of implant placement surgery to derive *changes from baseline* values. Differences will be calculated against historical controls and used to determine if the crestal bone changes are different. A difference of 5% will be considered relevant.

Implant Integration Success

An implant will be considered successful in this study as long as it is immobile when tested with instrument pressure at follow-up evaluations. It must not show evidence of peri-implant radiolucency on periapical radiograph, and must not have persistent or irreversible signs and symptoms of pain, infection, neuropathies, paresthesia, and violation of the mandibular canal.

Interpretation of Click Assessment

There will be two operator and two interface variables at play: Perception/No perception and seating/No (inadequate) seating yielding four possible outcomes.

	Click Heard or Felt	No Click
Good Radiograph Seating	1	2
No Good (Inadequate) Radiographs Seating	3	4

Outcome 1 – The operator hears or feels something that suggests that a successful connection has been made AND the radiograph data confirms that an adequate interface has been achieved.

Outcome 2 – The operator does not receive a signal that suggests that a successful connection has been made BUT the radiograph data confirms that an adequate interface has been achieved.

Outcome 3 – The operator hears or feels something that suggests that a successful connection has been made BUT the radiograph shows that an inadequate interface has been achieved.

Outcome 4 – The operator does not receive a signal that suggests that a successful connection has been made AND the radiograph data show that an inadequate interface has been achieved.

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Outcomes 1 and 4 are desirable because they support the claim that the product's feedback features are in fact diagnostic of a good interface.
Outcomes 2 and 3 and confounding issues where the operator thinks things are adequate whey they are not or that things are OK but the operator assumes that intervention is required.

The success of the internal connection system in regards to its adequacy indicating feature will be based on the proportion of Outcome 1 and 4 scores compared to the proportion of Outcome 2 and 3 scores. A > 90% difference with Outcomes 1 and 4 predominating will be considered a success.

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 MEDICAL AND DENTAL 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 (6-1). If the implant fails, it must be reported on the Implant Failure form (7-1). *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 (6-1) and Implant Failure (7-1) 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.

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- 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 (7-1).

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 (6-2). 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 ANALYSIS

This is a comparison between the Osseotite IIOS Lateralized implant system and the "classic" Osseotite (external) dental implants. The primary question of this study is to the equivalence in bone level and periodontal outcome between the two types of implants. The test (Osseotite IIOS lateralized) and the historical control (Osseotite, external) implants will be considered the experimental units. The influence of the length of the implants as a covariate on survival will be determined during the analysis. A patient may receive only one experimental unit. All implants will support one prosthesis (a case).

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The primary efficacy parameter will be the duration of implant success (survival or lack of mobility or a combination of secondary variables) from implant placement and prosthesis loading. In addition, the fraction of surviving implants and cases at the completion of prosthesis loading, one year, and three years will be evaluated. Implant success differences of > 10% will be considered clinically relevant. Safety will be evaluated by clinical signs and symptoms and dental and medical events. Secondary efficacy endpoints will include implant and prosthesis function as assessed by gingival health, bone level, and clinical outcomes.

Safety and efficacy outcomes between groups will be measured at the completion of prosthesis loading (when the last enrolled patient has prosthesis loaded), and at the completion of one, two, and three years of patient follow-up evaluations. Duration of implant success will be the primary efficacy outcome variable. Survival analysis, including tables and plots of the survival distributions using both the traditional life table and Kaplan-Meier methods will be used as the primary demonstration of implant survival.

Click Assessment Outcomes

Variables: Independent: Click Perception (discrete and dichotomous): X: Yes=1, No=0
Dependent: Implant Seating (discrete and dichotomous): Y: Yes=1, No=0

Statistical Technique: Logistic Regression.

Assessment Metrics:

Probabilities

The logistic regression model predicts the probability of Y due to a value of X, or:

$$P(Y|X_1) = p_{X_1} = \frac{e^{(b_0+b_1x_1)}}{1+e^{(b_0+b_1x_1)}} \quad (1)$$

where the intercept term, b_0, describes the probable association between confirmed implant seating (Y=1) for cases where no click is perceived (X=0), or:

$$p_0 = \frac{e^{b_0}}{1+e^{b_0}} \quad (2)$$

The slope coefficient, b_1, provides a measure of impact (or association) of click perception, X, on implant seating, Y. This level of impact is presented as an Odds Ratio.

Odds Ratio

This ratio is a measure of the effect of a perceived click (X=1) compared to no perceived

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click (X=0). The odds is the ratio of the probability that one event will occur divided by the probability that the same event will not occur, or:

$$\text{Odds } (X=1) = p_1/p_0 = p_1/(1-p_1) \quad (3)$$

The Odds Ratio (OR), is then the ratio of the two odds, as quantified by the slope coefficient:

$$\text{OR} = \frac{\text{odds (click)}}{\text{odds (no click)}} = \frac{e^{(b_0+b_1)}}{e^{b_0}} = e^{b_1} \quad (4)$$

The OR can be determined separately for either adequate (Y=1) or insufficient (Y=0) implant seating.

Wald and Likelihood Ratio Tests

Statistical tests of the resulting coefficients include the Wald test and the Likelihood Ratio test. The Wald test produces a p-value regarding the relationship between the clicking and seating variables based on the size of b_1 in relation to the standard error of this estimate. The Likelihood Ratio test produces a p-value and tests the overall fit of the logistic regression by computing the likelihood of obtaining the study observations if the clicks had no effect on whether or not the implant was seated.

Hypothesis testing

The Wald test described above can also test the null hypothesis (H_0:b_1=0) as indicated by the resulting p-value. In addition, the p-value produced by equation (2) can indicate a disconnection between the click perception and actual implant seating (type 1 and type 2 errors).

Contingency Table and Observed Frequencies

Since this study uses only simple dichotomous explanatory variables, the logistic model does not take advantage of any linear assumption. Thus, many of the above results can be confirmed via the standard 2x2 frequency table for all assembled implants:

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	Yes Click	No Click	Totals
Yes Seating	1	2	1+2
No Seating	3	4	3+4
Totals	1+3	2+4	1+2+3+4

Here, the frequency and thus the probability of each combination of dependent and independent variable will be determined.

The comparability of treatment groups will be determined with regard to demographic variables (including age and sex) and variables relating to the severity of disease (such as existing dental pathology and dental hygiene, previous dental implant grafts and other previous vascular procedures). For the continuous variables of age and evaluations of oral hygiene, the groups will be compared using either the analysis of variance or blocked Wilcoxon, as appropriate. For the qualitative variables of sex, smoking habit, existing dentition, concomitant conditions, previous implants, a chi-square contingency table analysis will be used. The sample size determinations will be based upon survival to the three-year point as a measure of efficacy. Analysis to determine association with other variables will use "exact" rather than "asymptomatic" 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.

RECORDS / DATA RETENTION

Case Report Forms (CRFs) will be prepared by 3i on a 3-ply NCR (no carbon required) sheets for the collection of data. These forms will be used for the entire duration of the study. The original top two (2) copies of the completed CRFs 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.

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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 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 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.

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REFERENCES

1. Meskin LH, Brown LJ, Brunelle JA, Warren GB. Patterns of tooth loss and accumulated prosthetic treatment potential in U.S. employed adults and seniors. 1985-1986. *Gerodontics* 1988; 4:126-135.

2. Jordan R, Abrams L, Kraus B. Kraus' Dental Anatomy and Occlusion. 1992, St. Louis, Mosby Year Book, Inc.

3. Jemt T. Modified single and short-span restorations supported by osseointegrated fixtures in the partially edentulous jaw. *J Prosth Dent* 1986;55:243-247.

4. Lekholm U, Rockier B, Branemark P-I. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Oral Surg* 1981; 10:387-416.

5. Albrektsson T, Dahl E, Enbom L, et al. Osseointegrated oral implants. A Swedish multicenter study of 8139 consecutively inserted Nobelpharma implants. *J Periodontol* 1988; 59:287-296.

6. Bower R, Radny N, Wall C, Henry P. Clinical and microscopic findings in edentulous patients 3 years after incorporation of osseointegrated implant-supported bridgework. *J Clin Periodontol* 1989; 16:580-587.

7. Ericsson I, Lekholm U, Branemark P-I, Lindhe J, Glanz P-O, Nyman S. A clinical evaluation of fixed-bridge restorations supported by a combination of teeth and osseointegrated titanium implants. *J Clin Periodontol* 1986; 13:307-312.

8. Jemt T, Lekholm U, Adell R. Osseointegrated implants in the treatment of partially edentulous patient: A preliminary study on 876 consecutively placed fixtures. *Int J Oral Maxillofac Implants* 1989; 4:211-217.

9. Vam Steembergje D. A retrospective multi-center evaluation of the survival rate of osseointegrated fixtures supporting fixed partial prostheses in the treatment of partial edentulism. *J Prosthet Dent* 1989; 61:217-223.

10. Van Steenberghe D, Lekolm U, Bolender C. The applicability of osseointegrated implants in the rehabilitation of partial edentulism: A prospective multi-center study on 558 fixtures. *Int J Oral Maxillofac Implants* 1990; 5:272-281.

11. Quirynen M, Naert I, van Steenberghe D, Dekeyser C, Callens A. Periodontal aspects of osseointegrated fixtures supporting a partial bridge. An up to 6-years retrospective study. *J Clin Periodontol* 1992; 19:118-126.

12. Zarb GA, Schmitt A. The longitudinal clinical effectiveness of osseointegrated dental implants in posterior partially edentulous patients. *Int J Prosthodont* 1993; 6:189-196.

13. Jemt T, Lekholm U. Oral implant treatment in posterior partially edentuous jaws: A 5-year follow-up report. *Int J Oral Maxillofac Implants* 1993; 8:635-640.

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14. Barboza E, Caula A, Carvalho W. Crestal bone loss around submerged and exposed unloaded dental implants: A radiographic and microbiological descriptive study. *Implant Dent* 2002; 11: 162-169.

15. Larheim TA, Wie H, Tveito L, Eggen S. Method for radiographic assessment of alveolar bone level at endosseous implants and abutment teeth. *Scand J Dent Res* 1979; 87: 146-154.

16. Hermann J, Schoolfield J, Nummikoski P, Buser D, Schenk R, Cochran D. Crestal bone changes around titanium implants: A methodologic study comparing linear radiographic with histometric measurements. *Int J Oral Maxillofac Implants* 2001; 16: 475-485.

17. Kline R, Hoar J, Beck G, Hazen R, Resnik R, Crawford E. A prospective multicenter clinical investigation of a bone quality-based dental implant system. *Implant Dent* 2002; 11: 224-234.

18. Warren P, Chaffee N, Felton D, Cooper L. A restrospective radiographic analysis of bone loss following placement of TiO_2 grit-blasted implants in the posterior maxilla and mandible. *Int J Oral Maxillofac Implants* 2002; 17: 399-404.

19. King G, Hermann J, Schoolfield J, Buser D, Cochran D. Influence of the size of the microgap on crestal bone levels in non-submerged dental implants: A radiographic study in the canine mandible. *J Periodontol* 2002; 73: 1111-1117.

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