Protocol 2406 - A Prospective, Observational Multicenter Study of the Certain® PREVAIL™ Implant System in Maxillary and Mandibular Regions; "The PREVAIL Multicenter Study"

STATISTICAL PLAN

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

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.

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.

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 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:

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

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:

	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.