Dexcel Pharma Technologies Ltd.

The Efficacy and Safety of Chlorhexidine Gluconate Chip (PerioChip®) in Therapy of Peri-implantitis

Statistical Analysis Plan

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SUMMARY OF SECTIONS

ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BOP	Bleeding on Probing
RAL	Relative Attachment Level
CI	Confidence Interval
GI	Gingival Index
ICH	International Conference on Harmonisation
ITT	Intent to Treat
Mg	Milligram
mITT	Modified Intent to Treat
mm	Millimeters
PD	Probing Pocket Depth
PP	Per Protocol
R	Recession
WHO	World Health Organization

1. INTRODUCTION

1.1 Objectives

This document details the statistical analysis that will be performed for the Dexcel Pharma Technologies, Ltd. study CLI/016P. The statistical methods described in the SAP are elaboration of the statistical section included in the study protocol.

The primary objective of the study is to compare the mean probing Pocket Depth (PD) reductions (absolute change) for the selected target implant/s at week 24 compared to baseline.

The secondary objectives of the study are:

- PD measurement at week 24 compared to baseline in patients with baseline PD measurement of 6-8 mm inclusive.
- Bleeding on Probing (BOP) measurements at week 16 and 24 compared to baseline.
- PD measurement at week 16 compared to baseline

The exploratory objectives of the study are:

- PD, BOP and Relative Attachment Levels (RAL) measurements at week 24 compare to baseline in Responders patients. Responder patients are those patients which demonstrated at week 24 PD reduction of at least 1 mm from baseline PD of 5 mm or PD reduction of at least 2 mm from baseline PD of 6-8 mm inclusive.
- PD and BOP measurements at weeks 8 and 12 compared to baseline.
- Recession (R) and RAL measurements at weeks 8, 12, 16 and 24 compare to baseline.
- PD measurement at week 12 and 16 compared to week 24.
- PD, BOP, RAL and R measured at weeks 8, 12, 16 and 24 for all 4 sites (mesio-buccal, mid-buccal, disto-buccal and mid-lingual), surrounding the selected target implant/s, compared to baseline.

The safety objective of the study is to assess the safety of the PerioChip®.

1.2 Design

This study is a multi-center, randomized, single-blind masking, parallel, two-arm clinical study.

The study duration will be 25-28 weeks (6 months) and will comprise a total of 10 visits: Screening and hygienic phase therapy (weeks -3 to -1), Baseline (week 0), week 2, week 4, week 6, week 8, week 10, week 12, week 16 and week 24 (follow up visit).

During the Baseline visit, eligible patients will be randomized to one of the following treatment regimens:

Treatment 1 – Subgingival debridement + Chlorhexidine Gluconate chip (PerioChip®) inserted every fortnight, for the first 12 weeks.

Treatment 2 – Subgingival debridement.

These treatments will be applied for at least 1 (one) and not more than 2 (two) implants in the oral cavity with clinical and radiographical signs of peri-implantitis. Peri-implantitis is defined as marginal bone loss of at least 3 mm from implant shoulder, and at least 2 mm distal and mesial supporting bone left from the apex to the coronal direction, in combination with bleeding and/or suppuration on probing and a peri-implant Probing Depth (PD) of 5-8 mm.

All pocket measurements (PD, BOP and R) and chip insertions will be made in the same order of procedures every time.

The same examiner will perform all the measurements during the study.

The person (physician/hygienist) placing the Chlorhexidine chips in the periodontal pockets or performing the Subgingival debridement, according to the randomization, will not be involved in target pockets measurements (i.e. the examiner and the physician/hygienist placing the chip or performing the Subgingival debridement will be two different persons).

In each patient meeting the entrance criteria, the deepest periodontal pocket of at least 1 (one) and no more than 2 (two) implant/s (if available) will be selected as a target pocket, and will be used for chip/s insertion or Subgingival Debridement and as the primary efficacy end-point.

The target pocket in the selected implant/s, will be treated at each visit with the same treatment arm, initiated at Baseline visit, as described below.

Implant/s which were not selected as target implant/s will be treated as per the investigators discretion as long as it does not affect the study inclusion/exclusion criteria (e.g. treatment with antibiotics or surgery next to a target implant included in the study).

Treatment 1: (PerioChip®)

Subgingival debridement will be carried out for each one of the target implant which its probing pockets depth (PD of 5-8 mm) were selected as target pockets. The Subgingival debridement procedure will be employ twice: at baseline (visit 2) and after 3 months, at visit 8.

Upon completion of the debridement a PerioChip® will be inserted in each one of the target implant.

PerioChip® contains 2.5 mg Chlorhexidine Gluconate formulated in a biodegradable cross linked gelatine matrix. The maximum dosage for each implant is 5 mg Chlorhexidine Gluconate (i.e. up to 2 PerioChips can be inserted to one implant) and 10 mg of Chlorhexidine Gluconate for each patient per visit. The total number of PerioChips that can be inserted to one patient in one given visit will not exceed 4 PerioChips.

The number of chips inserted to one implant will be a function of the pocket width. In case 2 chips are used in one implant, the insertion will be to the target pocket and the implant surface which is not adjacent to the target pocket (i.e. Buccal - Lingual or Mesial - Distal).

The insertion place should be recorded in the Source Document. All subsequent insertion must be repeated to the exact place chosen in the first insertion procedure.

Treatment 2: (Subgingival Debridement)

Subgingival Debridement will be carried out for each one of the target implant which its probing pockets depth (PD of 5-8 mm) were selected as target pockets.

The Subgingival debridement procedure will be employ twice: at baseline (visit 2) and after 3 months, at visit 8.

1.3 Responsibilities

Medistat on behalf of the Sponsor (Dexcel Pharma Technologies, Ltd.) will conduct the statistical analysis.

1.4 Study Populations

Intent-to-treat (ITT) population

Intent-to-treat (ITT) population – all patients randomized for one of the treatment arms and treated with at least one chip of study treatment or underwent Subgingival debridement will be used for assessments related to efficacy and all safety evaluations.

Safety population

Safety population will be the same as ITT population and will be used for safety analyses.

Modified-Intention-to-Treat (mITT) population

All patients in the ITT population with no major protocol violations, used to confirm the assessments related to efficacy.

Per Protocol (PP) Population

All patients in the ITT population who completed the study according to the protocol and with no major protocol violations. Subjects who exceeded the time window allowed between visits as described in the protocol, will be excluded from the PP cohort:

The allowances between screening (visit 1) and baseline (visit 2) should not exceed 14±7 days

The allowances for visits 3, 4, 5, 6, 7 and 8 should not exceed 14±4 days

The allowances between visit 8 and visit 9 should not exceed 28±4 days

The allowances between visit 9 and visit 10 should not exceed 56±10 days

Additional PP population (PP2) will be defined, based on different time window allowances:

No limitation for the allowances between screening (visit 1) and baseline (visit 2)

The allowances for visits 3, 4, 5, 6, 7 and 8 should not exceed 14+7 days or 14-4 days

The allowance between visit 8 and 9 should not exceed 28±7 days

The allowance between visit 9 and 10 should not exceed 56+28 days or 56-14 days

1.5 Primary Efficacy Endpoint

At week 24, compared to baseline, the mean probing Pocket Depth (PD) reductions (absolute change) for the selected target implant/s will be used as the primary efficacy endpoint

1.6 Secondary Efficacy Endpoints

- PD measurement at week 24 compared to baseline in patients with baseline PD measurement of 6-8 mm inclusive.
- Bleeding on Probing (BOP) measurements at week 16 and 24 compared to baseline.
- PD measurement at week 16 compared to baseline.

Exploratory Analyses

The tertiary efficacy endpoints will include:

- PD, BOP and Relative Attachment Levels (RAL) measurements at week 24 compare to baseline in Responders patients. Responders patients are those patients which demonstrated at week 24 PD reduction of at least 1 mm from baseline PD of 5 mm or PD reduction of at least 2 mm from baseline PD of 6-8 mm inclusive.
- PD and BOP measurements at weeks 8 and 12 compared to baseline.
- Recession (R) and RAL measurements at weeks 8, 12, 16 and 24 compare to baseline.
- PD measurement at week 12 and 16 compared to week 24.
- PD, BOP, RAL and R measured at weeks 8, 12, 16 and 24 for all 4 sites (mesio-buccal, mid-buccal, disto-buccal and mid-lingual), surrounding the selected target implant/s, compared to baseline.

1.7 Safety Analysis

Safety will be evaluated based on AEs and oral inspections recorded at each visit.

1.8 Sample size

A total of 290 patients will be randomized, in order to analyse at least 123 patients for the Subgingival debridement + PerioChip® arm and at least 123 patients for the Subgingival debridement alone arm. Based on the current drop-out rate (after randomization) of 9%, the expected drop-out rate (after randomization) should be between 12%-15%

Based on previous phase IIa studies, the expected drop-out rate in this study will be between 20%-25%. Thus, it is estimated that approximately 375 patients will be screened in order to randomize up to 290 patients.

The sample size is determined based on relevant literature (Machtei et al. 2012) and previous phase IIa study (CLI/013P) that demonstrated substantial improvement (trend toward significant, $p = 0.07$) in PD reduction between PerioChip® and Placebo chip.

The rationale for sample size calculated is based on detecting a difference of 0.50 mm in PD reduction from baseline between PerioChip® and Placebo chip, with 5% statistical significance and 85% power.

A sample size of 123 in each group will have 85% power to detect a difference in means of -0.50 mm (the difference between a Group 1 mean, of -2.29 and a Group 2 mean, of -1.79) assuming that the common standard deviation is 1.30 using a two group t-test with a 0.05 two-sided significance level.

Statistical significance level for all statistical analysis was set to 5%.

1.9 Interim Analyses

No interim analyses are planned.

2. STATISTICAL METHODS

2.1 General

The change in efficacy parameters, PD, R and RAL during the 24 week treatment, will be modelled using a linear-mixed model (SAS® 9.3 Mixed Procedure) with treatment as fixed factors. Patient and pocket will be entered as random effects. The treatment-by-center interaction will be tested and if achieve statistical significance of ≤5% will be added to the model as covariate. The analysis will be adjusted to the following covariates known to have influence on the efficacy parameters: age, gender, smoking status and baseline measurements. The adequacy of the Mixed Model will be checked and if needed a normalizing transformation will be performed. This model will be used for the reduction in PD, R and for improvement in RAL.

Contrasts with 95% Confidence Interval (C.I.) for the difference or ratio between the changes will be computed.

The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the decrease in PD at each time point within each study group.

The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the percent PD decrease from baseline between the study groups.

Patients may have multiple pockets being treated. All treated pockets will be taken into account to create a by-pocket analysis in addition to the by-patient analysis.

Corresponding 95% C.I. for the difference between treatments not including zero for linear model, or 95% C.I. for the ratios between treatments not including unity for the log-linear regression will prove superior to treatment with PerioChip® versus Subgingival debridement.

Analysis for the number of pockets with at least 1 mm and at least 2 mm reduction in PD, and analysis for BOP for the target implant/s measured at each visit will be analyzed by a Chi-square test or Fisher's exact test as is appropriate.

Logistic regression will be applied for testing the above differences with adjustment to smoking status, Gingival Index (GI), medical center and other suspected confounders, if found. Odds Ratio and 95% Confidence Interval will be calculated using the Logistic model.

Similar mixed models for PD, R and RAL with time as a fixed repeated covariate will be used to reveal the changes of these parameters over time.

All treatment comparison will be two-sided at the 0.05 level of significance.

The data will be analyzed using the SAS® version 9.3 (SAS Institute, Cary North Carolina) or higher version.

2.2 Data Summaries

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

2.3 Continuous

For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), median, minimum and maximum, percentiles and 95% C.I. (Confidence Interval) by study arm for means of variables.

2.4 Categorical

For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% C.I. (Confidence Interval) for proportions by study arm.

2.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2.

3. ANALYSIS PLAN

3.1 Introduction

All summaries and analyses documented below will be presented in the final integrated statistical/clinical report and tables that will be based on the E3 guidelines published by ICH. However, it is noted here that no analysis plan prepared in advance of database lock can be absolutely definitive and so the final report may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final report.

3.1 Disposition of Subjects

The number of subjects within each analysis population will be summarized. The number of subjects entering each phase of the study will be tabulated along with number of subjects who withdraw. The calculated percentages will be based on the number of subjects in that particular

phase of the study. The phase of the study, timing of withdrawal and reasons for withdrawal will be summarised by treatment (Table 14.1.1).

3.2 Baseline Comparability

3.2.1 Intent

Subject demographics and baseline characteristics will be presented for all subjects within the safety population. The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

3.2.2 Variables Considered

Standard continuous or categorical variable summaries will be presented overall and by treatment group for the following variables.

Demography (Table 14.1-3)

- Age at screening visit (years)
- Height and weight at screening
- BMI at screening
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not recorded)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian/Pacific Islander, White, Other, Not recorded)

Medical History (Tables 14.1-4 to 14.1-5)

- Relevant previous and ongoing medical history (Yes/No).
- Tobacco use history

Separate tabulations will be produced for previous and ongoing conditions using the MedDRA primary system organ class and preferred term (Version 13.1).

Concomitant medications (Tables 14.3.3-11 to 14.3.3-12)

Concomitant medications ongoing at time of first dose of study medication will be coded. Concomitant medications will be coded using the World Health Organization (WHO) Drug

Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

3.3 Primary Efficacy Endpoint

At week 24, compared to baseline, the mean probing Pocket Depth (PD) reductions (absolute change) for the selected target implant/s will be used as the primary efficacy endpoint. The analysis of the primary endpoint will be based on ITT, mITT, PP and PP2 populations, by-pocket and by-patient analyses.

3.3.1 Principal Analysis

The change in efficacy parameters, PD, during the 24 week treatment, will be modelled using a linear-mixed model (SAS® 9.3 Mixed Procedure) with treatment as fixed factors. Patient and pocket will be entered as random effects. Interactions between treatment and the covariates will be tested and if achieve statistical significance of ≤5% will be added to the model as covariate. The analysis will be adjusted to the following covariates known to have influence on the efficacy parameters: age, gender, smoking status, site and baseline measurements. The adequacy of the Mixed Model will be checked and if needed a normalizing transformation will be performed.

Contrasts with 95% C.I. for the difference between the changes by week will be computed.

The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the decrease in PD at each time point within each study group.

The two-sample T-test or Non-parametric Median test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the PD decrease from baseline between the study groups.

Categorical analysis will be applied for PD change at week 24, using median value calculated overall subjects. Logistic regression will be applied for categorical PD change with adjustment to baseline measure, age, gender, site and smoking status. Interactions between treatment and the covariates will be tested and if found statistically significant, will be added to the model.

Analysis of Variance (ANOVA) will be applied for analysing PD change at week 24, with adjustment to baseline measure, age, gender, site and smoking status. Interactions between treatment and the covariates will be tested and if found statistically significant, will be added to the model.

Missing data will be handled for imputation the primary endpoint data using the MMRM model (Mixed-effect Model for Repeated Measures), which is based on MAR (missing at random) assumption.

3.4 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- PD measurement at week 24 compared to baseline in patients with baseline PD measurement of 6-8 mm inclusive.
- Bleeding on Probing (BOP) measurements at week 16 and 24 compared to baseline.
- PD measurement at week 16 compared to baseline.

The analysis of the secondary endpoints will be based on ITT, mITT, PP and PP2 populations.

Multiplicity

The secondary efficacy endpoints will be analysed according to pre-defined order:

1. PD changes at 24 weeks from baseline in patients with baseline PD of 6-8 mm inclusive.
2. BOP changes at 24 weeks from baseline
3. BOP changes at 16 weeks from baseline
4. PD changes at 16 weeks from baseline

The following stages will be applied:

1. The 1st secondary endpoint in the ordered list will be tested at 5% significance level. If it achieves statistical significance then the 2nd secondary endpoint will be analysed (stage 2). Otherwise the other secondary endpoints in the list will not formally be tested.
2. The 2nd secondary endpoint in the ordered list will be tested at 5% significance level. If it achieves statistical significance then the 3rd secondary endpoint will be analysed (stage 3). Otherwise the other secondary endpoints in the list will not formally be tested.
3. The process will continue for all the secondary endpoints according to the list until a secondary endpoint is not significant or until all secondary endpoints have been found significant.

3.5 Exploratory Analysis

- PD, BOP and RAL measurements at week 24 compare to baseline in Responders patients. Responders patients are those patients which demonstrated at week 24 PD reduction of at least 1 mm from baseline PD of 5 mm or PD reduction of at least 2 mm from baseline PD of 6-8 mm inclusive.
- PD and BOP measurements at weeks 8 and 12 compared to baseline.
- Recession (R) and Relative Attachment Levels (RAL) measurements at weeks 8, 12, 16 and 24 compare to baseline.
- PD measurement at week 12 and 16 compared to week 24.
- PD, BOP, RAL and R measured at weeks 8, 12, 16 and 24 for all 4 sites (mesio-buccal, mid-buccal, disto-buccal and mid-lingual), surrounding the selected target implant/s, compared to baseline.

The statistical methods described in the subsequent paragraphs will be used for analysis of both primary and secondary endpoints. The change in efficacy parameters, PD, R and RAL during the 24 week treatment, will be modelled using a linear-mixed model (SAS® 9.3 Mixed Procedure) with treatment as fixed factors. Patient and pocket will be entered as random effects. The interactions between treatment and the covariates will be tested and if achieve statistical

significance of ≤5% will be added to the model as covariate. The analysis will be adjusted to the following covariates known to have influence on the efficacy parameters: age, gender, smoking status and baseline measurements. The adequacy of the Mixed Model will be checked and if needed a normalizing transformation will be performed. This model will be used for the reduction in PD, R and for improvement in RAL.

Contrasts with 95% C.I. for the difference between the changes by week will be computed.

The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the decrease in PD at each time point within each study group.

The two-sample T-test or Non-parametric Median test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the PD decrease from baseline between the study groups.

Patients may have multiple pockets being treated. All treated pockets will be taken into account to create a by-pocket analysis in addition to the by-patient analysis.

Analysis for the number of pockets with at least 1 mm and at least 2 mm reduction in PD, and analysis for BOP for the target implant/s measured at each visit will be analyzed by a Chi-square test or Fisher's exact test as is appropriate.

Logistic regression will be applied for testing the above differences with adjustment to smoking status, GI, medical center and other suspected confounders, if found. Odds Ratio and 95% Confidence Interval will be calculated using the Logistic model.

Similar mixed models for PD, R and RAL with time as a fixed repeated covariate will be used to reveal the changes of these parameters over time.

3.6 Safety analysis

Safety assessment will be based on AEs and oral inspections recorded at each visit.

All AEs will be coded using coding dictionaries MedDRA version 16.0 or higher and will be summarized by system organ class and preferred term. AEs will be described by seriousness, onset and resolution dates, duration, severity, pattern, action taken, relationship to the study drug and outcome.

The primary safety evaluation of the PerioChip® will be performed by comparison to the Subgingival debridement treatment. Specifically, the number of AEs reported for each treatment group will be compared to see if there is a treatment-related difference in the appearance of the following:

1. Number of dental-related AEs, such as dental or gingival pain.
2. Observed changes in the clinical appearance of the tissues at each of the oral inspections relative to baseline.

The number of dental-related AEs reported and the time of first occurrence of dental-related events will be evaluated to assess if the event is associated with the chip insertion. In addition, all other reported AEs will be evaluated for any treatment related effects. To clarify, AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Chi-square test or Fisher's Exact test will be applied for testing the above differences between the groups.

Oral inspections will evaluate any changes from baseline in the target implant/s that can be attributed to treatment.

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Listing 16.2.8-3: Oral Hygiene
Listing 16.2.8-4: Supra-Gingival Scaling
Listing 16.2.8-5: Supra-Gingival Plaque Removal
Listing 16.2.8-6: Subgingival Debridement
Listing 16.2.8-7: Hygienic Phase Program
Listing 16.2.8-8: Chip Insertion
Listing 16.2.8-9: Pregnancy, Concomitant Medication, Adverse Event, and Dental Treatment by visit
Listing 16.2.8-10: Additional Comments
Listing 16.2.8-11: Concomitant Medication

Approval for Implementation of

Statistical Analysis Plan

Title: **The Efficacy and Safety of Chlorhexidine Gluconate Chip (PerioChip®) in Therapy of Peri-Implantitis**

Reference: **CLI/016P SAP**

Version: **Final**

Date effective: **15-Aug-2018**

Author: [redacted]

Author's signature [redacted] Date: [redacted]

Reviewer [redacted]

Reviewer's signature [redacted] Date: [redacted]

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Approver: [redacted]

Position: [redacted]

Signature: [redacted] Date: [redacted]

Name of Approver: [redacted]

Position: [redacted]

Signature: [redacted] Date: [redacted]