Statistical Analysis Plan

NCT Number	NCT03283241
Study Title:	A randomized, multicentre, double blind, parallel study to evaluate the performance and safety of the Zolidd One ExHex dental implant compared to uncoated One ExHex dental implant in subjects with partial edentulism
Study Code:	ADD-001
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Statistical Analysis Plan

FINAL

Zolidd One ExHex dental implant
ADD-001

A randomized, multicentre, double blind, parallel study to evaluate the performance and safety of the Zolidd One ExHex dental implant compared to uncoated One ExHex dental implant in subjects with partial edentulism

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
CI	Confidence Interval
DD	Device Deficiency
DMFT	Decayed Missed Filled Teeth
GEE	Generalized estimating equation
ISQ	Implant Stability Quotient
ITT	Intention-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary Drug Regulatory Affairs
PP	Per Protocol
PT	Preferred term
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class

1 STUDY DETAILS

1.1 Study Objectives

Primary Objective

The primary objective is to compare the change in stability from day 1 (implantation) to 12 weeks after surgery of the “index implant” between coated and uncoated implants.

Secondary Objectives

The secondary objectives Part I:

- To compare absolute ISQ highest values between coated and uncoated “index implants” at week 8 and week 12 after implantation
- To compare safety as assessed by complications post-surgery and any other adverse event up to week 12 between all coated and all uncoated implants
- To compare change in stability from day 1 to week 8 between the coated and the uncoated “index implants”
- To compare change in stability day 1 to week 8 and 12 between all other coated and all other uncoated implants
- To compare absolute ISQ highest value at week 8 and 12 between all other coated and all other uncoated implants
- To compare change in marginal bone height between all coated and all uncoated implants from day 1 to week 8 and 12
- To compare survival rate of implants up to 12 weeks between all coated and all uncoated implants

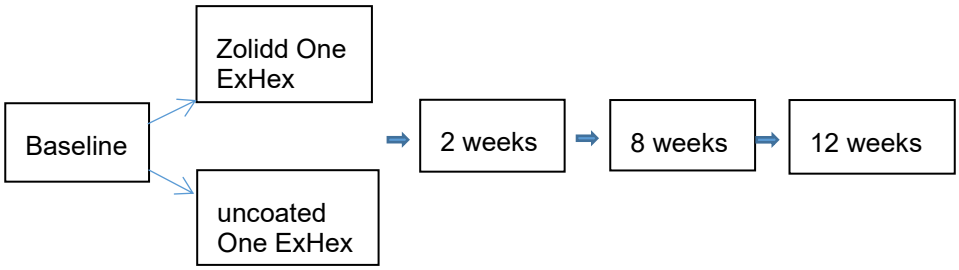
The secondary objectives Part II:

- To compare safety as assessed by complications post-surgery and other adverse events up to month 24 post-implantation visit between all coated and all uncoated implants
- To compare survival rate of implants up to 24 months between all coated and all uncoated implants
- To compare change in marginal bone height from day 1 to month 12 and 24 between all coated and all uncoated implants
- To compare signs of peri-implantitis frequency at 12 and 24 months between all coated and all uncoated implants.

1.2 Study Design

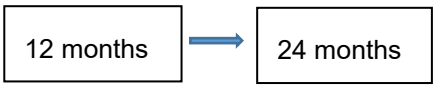
This is a randomised, multicentre double-blind, parallel study where subjects will be randomised to receive coated or uncoated dental implant. Subjects will be assessed during the 12 weeks’ post-operative period (Part I) with an extended Post follow-up period up to 24 months after implantation (Part II). There will be two Clean file meetings, two data-base locks, two reports with tables, figures and analyses. One for Part I when all subjects have completed 12 weeks visit and one after all subjects have completed the 24 months follow-up. Marginal bone loss data will be analyzed and locked only once, at the end of the study, and all time-points will be analyzed at that time.

Part I



Visit 1 Visit 2 (surgery) Visit 3 Visit 4 Visit 5

Part II (post follow-up)



Visit 6 Visit 7

1.3 Treatment Groups

The test implant, Zolidd One ExHex, and the control implant One ExHex consist of a generic model of the established Brånemark dental implant. The test implant is coated with Zolidd and the control implant is uncoated. Zolidd is a nano-coating combination of heated fibrinogen and zoledronic acid which adheres to the surface of the thread profiles of the dental implants. This Zolidd coating is aimed to enhance the bone integration properties, by strengthening the bone surrounding the implant. The control implant, One ExHex is blasted and cleaned according to the same protocol as the coated implant. The only difference between the control and the coated implants are the addition of Zolidd. Both of the coating ingredients of the Zolidd coating have a long established history of use as pharmaceuticals.

1.4 Sample Size

The power analysis based on Abtahi et al. 2012: The SD for change in ISQ value from placement to month 6 was 5.3 in the active group and 5.4 in the control group. In order to be able to find a clinical difference of five ISQ highest values in change between placement and 12 weeks between the coated and the uncoated group with Fisher's non-parametric permutation test with 90% power 28 evaluable subjects are needed in each group assuming a SD for change in ISQ in each group of 5.6 and a significance level 0.05. Thirty-one subjects will be randomized to each study group to compensate for 10% drop-out. A total of 62 subjects will be randomized to the two groups.

2 STUDY POPULATIONS

2.1 Definition of Study Populations

2.1.1 Intent-to-Treat Population

All randomized subjects with at least one study implant will be included in the Intention-to-Treat (ITT) population. The final decisions regarding the ITT population will be taken at the Clean File meeting before the database lock. All analyses will be performed on as-randomized treatment group, unless otherwise specified below.

Post first clean-file meeting notes:

The three subjects wrongly included in the study, i.e. not fulfilling all inclusion criteria or fulfilling any of the exclusion criteria, each case will be separately handled and based on the severity of the deviation they will be either excluded (exclusion criteria 6 [ID 219] and 8 [ID 209]) or included (exclusion criterion 4 [ID 112]) in the Intention-to-Treat (ITT) population.

The four subjects that have had surgery performed at 2 different visits will be included in the ITT population and handled in following way:

1. ID 301 randomized once, the same type of implant has been used. The data from the second surgery and onwards for follow-up visits will be included in the database for each visit respectively for correct tooth position as if they had surgery at the same time. A separate datafile with the date for the second surgery and specification for which position(s) it applies will be provided. This date will only be used and affect the analysis of survival rate of the implant.
2. ID 302: same as for 301
3. ID 312: same as for 301
4. ID 222 and ID 225: This is one and the same subject that have had two surgeries but also have been randomized twice, i.e. at the time of this SAP writing we are not aware of whether all implants are belonging to the same group or not. This subject will get number ID 222/225 and all data will be merged. The index implant will be the first defined index implant, i.e. implant defined for ID 222. The treatment group in the ITT population analyses will be set to the first treatment group that patient has been randomized to. In case the implants from the second surgery (ID 225) are belonging to the same treatment group all implants will used in the efficacy analyses of all implants. In case the implants from the second surgery are not belonging to the same treatment group, they will not be used in the efficacy analyses of all implants. Regarding safety (adverse events) data, the worst case scenario will be applied, i.e. in case any of the implants are from the coated implant group then all adverse events will be assigned to this group.

The subject ID 321 that has performed surgery at two different occasions at one and the same implant position (both time with implant loss) will be handled in similar way as 301 above regarding collection of data. The patient should have been excluded after the first implant loss. Only first implant will be used in the efficacy analyses, however all safety data will be summarized.

According to the guidelines all randomized subjects are to be part of the ITT population. In this study, due to practical reasons, the randomization was performed ahead of Visit 2 in order to have the implants at the clinic in time for the surgery. Therefore, there might be subjects discontinuing or due to no longer eligible for inclusion at Visit 2 end up being

randomized but not having surgery, or even randomization number used but not assigned to a patient. These subjects (ID 303, ID 317, ID 322, ID 332) will be specified as *Randomized Subject but Not Treated* and randomization numbers (ID 305) will be specified *Randomized Number but not Assigned to a Subject* and will not be part of the ITT population. Subject ID 305 has been re-randomized to ID 319 and follow-ed up according to the protocol. Subject ID 225 that is also randomized as ID 222 will be specified as *Randomized subject twice* and will be excluded from the ITT population as ID 225 but included according to its randomization code as ID 222.

2.1.2 Per-Protocol Population

All subjects included in the ITT population with no major protocol violations will be included in the Per Protocol (PP) population. The final decisions regarding the PP population will be taken at the Clean File meeting before the database lock.

Post first clean file meeting notes: All analyses will be performed on as-treated treatment group, except potentially for the subject ID 222/225, where regarding efficacy data only implants from first surgery will be analysed in case the implants surgery at first and second visit are not belonging to the same treatment group. In case they are from the same treatment group, then all implants will be used in the PP analyses.

The rules for exclusion from PP population were: visit window for V4 +/-7 days and visit window for V5 +/-14 days.

2.1.3 Safety Population

All enrolled subjects who received at least one study implant will be included in the safety population.

Post first clean file meeting notes: All analyses will be performed on as-treated treatment group, except potentially for the subject ID 222/225, where worst case scenario will be applied for adverse events, i.e. in case any of the implants are from the coated implant group then all adverse events will be assigned to this group.

3 STUDY VARIABLES

3.1 Baseline Variables

3.1.1 Demographics and Baseline Characteristics

- Age
- Gender
- Childbearing status
- Implant position
- Alcohol status

3.1.2 Tobacco status
Surgical Variables

Implants position.

3.1.3 Medical History

Each category will be coded as Past or Current.

3.1.4 Prior and Concomitant Medications and Other Dental Procedures

At each visit the concomitant medication and procedure will be collected. The medication will be coded with ATC code.

3.2 Efficacy Variables

ISQ values and measured at Day 1, 8 weeks and 12 weeks from surgery and x-ray with measurement of marginal bone height will be performed Day 1, 8 weeks, 12 weeks, 12 months and 24 months from surgery

3.2.1 Primary Efficacy Variable

The primary endpoint is change in stability from day 1 to 12 weeks after implantation of the "index implant" comparing coated and uncoated implants. This will be assessed in terms of induced micro motion of the implant using the Osstell device. The ISQ values are recorded from two directions. The directions should be bucco-lingual and mesio-distal, whereof highest value of the two measurements will be used in the analyses.

3.2.2 Secondary Efficacy Variables for Part I

- Absolute ISQ highest value at day 1, week 8 and week 12 after implantation for "index implant"
- Incidence of post-surgery complications and adverse events up to week 12 post-implantation visit
- Change in ISQ highest value from day 1 to 8 weeks for the "index implant"
- Change in ISQ highest value from day 1 to week 8 and 12 for all other implants
- Absolute ISQ highest value at day 1, week 8 and 12 for all other implants
- Survival rate up to 12 weeks for all implants.

3.2.3 Secondary Efficacy Variables for Part II

- Post-surgical complications and other adverse events up to month 24 post-implantation visit for all implants
- Survival rate up to 24 months for all implants
- Marginal bone height at day 1, week 8, week 12, month 12 and month 24 for all implants

- Change in marginal bone height from day 1 to week 8, week 12, month 12 and month 24 for all implants
- Occurrence of signs associated with peri-implantitis at month 12 and month 24 for all implants

3.3 Safety Variables

3.3.1 Adverse Events/Serious Adverse Events/Adverse Device Effects/Serious Adverse Device Effects/ Device Deficiencies

Adverse events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs), Device Deficiencies (DDs) are collected at all visits during the study. Treatment emergent events are new events after surgery or old events with wors severity. The events will be coded with MedDRA dictionary.

3.3.2 Implant Status and Soft Tissue Status

Implant status and Soft tissue status are measured at each visit.
Implant status is coded as: OK / Questionable / Loose.
Soft tissue status is coded: Neither red or swollen / Red / Swollen / Red and swollen

3.3.1 Dental Examination

Dental examination will be performed at all visits except visit 3, 2 week visit surgery. Decayed Missed Filled Teeth (DMFT) is not performed at one of the sites and will therefore only be summarized for a subgroup of subjects.

4 STATISTICAL METHODOLOGY

4.1 General Methodology

The design of the study is a two parallel group design. All main efficacy analyses will be performed on the ITT population. Complementary efficacy analyses will be performed on the PP population.

For comparison between the two groups (coated vs uncoated), when we have only one observation per subject, Fisher's non-parametric permutation test will be used for continuous variables, Fisher's exact test for dichotomous variables, Mantel-Haenszel chi-square test for ordered categorical variables and Chi-square test for unordered categorical variables.
For primary efficacy variables and for other important continuous efficacy variables the mean difference between the two groups with 95% confidence interval (CI) will be given. For dichotomous variables the percentage in each group together with the difference in percentage between the two groups with 95% confidence interval will be calculated with Miettinen and Nurminen's method.

If clinically relevant significant differences are found between the two randomised groups in important baseline predictors a complementary primary efficacy analyses will be performed

adjusted for these variables using analysis of covariance (ANCOVA) for continuous outcome variables and with multivariable logistic regression for dichotomous outcome variables.

For comparison between the two groups (coated vs uncoated), when we have more than one observation for all or for some subjects, a mixed model with random effects will be used for continuous outcome variables and a General Estimating Equation (GEE) model is used for dichotomous outcome variables. In both these models the dependence within observation are taken into account correctly. For non-normal continuous variables the mixed model will include an empirical bias correction with robust standard errors.

For comparison over time of index implants within randomized groups Fisher's non-parametric permutation test for paired observations will be used for change in continuous and Sign test for change in ordered categorical variables or change in dichotomous variables. When all implants are analyzed the same methods as specified above, i.e. mixed and GEE models will be applied.
The distribution of the variables will be given as mean, SD, median, minimum and maximum for continuous variables and as number and percentages for categorical variables.

The survival rate of implant (implant loss) will be described with Kaplan-Meier curves with 95% CIs adjusted for within-subject correlation and analyzed with suitable Log-rank test, also adjusted for within-subject correlation,between the two randomised groups.

All tests will be two-tailed and conducted at 0.05 significance level. All analyses will be performed by using SAS® v9.2 (Cary, NC).

4.2 Patient Disposition and Data Sets Analyzed

The number of subjects included in each of the ITT, PP and safety populations will be summarized for each treatment group and overall. The number and percentage of subjects randomized and treated will be presented. Subjects who completed the study and subjects who withdrew from study prematurely will also be presented with a breakdown of the reasons for withdrawal by treatment group for the ITT, PP and safety populations.

4.3 Protocol Violations/Deviations

Major protocol deviations are those that are considered to have an effect on the analysis. A list of potential major protocol deviations will be generated programmatically from the data captured before the clean file meeting. The clinical monitor of the study will review the list and the finalisation of the major protocol deviations will be done at the clean file meeting.

The number of subjects with major protocol deviations will be summarized per treatment group.

4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the ITT and PP populations and analyzed according to the methods described in section "General Methodology" above.

4.5 Medical History

Medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group for ITT population.

4.6 Surgical Variables

Implants position will be summarized for each treatment group for ITT population.

4.7 Prior and Concomitant Medications and Other Dental Procedures

Prior and concomitant medication will be summarized by higher level anatomical therapeutic classification (ATC) group and generic term for each treatment group for ITT population.

4.8 Efficacy Analyses

4.8.1 Primary Efficacy Analysis

Primary efficacy analysis will be the comparison of change in ISQ highest value for coated implant with change in ISQ highest value for the uncoated implant on the “index implant” from day 1 to 12 weeks visit with Fisher’s non-parametric permutation test on the ITT-population at significance level 0.05. For primary efficacy variable the 95% confidence interval for the mean difference between the coated and the uncoated implants is obtained by inversion of Fisher’s non-parametric permutation test by means of simulation.
If the 12 weeks ISQ highest values are missing Last observation carry forward (LOCF) will be used from 8 weeks, if available. For the cases of implant loss ISQ = 0 at 12 weeks will be imputed in the main analysis, i.e. resulting in negative difference in ISQ for the subject. For the cases where week 8 and week 12 values are not available due to other reasons than implant loss, same value as baseline value will be imputed, i.e. the difference of 0 will be imputed.

Primary efficacy analysis will be presented per centre and a separate analysis will also be performed in order to study centre effect for primary variable. In case of few centres, centre will be analyzed as fixed effect.
If significant differences are found between the two randomised groups in important baseline predictors a complementary primary efficacy analyses will be performed adjusted for these variables using analysis of covariance (ANCOVA).

Following sensitivity analyses will be performed for the primary efficacy variable:

- Multiple imputations: using analysis of variance for the unadjusted analysis and analyses of covariance for the adjusted analysis if needed. When using multiple imputations LOCF should not be applied. For the sensitivity analysis missing values due to lost implants will be handled with multiple imputation. Following rules will be applied:
    - The multiple imputation will be performed separately for the two study treatment groups to avoid cross-contamination of imputation models between the groups, using PROC MI procedure in SAS version 9.4 and fully conditional specification (FCS) with regression method (REG), per treatment group.
    - The following seed will be used for both groups: 545399
    - The outcome variable of change in ISQ from day 1 will be imputed
    - All baseline characteristics, baseline ISQ value and any follow-up ISQ will be included if they are associated with at least $r \geq 0.40$ to the difference in ISQ at 12 weeks or the actual ISQ value at 12 weeks, or if the variables are

associated with the missingness of the difference in ISQ at of at least 0.10 significance level.
    - 50 study samples will be imputed and pooled by using PROC MIANALYZE procedure
    - Trace plots of means and standard deviations of imputed variables will be reviewed checking that the multiple imputation has worked properly
- Worst case scenario analysis: using the same imputation rules as specified above for the coated implant group, but imputing the difference in ISQ equal to 0, i.e. impute baseline value for week 12 visit, for uncoated implant group no matter the reason for missing data (also for implant loss).

Complementary analyses between the two randomized groups of the primary efficacy variable will be done on the PP-population.
The results from the analyses of primary variable will be given both in tables and figures.

4.8.2 Secondary Efficacy Analyses Part I

Secondary efficacy analyses for Part I will be the comparison between the two randomized groups regarding all the secondary efficacy variables given in section 3.2.2 using the statistical methodology given in sections 4.1 above on the ITT-population.
Complementary analyses between the two randomized groups of secondary efficacy variables will be done on the PP-population.

4.8.3 Secondary Efficacy Analyses Part II

Secondary efficacy analyses for Part II will be the comparison between the two randomized groups regarding all the secondary efficacy variables given in section 3.2.3 using the statistical methodology given in sections 4.1 above on the ITT-population.
Complementary analyses between the two randomized groups of secondary efficacy variables will be done on the PP-population.

4.8.4 Exploratory Efficacy Analyses

Univariable and multivariable analyses of baseline predictors to primary efficacy variable will be performed using mixed models as specified in *General Methodology* above followed by forward stepwise multivariable model on the ITT population on all implants. The variables to be examined are:

- Age
- Sex
- Bone quality
- Bone quantity
- Implant position
- Smoking
- Alcohol
- Diabetes.

4.8.5 Subgroup Analyses

Interaction analyses will be performed between baseline variables and group effect, coated vs uncoated, regarding primary efficacy variable on the ITT population.
Interactions effect with ($p<0.10$) will be followed by suitable subgroups analyses for that baseline variable.

4.8.6 Handling of Missing or Spurious Data

The missing data for the primary efficacy variable will be handled as specified in the section 4.8.1 above.

4.9 Safety Analyses

4.9.1 Adverse Events/Serious Adverse Events/Adverse Device Effects/Serious Adverse Device Effects/Device Deficiencies

AEs/SAEs/ADEs/SADEs/DDs will be listed and summarized by body system, incidence, severity, seriousness and duration/outcome. All AE's will be coded with MedDRA dictionary and tabulated by Preferred Term (PT) code and System Organ Class (SOC) code. Serious Adverse Events (SAEs) or Serious Adverse Device Effects (SADEs) will be summarized separately. Any premature discontinuations due to adverse events and deaths will be listed and summarized by treatment group.

Only treatment-emergent AEs will be included in the summaries for safety population.

A summary of subjects reporting at least one of the following AEs will be presented in an overview table:

- Any AE
- Any SAE
- Any ADE
- Any SADE
- Any AE leading to discontinuation
- Any DD
- Death

Summaries per SOC and PT presenting n (%) of AEs and n (%) of subjects with at least one AE will be provided for:

- All AEs/ADEs (includes all serious and non-serious AEs and ADEs)
- All AEs/ADEs by maximum reported intensity
- All ADEs
- All SAEs/SADEs
- All AEs leading to discontinuation
- All DDs

4.9.2 Implant status and Soft Tissue Status

Implant status and Soft tissue status will be summarized for safety population.

4.9.3 Dental Examination

Dental examination will be summarized for safety population.

5 INTERIM ANALYSES

No interims analysis will be performed.

6 CHANGES OF ANALYSIS FROM PROTOCOL

This statistical analysis plan has been written and finalised prior to database lock and revealing of randomized treatment groups. Following changes to protocol were made:

- Added survival rate up to 12 weeks for all implants in Part I analysis/report.
- Marginal bone height will only be analyzed in Part II analysis/report for all study visits.
- ITT population has been changed from ‘all randomized subjects with at least one performance measurement after implantation’ to ‘randomized subjects with at least one study implant’ including few specific cases as described in section 2.1.1.
- The imputation of missing data has been updated to also handle implant loss cases.

7 LISTING OF TABLE, FIGURES AND LISTINGS

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