Dexcel Pharma Technologies Ltd.

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

Protocol Number:	CLI/016P
NCT Number	NCT02080403
Sponsor:	Dexcel Pharma Technologies Ltd.
Date:	02/August/2017
Version:	7

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PROTOCOL APPROVALS

Protocol Title: The Efficacy and safety of Chlorhexidine Gluconate Chip (PerioChip®) in Therapy of Peri-implantitis

Protocol Number: CLI/016P

Sponsor:

Dexcel Pharma Technologies Ltd.

1 Dexcel St., Or-Akiva, 3060000, Israel

Representative:

[redacted]

Signature:_____ Date: _____

Principal Investigator's Agreement:

I have carefully read and understood the provisions of this protocol, and I am prepared to follow them in every detail in the conduct of this study.

Principal Investigator Name: _____

Signature:_____ Date: _____

CLINICAL STUDY PROTOCOL - OVERVIEW

STUDY NUMBER	CLI/016P
STUDY TITLE	The Efficacy and safety of Chlorhexidine Gluconate Chip (PerioChip®) in Therapy of Peri-implantitis
CLINICAL TRIAL PHASE	Phase III
SPONSOR	Dexcel Pharma Technologies Ltd. 1 Dexcel St., Or-Akiva, 3060000 Israel
DATE OF PROTOCOL	02 August 2017

PROTOCOL SYNOPSIS

1. Study Title:

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

2. Study Design:

Multicenter, randomized, single blind masking, parallel, two-arm clinical study.

3. Study Objective:

To assess the efficacy of Chlorhexidine gluconate chip (PerioChip®) versus Subgingival debridement in Peri-implantitis patients.

4. Study Treatments:

Treatment 1: Subgingival debridement + Chlorhexidine Gluconate chip (PerioChip®) inserted every fortnight for the first 12 weeks
Treatment 2: Subgingival Debridement

5. Number of Patients:

A total of 290 patients in at least nine clinical sites will be randomized. At least 123 patients for the Subgingival debridement + PerioChip® arm, and at least 123 patients for Subgingival debridement alone arm will complete all required study visits, considering withdrawal rate estimation of between 12%-15%

6. Study Duration and Visits:

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).

7. Target Pockets:

For each patient at least one and not more than two stable implants, with pockets depth (PD) of 5-8 mm in the implant/s (i.e. the target pockets), will be used for either Subgingival debridement + chips insertion or Subgingival debridement.

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

8. Dosage:

Chlorhexidine Gluconate chip (PerioChip®) - The dosage of a single PerioChip® contains 2.5 mg Chlorhexidine Gluconate; 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.
Subgingival Debridement – twice, in baseline visit (week 0) and in visit 8 (week 12).

9. Study Criteria

Inclusion Criteria:

1. Signed and dated Informed Consent Form.
2. Good general health.
3. Male or female patients aged ≥18 years old.
4. Availability for the 25 to 28 weeks duration of the study.

5. The patient has at least one implant in the oral cavity with clinical and radiographical signs of peri-implantitis. In the affected implant, at least one of the four aspects measured [mesio-buccal (MB), mid-buccal (MiB), disto-buccal (DB) and mid-lingual (MiL)] must show radiographic evidence of 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.
6. The implants have been in function for more than 2 years.
7. Fixed prosthetic restoration of the implant.
8. Females of childbearing potential must be non-pregnant and non-lactating at entry and agree to use an adequate method of birth control during the study.

Exclusion Criteria:

1. Patient uses Chlorhexidine oral rinses/ mouthwashes on a regular basis.
2. History of allergic reaction to Chlorhexidine.
3. Horizontal inter implant distance or tooth-implant of < 2 mm (if an adjacent implant exists).
4. Active Periodontitis which required definitive treatment.
5. Presence of oral local mechanical factors that could (in the opinion of the Investigator) influence the outcome of the study.
6. Presence of orthodontic appliances, or any removable appliances, that impinges on the tissues being assessed.
7. There is technical and/or other limitation to insert a chip and/or carry out debridement or permit appropriate probing.
8. Presence of soft or hard tissue tumours of the oral cavity.
9. Patients treated with systemic antibiotic therapy or periodontal/mechanical/local delivery therapy within 6 weeks prior to study entry and throughout the study duration.
10. Patients chronically (i.e. two weeks or more) treated with non-steroidal anti-inflammatory drugs (NSAIDs)or any medications known to affect soft tissue condition (excluding treatment of Acetylsalicylic acid ≤ 100 mg/day). A comprehensive list can be found in the Patient information sheet – list of prohibited medications.
11. Patients with any history of use of Medications known to cause Medication related osteonecrosis of the jaw: Bisphosphonates, RANKL inhibitors, Antiangiogenic agents and m-TOR inhibitors administered Intravenously (IV), Intramuscularly (IM) or Subcutaneously (SC).

    Patients with a history of a one year or more of Per-Os (PO) use of the medications known to cause Medication related osteonecrosis of the jaw , with last dose being under 3 months prior to the screening visit, and a CTX test value of < 150 ng/ml.
12. Patients with uncontrolled diabetes, of any type, and/or patients with HbA1c test value >7.5% dated 3 months prior to the screening visit.
13. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.
14. The presence of any medical or psychiatric condition or any other condition that, in the opinion of the Investigator, could affect the successful participation of the patient in the study.
15. Drug and alcohol abuse.
16. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.

10. Efficacy Endpoints:

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.

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 Endpoints:

- 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 2mm from baseline PD of 6-8mm 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.

11. Statistical Methods:

Sample Size:

A total of up to 290 patients will be randomized. At least 123 patients for the Subgingival Debridement + PerioChip® arm and 123 patients for the Subgingival Debridement alone arm to complete all required study visits 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 that complete all required study visits.

The sample size is determined based on previous phase IIa study (CLI/013P) that demonstrated substantial improvement (trend toward significant, $p = 0.07$) in PD reduction between the PerioChip® and Placebo chip in therapy of Peri-implantitis.

The rational 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 was set to 5% for all statistical analysis and comparisons.

Study Population:

Three populations will be defined for data analysis.

1. 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.

2. Modified-Intent-to-Treat (mITT) population – all patients in the ITT population with no major protocol violations, will be used to confirm the assessments related to efficacy.
3. Per Protocol (PP) population - all patients in the ITT population who completed the study according to the protocol and with no major protocol violations.

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. 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. 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 by study arm for means of variables.

The change in efficacy parameters, PD, R and RAL during the 24 week treatment, will be modelled using a linear-mixed model (SAS® 9.2 Mixed Procedure) with treatment as fixed factors. Patient and pocket will be entered as random effects. The model will be adjusted for smoking status Gingival Index (GI) and medical center. Additional potential parameters suspected as influencing the outcome variable will be tested at 0.10 confidence level. Parameters that will achieve statistical significance ≤10% will be added to the model as covariates. 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 for the treated peri-implant pockets.

Contrasts with 95% 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 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.

A hierarchical model will be used for analyzing the secondary endpoints (refer to section 8.4).

Analysis will be performed by Procedure Mixed SAS® 9.2, or a higher Edition

12. Safety Evaluation

Safety assessments will be based on Adverse Events (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. 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.

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.

ABBREVIATIONS

AE	Adverse Event
BOP	Bleeding on Probing
RAL	Relative Attachment Level
CI	Confidence Interval
CRF	Case Report Form
DPT	Dexcel Pharma Technologies
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Institutional Ethic Committee
INN	International Nonproprietary Name
Mg	Milligram
mm	Millimeters
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	Probing Pocket Depth
Pg	Porphyromonasgingivalis
R	Recession
SAE	Serious Adverse Event
SD	Source Document
SRP	Scaling and Root Planning
Td	Treponema Denticola
Tf	Tannerella Forsythia
UNC	University of North Carolina
MB	Mesio-Buccal
MiB	Mid-Buccal
DB	Disto-Buccal
MiL	Mid-Lingual

STUDY SCHEDULE

Evaluations/Activities	Study Visits									
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Week -3* (Screening)	Week 0 (Baseline)	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 24
Informed Consent	X									
Demographic Data	X									
Inclusion/Exclusion Criteria	X	X								
Relevant Past Medical History and Concomitant Diseases	X									
Periapical Dental Radiography	X[1]									
Oral Inspection	X	X	X	X	X	X	X	X	X	X
Pocket (Site) examination[2]	X[3]	X[4]				X[5]		X[5]	X[5]	X[5]
Selection of Eligible Target Pockets (Sites)		X								
Plaque and Gingival Indices		X[3]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[3]
Supragingival Scaling	X							X		
Supragingival plaque removal		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]		
Oral Hygiene Instructions	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Chip Insertion**		X[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]		
Subgingival Debridement		X						X		
Pregnancy Assessment	X	X	X	X	X	X	X	X	X	X
Medication history and Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse Events recording		X	X	X	X	X	X	X	X	X

The allowances (windows) between the Screening visit and the Baseline visit should not exceed 14 ± 7 days.
The allowances (windows): For visits 3, 4, 5, 6, 7 and 8 should not exceed 14 ±4 days from the previous visit. For visit 9 the allowance (window) should not exceed 28 ± 4 days from the previous visit. For visit 10 the allowance (windows) should not exceed 56 ± 10 days from the previous visit.

* Hygienic Phase Therapy - subjected to screening oral examination and treatment need assessment

** Only for the subgingival debridement + PerioChip® treatment group (i.e. treatment group 1)

[1] Periapical Dental Radiography evaluation dated within 1 (one) year prior the Screening visit

[2] In case chips are pop-out recurrently in visits 3, 4, 5 and 7 a pocket examination will be conducted by the designated examiner to verify PD ≥ 5 mm

[3] Full mouth inspection and recording

[4] Only on implant/s which had a periodontal pocket of 5-8 mm in depth at the Screening visit

[5] Only on target implant/s

[6] Chip/s will be inserted only in target implant/s which had previously received a chip

1. INTRODUCTION

1.1 Peri-implantitis

Peri-implantitis is an inflammatory process caused by micro-organisms affecting the tissues around an osseointegrated implant in function, resulting in a loss of supporting bone (Albrektsson & Isidor, 1994).

The above definition was consecutively reviewed and followed by Zitzmann and Berglundh (2008) and the Consensus of Lindhe and Meyle (2008) was: "Peri-implant Mucositis and Peri-implantitis are infectious diseases. In Peri-implantitis the inflammatory lesion affect the supporting bone and there should be loss of the supporting marginal bone".

Peri-implantitis may display some or all of the following symptoms; bleeding on probing (BOP), increased Probing Pocket Depth (PD), mobility, suppuration and pain. In peri-implantitis the bio-film in the peri-implant area is dominated by pathogens also found in Periodontitis lesions with high levels of spirochetes and Gram negative rods (Zitzmann & Berglundh, 2008).

The treatment in peri-implants infections basically used the same intervention protocols as in Periodontitis treatment. The aim in both diseases is maximum reduction of the subgingival bacterial load presenting the deepened and inflamed pockets. In peri-implant infections a greater difficulty in mechanical treatment is experienced because of the often rough implant surfaces and the screw-like morphology of many implant systems (Renvert, Roos-Jansaker, & Claffey, 2008).

1.2 Chlorhexidine and Peri-implantitis

Chlorhexidine is active against a broad spectrum of microbes. The Chlorhexidine molecule, due to its positive charge, reacts with the microbial cell surface, destroys the integrity of the cell membrane, penetrates into the cell, precipitates the cytoplasm, and the cell dies. Chlorhexidine gluconate is a synthetic antimicrobial drug that has been in use as a broad spectrum antiseptic

in clinical dentistry for many decades (Heasman, Heasman , Stacey & McCracken, 2001; Fardall, & Turnbull, 1986). For several decades it is used in oral rinses in various concentrations ranging from 0.02% to 0.2% (Briner, Grossman, & Buckner, 1986). It is applied in dentifrices, gels, toothpaste gels and in carriers allowing sustained delivery of the drug.

In several in vitro and in vivo studies it has been demonstrated that Chlorhexidine exerts a bactericidal as well as an anti-collagenolytic effect if administered locally in the periodontal pockets. Recent data from animal experiments even suggest a beneficial action inside the body (Houri-Haddad, Halabi, & Soskolne, 2008).

Several in vitro investigations have demonstrated that Chlorhexidine is adsorbed to the oxide layer of titanium surfaces. Recent data indicate that the type of oxide may influence the amount of Chlorhexidine absorbed (Barbour, Gandhi, el-Turki, O'Sullivan, & Jagger, 2009; Morra, Cassinelli, Cascardo, Carpi, Fini, Giavaresi, et al. 2004). It has also been shown that the amount increases with greater surface roughness and correlates positively with the concentration of the Chlorhexidine solution. A desorption occurs within 24 hours and inhibits bacterial growth (Kozlovsky, Artzi, Moses, Kamin-Belsky, & Greenstein, 2006).

In peri-implantitis lesions, mechanical debridement in conjunction with the application of a 0.2% Chlorhexidine gel resulted in clinical improvement including significant reduction of BOP, pocket depth (PD) reduction and clinical attachment gain (Salvi, Persson, Heitz-Mayfield, Frei, & Lang, 2007).

Data collected in case series and randomized controlled clinical trials pointed toward the benefits of an adjunctive local antimicrobial regimen (Minocycline spheres) as well as a disinfective treatment with 1% Chlorhexidine gel (Persson, Salvi, Heitz-Mayfield, & Lang, 2006; Renvert, Lessem, Dahle'n, Lindahl, & Svensson, 2006; Salvi et al. 2007). The effect of local disinfection was less pronounced than the local administration of antibiotics (Renvert, Lessem, Lindahl, & Svensson, 2004; Renvert, et al. 2006; Renvert S., Roos-Jansaker,

Lindahl, Renvert, H., & Persson, 2007). Although it might have an effect, the adjunctive use of antibiotics (Minocycline microspheres) to mechanical debridement fell to be advantages over other adjunctive therapy method (Schär, Ramseier, Eick, Arweiler, Sculean, & Salvi, 2013).

1.3 PerioChip®

PerioChip® is a small rectangular chip (rounded at one end), orange-brown, rigid, thin film chip that is 4.8 mm in length, about 3.8 mm wide and about 350 μm thick. It contains 2.5 mg Chlorhexidine gluconate in a cross-linked gelatin matrix. The PerioChip® biodegrades within the periodontal pocket, slowly releasing the Chlorhexidine gluconate directly into the gingival crevicular fluid.

Following insertion of a PerioChip®, Chlorhexidine concentrations greater than 100 μg/mL within the periodontal pocket are achieved for a week or longer. Sub-gingival bacteria have been demonstrated to be suppressed for up to 11 weeks following PerioChip® insertion. The bio-degradable matrix of the chip degrades over 7-10 days, eliminating the need for a second dental appointment for removal.

Studies with PerioChip® showed reductions in the numbers of the putative periodontopathic organisms Porphyromonas (Bacteroides) gingivalis, Prevotella (Bacteroides) intermedia, Bacteroides forsythus, and Campylobacter rectus (Wolinella recta) after insertion of the chip. No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted.

A recent placebo-controlled clinical study which compared PerioChip® and Placebo chip found greater reduction in the number of "red complex" (Specifically: Pg, Tf and Td) organisms and improved clinical attachment level following PerioChip® insertion (Gonzales, Harnack, Schmitt-Corsitto, Boedeker, Chakraborty, Domann, et al. 2011). Moreover, Meyle, Ammoura, Hamid, Rolf-Hasso, Trinad, & Eugen (2005), found that even in the absence of mechanical treatment Chlorhexidine chip demonstrated significant reduction in periodontopathic organisms and improved clinical results. These results are in

line with former multi-center studies which demonstrated a clinical and microbiological advantage for using the PerioChip® in conjunction with scaling and root planning (SRP) (Paolantonio, D'Angelo, Grassi, Perinetti, Piccolomini, Pizzo, et al. 2008).

Jeffcoat, Bray, Ciancio, Dentino, Fine, Gordon, et al. (1998) reported a mean probing depth reduction of 0.95 mm after 9 months in patients treated with SRP + PerioChip® compared to 0.65 mm in patients treated only with SRP. All pockets measured 5.0 - 8.0 mm initially. Although a 0.95 mm reduction may seem to be of modest clinical significance, the percentage of patients experiencing a decrease of more than 2.0 mm was 30.3% for the SRP + PerioChip® group vs. 13.5% for the SRP-only group. A reduction of 2.0 mm or greater is generally considered clinically significant (see also Jeffcoat, Palcanis, Weatherford, Reese, Geurs, & Flashner, 2000).

The use of PerioChip® as a treatment of peri-implant disease infection, e.g. Peri-implantitis, was recently studied in a phase IIa multi-center, randomized, double-blind, parallel, two-arm placebo-controlled clinical trial. The results showed that controlled-release chlorhexidine delivery treatment in peri-implantitis is effective and has high safety profile without any related SAE's and without worsening of peri-implantitis clinical symptoms (Machtei, Frankenthal, Levi, Elimelech, Shoshani, Rosenfeld, et. al. 2012).

1.4 Study Rationale

On the basis of the information on the effectiveness of Chlorhexidine and the local application of sustained delivery system with Chlorhexidine gluconate (PerioChip®) in periodontal disease and the very recent data from a phase IIa study (CLI/013P) in 60 patient with Peri-implantitis, it is reasonable to expect that use of PerioChip® will benefit the treatment of peri-implant infections for several reasons:

1. PerioChip® has been proven clinically beneficial in the treatment of moderate periodontitis lesions and in a small population of peri-implantitis patients. Given these promising results with peri-implantitis

and similarity of Periodontitis to peri-implant lesions, there is no reason to assume that the system will not provide similar beneficial results in peri-implant mucositis and peri-implantitis.

2. Local application of Chlorhexidine at the site of infection is a more rational approach than rinsing with Chlorhexidine, a measure that is often taken for this infection. Local application will reduce unwanted side effects such as staining of the teeth, a side effect that can only be counteracted by a time-consuming polishing treatment of the teeth.
3. Local application of Chlorhexidine can replace the systemic use of antibiotics, a treatment that is often provided in cases of peri-implantitis. Systemic antibiotic use has several disadvantages such as side effects, drug interactions and development of bacterial resistance.
4. Local application of Chlorhexidine may reduce the need for surgical intervention in peri-implantitis, an approach which is far more costly that local treatment with an antiseptic drug.
5. The risks of local application of Chlorhexidine have shown to be minimal in terms of medical complications. Apart from occasionally reported complaints of discomfort, the side effects of the PerioChip® are minimal.
6. The slow release of PerioChip® provides long-term maintenance of therapeutic levels of the drug without concerns for patient compliance.

Based on the available scientific information reported in peer reviewed studies, one may expect beneficial clinical and microbiological effects of local application of a high concentration of Chlorhexidine provided in a sustained delivery system such as the PerioChip® in the control of peri-implant infections. There is a worldwide need of adjunct antiseptic devices in the control of peri-implant mucositis and peri-implantitis. There is a preference of local antiseptic treatment of these infections over the use of systemic antibiotics. The PerioChip® therefore should be investigated in the anti-infective treatment of

peri-implant lesions as a valuable adjunct to mechanical anti-infection measures.

2. OBJECTIVE

The objective of this clinical study is to assess the efficacy and the safety of Chlorhexidine gluconate chip (PerioChip®) versus Subgingival debridement in Peri-implantitis patients.

3. ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted according to globally accepted standards of International Clinical Harmonization Good Clinical Practice (ICH-GCP), in agreement with the revision of the Declaration of Helsinki (2008) and in compliance with the protocol and all applicable laws, guidelines and regulations of the local laws.

It is the responsibility of the Investigator that this study will not be initiated until the Protocol, Investigator Brochure, the Informed Consent Form, and any study related document have been reviewed and approved by a duly constituted Institutional Ethics Committee (IEC).

It is the responsibility of the Investigator to ensure that each patient and/or legal representative reads, understands, signs and dates the Informed Consent Form.

Where the patient in the study or his legal representative cannot read the Informed Consent Form, an independent witness must be present throughout the explanation about the nature of the clinical study. After the participant or legal representative thereof has expressed their oral consent to participate in the trial, the witness shall sign and date the consent form.

It is the responsibility of the Investigator to inform the patient that while personal information may be examined during audit or monitoring by properly authorized persons, personal information will be treated as strictly confidential and will not be publicly available.

All revisions and/or amendments to the protocol must be approved in advance and in writing by the Investigator, the Sponsor's representative, and the appropriate IEC.

Indemnification of the Investigator, co-workers and the institution is provided as specified

in the clinical study agreement.

4. STUDY DESIGN AND DURATION

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

The duration of patient follow-up will be 25-28 weeks (including Screening and hygienic phase visits), with interim visits at 0, 2, 4, 6, 8, 10, 12, 16 and 24 weeks.

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, starting at baseline, for the first 12 weeks.

Treatment 2 – Subgingival debridement.

The reason for preferring the above design over the Double-blind, Placebo-controlled design is that in previous clinical studies with PerioChip® it was evident that when used Placebo chips have worse clinical outcome compare to No-chip. Namely, periodontal pockets treated with Placebo chips showed less improvement in PD and attachment levels compare to No-chip treated pockets. It was also noted that at six months following the use of Placebo chips fewer incidences of patients were considered to have healthy pockets. The results of these studies suggest, that placing of the Placebo chip acting as a mechanical barrier preventing environmental/outside improvement in the pockets (Perio Products-I; Perio products-II). Due to the above mentioned findings the use of Placebo treatment arm is less adequate. In this case excluding the Placebo arm from the study design ultimately prevents the establishment of Double-blind procedure.

The above 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.

Calibrated examiners will perform all the measurements during the studyThe 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).

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

For secondary endpoints the following will be used:

- 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.

For exploratory endpoints the following will be used:

- 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 measurement 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.

5. STUDY POPULATION

5.1 Number of Patients

A total of 290 patients, with symptoms of peri-implantitis, will be randomized At least 123 patients for the Subgingival debridement + PerioChip® arm, and at least 123 patients for Subgingival debridement alone arm will complete all required study visits, considering withdrawal rate estimation of between 12%-15%.

Based on previous phase IIa studies, the expected drop-out rate in this study will be between 20%-25%. Based on updated current study data the expected rate of patients that are randomized and later drop out will be between 12%-15%. Thus, it is estimated that approximately 375 patients will be screened in order to randomize up to 290 patients, of which 246 patients will complete all required study visits.

To be eligible for this study, patients must have at Screening and Baseline visits at least 1 (one) implant with a loss of marginal bone 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.

5.2 Entry Criteria

5.2.1 Inclusion Criteria

Patients recruited to the study must conform to the following criteria:

1. Signed and dated Informed Consent Form.
2. Good general health.
3. Male or female patients aged ≥18 years old.
4. Availability for the 25 to 28 weeks duration of the study.
5. The patient has at least one implant in the oral cavity with clinical

and radiographical signs of peri-implantitis. In the affected implant, at least one of the four aspect measured (mesio-buccal, mid-buccal, disto-buccal and mid-lingual) must show radiographic evidence of 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.

6. The implants have been in function for more than 2 years.
7. Fixed prosthetic restoration of the implant.
8. Females of childbearing potential must be non-pregnant and non-lactating at entry and agree to use an adequate method of birth control during the study.

5.2.2 Exclusion Criteria

Patients cannot enter the study if any of the following criteria apply:

1. Patient uses Chlorhexidine oral rinses/ mouthwashes on a regular basis.
2. History of allergic reaction to Chlorhexidine.
3. Horizontal inter implant distance or tooth-implant of<2 mm (if an adjacent implant exists).
4. Active Periodontitis which required definitive treatment.
5. Presence of oral local mechanical factors that could (in the opinion of the Investigator) influence the outcome of the study.
6. Presence of orthodontic appliances, or any removable appliances, that impinges on the tissues being assessed.
7. There is technical and/or other limitation to insert a chip and/or carry out debridement or permit appropriate probing.
8. Presence of soft or hard tissue tumours of the oral cavity.
9. Patients treated with systemic antibiotic therapy or

periodontal/mechanical/local delivery therapy within 6 weeks prior to study entry and throughout the study duration.

10. Patients chronically (i.e. two weeks or more) treated with non-steroidal anti-inflammatory drugs (NSAIDs), and/or any medications known to affect soft tissue condition (excluding treatment of Acetylsalicylic acid ≤ 100 mg/day). A comprehensive list can be found in the Patient information sheet – list of prohibited concomitant medications.
11. Patients with any history of use of Medications known to cause medication related osteonecrosis of the jaw: Bisphosphonates, RANKL inhibitors, Antiangiogenic agents and m-TOR inhibitors administered Intravenously (IV), Intramusculary (IM) or Subcutaneously (SC);

    Patients with a history of a one year or more use of the medications known to cause medication related osteonecrosis of the jaw, with last dose being under 3 months prior to the screening visit and a CTX value of < 150 ng/ml.
12. Patients with uncontrolled diabetes, of any type, and/or patients with HbA1c test value >7.5% dated 3 months prior to screening visit.
13. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.
14. The presence of any medical or psychiatric condition or any other condition that, in the opinion of the Investigator, could affect the successful participation of the patient in the study.
15. Drug and alcohol abuse.
16. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.

5.3 Patient Discontinuation/ Withdrawal Criteria

Patients are free to discontinue their participation in the study at any time, for

any reason, and without prejudice to further treatment.

When a patient decides to discontinue participation in the study, he or she should always be contacted in order to obtain information about the reason(s) for discontinuation and any Adverse Events (AEs). When possible, every effort should be made to return the patient to the clinic for last visit assessments at the time of discontinuation, or within 14 days. All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause. Serious Adverse Events (SAEs) which are still on-going at the end of the study period must be followed up to determine the final outcome.

Patients may be dropped from the study if any of the following situations or protocol violations occurs:

- Patient who was inappropriately enrolled.
- Patient substantially fails to comply with the study schedule, or treatment program as described in this Protocol.
- Patient uses prohibited concomitant medication, as detailed in this Protocol.
- Patient receives emergency dental treatment which may interfere with the assessment of study endpoints.
- Patient becomes pregnant.
- Patient skips 2 or more sequential visits or 3 or more non sequential visits.
- Patient skips one of the mandatory visits: screening (visit 1), baseline (visit 2) or week 24 follow-up (visit 10).
- Patient experiences an intolerable toxicity or change in medical condition which constitutes an undue risk to the patient or which would invalidate study observations.
- Patient voluntarily withdraws.

In the event of the above mentioned protocol violations, the patient will undergo Week 24 (Last Visit/Early Withdrawal) assessments.

5.4 Concomitant Medication Treatment

Patients will be assessed at Screening, Baseline, weeks: 2, 4, 6, 8, 10, 12, 16 and 24 for concomitant medications (prescriptions and over-the-counter, including vitamins and natural food supplements). All concomitant medications and procedures received by the patient within 6 weeks of screening and during the study should be recorded in the Source Documents (SDs) and on the patient's Case Report Form (CRF). The generic name of the medication (active ingredient or the International Nonproprietary Name - INN) or name of the procedure, the indication, dose, frequency, route and the duration of use should be included.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Patients will be instructed to refrain from:

- Any use of Chlorhexidine oral rinses/mouthwashes during the study.
- Any dental treatment (including visit to dental hygienist) without consulting the Investigator in advance.
- Any use of toothpicks and/or floss around the treated implant/s in the 24 hours following the chip insertion and advised to use such interproximal cleaning devices only to negotiate food impaction for the following 6 days.
- Any use of antibiotics and any chronically (i.e. two weeks or more) use of NSAIDs during the study which could possibly affect the periodontal inflammatory or healing process.
- Any use of radiation therapy to the head and neck area and/or any immunosuppressive therapy or any use of medication know to affect soft tissue condition and which might influence the pattern of tissue response.

There is no food restriction during the study.

6. STUDY PLAN

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 employed 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.

6.1 Study Schedule

Evaluations/Activities	Study Visits									
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Week -3* (Screening)	Week 0 (Baseline)	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 24
Informed Consent	X									
Demographic Data	X									
Inclusion/Exclusion Criteria	X	X								
Relevant Past Medical History and Concomitant Diseases	X									
Periapical Dental Radiography	X[1]									
Oral Inspection	X	X	X	X	X	X	X	X	X	X
Pocket (Site) examination[2]	X[3]	X[4]				X[5]		X[5]	X[5]	X[5]
Selection of Eligible Target Pockets (Sites)		X								
Plaque and Gingival Indices		X[3]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[3]
Supragingival Scaling	X							X		
Supragingival plaque removal		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]		
Oral Hygiene Instructions	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Chip Insertion**		X[5]	X[5]	X[6]	X[6]	X[6]	X[6]	X[6]		
Subgingival Debridement		X						X		
Pregnancy Assessment	X	X	X	X	X	X	X	X	X	X
Medication history and Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse Events recording		X	X	X	X	X	X	X	X	X

The allowances (windows) between the Screening visit and the Baseline visit should not exceed 14 ± 7 days. The allowances (windows): For visits 3, 4, 5, 6, 7 and 8 should not exceed 14 ±4 days from the previous visit. For visit 9 the allowance (window) should not exceed 28 ± 4 days from the previous visit. For visit 10 the allowance (windows) should not exceed 56 ± 10 days from the previous visit.

* Hygienic Phase Therapy - subjected to screening oral examination and treatment need assessment

** Only for the subgingival debridement + PerioChip® treatment group (i.e. treatment group 1)

[1] Periapical Dental Radiography evaluation dated within 1 (one) year prior the Screening visit

[2] In case chips are pop-out recurrently in visits 3, 4, 5 and 7 a pocket examination will be conducted by the designated examiner to verify PD ≥ 5 mm

[3] Full mouth inspection and recording

[4] Only on implant/s which had a periodontal pocket of 5-8 mm in depth at the Screening visit

[5] Only on target implant/s

[6] Chip/s will be inserted only in target implant/s which had previously received a chip

6.2 Study Procedures by Visit

6.2.1 Screening Visit and Hygienic Phase Therapy (Weeks (-3 to -1))

At the Screening visit (Weeks (-3 to -1)), patients will come to the clinical facility for screening by the examining Principal Investigator or delegated physician to identify those patients who meet the entrance criteria (inclusion/exclusion criteria). Prior to any study activities, patients will be asked to read an Informed Consent Form that has been approved previously by the IEC. Patients will be given adequate time to consider any information concerning the study and the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Written and personally signed and dated Informed Consent Form must be obtained from the patient prior to the patient entering the study. The consenting physician must also sign and date the consent form. A copy of the Informed Consent Form will be given to the patient.

Other assessments at this visit will include:

Demographic data (including date of birth, sex, weight, height, race, and tobacco use history), review of the inclusion and exclusion criteria, relevant past medical history and concomitant diseases, pregnancy assessment (will be done by questioning the patient regarding pregnancy), concomitant medication, periapical radiographic evaluation dated within 1 (one) year prior the Screening visit, oral inflammation and infection inspection and treatment need assessment.

In addition, number of natural teeth, implants and over all dental condition will be recorded and a full mouth (implant and natural teeth) periodontal pocket examinations, PD, R, and BOP, will be carried out and recorded.

6.2.1.1 Hygienic Phase Therapy

The period between screening visit and baseline visit which

patient, eligible to participate in the study, may undergo subjected to the Principal Investigator (PI) or delegated physician oral inspection. The hygienic phase period will be design to complete within the allowance window of 14 ± 7 days and at least 3 days prior to baseline visit.

6.2.1.2 Probing Pocket Depth (PD)

PD is the measurement of the distance from the coronal edge of the gingival margin to the base of the pocket. PD will be measured at four sites per implant: mesio-buccal , mid-buccal, disto-buccal and mid-lingual. Measurements will be taken with a standard 15-mm University of North Carolina (UNC) periodontal probe. For recording pocket depth, the probe tip will be placed at the bottom of the pocket and the pocket depth will be read directly from the millimetres markings on the probe.

6.2.1.3 Recession (R)

Recession is defined as the distance in millimetres that the free gingival margin has migrated apically from the gingival margin of the coronal line of the crown at the same site that PD was measured using a standard 15-mm UNC periodontal probe. If the reference point is other than the coronal line of the crown it should be exactly defined in the source document.

6.2.1.4 Relative Attachment Level (RAL)

Loss of attachment is defined as the distance in millimetres that the base of the pocket has migrated apically from the gingival margin of the coronal line crown. RAL will be calculated at the same site mentioned above, by adding the R measurement to the PD measurement. The RAL calculation will be performed by the Study Statistician.

6.2.1.5 Bleeding on Probing (BOP)

BOP will be measured at the same site immediately after measuring the PD. The scoring system used for recording the BOP is a dichotomous one:

0 = No bleeding

1 = BOP at the base of the pocket

Patients who qualify for the initial examination will be required to have:

- At least 1 (one) implant 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, in combination with bleeding and/or suppuration on probing and a peri-implant Probing Depth (PD) of 5-8 mm.
- The implants have been exposed to the oral environment for more than 2 years.
- At least 2 mm distal and mesial supporting bone left from the apex to the coronal direction.

The qualified patient will undergo Supragingival scaling for all the teeth and implants (if not done up to 6 weeks prior the Screening visit) and in addition the patients will be provided with toothpaste and tooth brushes by the Investigator or designee for exclusive use during the course of the study. The Investigator or designee will give full instructions to the patient regarding the importance of good hygiene of the mouth. Patients will be restricted from any use of Chlorhexidine oral rinses/mouthwashes during the study.

The period between Screening visit and Baseline visit should not exceed **14 ± 7 days**.

6.2.2 Baseline Visit (Week 0)

At Baseline visit (Week 0), patients will return to the clinic for the following procedures:

- Review of inclusion/exclusion criteria (the potential target implant/s from the Screening visit will be used for the inclusion criteria review at Baseline).
- Oral inspection.
- Pocket examination and measurements (i.e. PD, R and BOP) for all potential target implant/s (only on implant/s which had a periodontal pocket of 5-8 mm in depth at the Screening visit).
- Target pockets selection - All potential target implant/s from Screening visit will be re-assessed as follows:

  1. In cases where no more than 2 (two) potential target implants are present, the deepest periodontal pocket of each implant/s (out of the 4 sites per implant that were measured) will be selected as a target pocket.
  2. In case of presence of 3 (three) or more potential target pockets, in three or more different implants in one side of the jaw (upper **or** lower jaw) that are identical in depth, the two deepest pockets in the two implants that are furthest away from each other will be selected.
  3. In case of presence of 3 (three) or more potential target pockets in three different implants or more, that are identical in depth in both jaws (upper **and** lower jaws), the deepest potential target pocket from the upper and the lower jaw will be selected.
  4. In case of presence of 3 (three) or more potential target pockets in three implants or more, that are identical in depth in one or both jaws and equally distance one of the other, the following selection criteria should be taken by order of priority:

     a) The deepest pocket;

     b) Implant located between natural teeth or in edentulous ridge;

c) The implant with the easiest and or best accessibility;

The selected target pocket/s must demonstrate BOP.

- Full mouth Plaque and Gingival bleeding inspections and recording.
- Supragingival plaque removal - only on target implant/s.
- Subgingival debridement will be carried out for all the chosen target implant/s, regardless of the study arm randomization. The Subgingival debridement is the removal of all local irritants from the periodontal pockets and implant surface including the inflammatory tissue. The procedure will be carried out using metal based curettes and possibly ultrasonic management and/or irrigation with Saline .("blasting" cleaning is prohibited).
- Randomization into one of the treatment arms, i.e. the Subgingival debridement + PerioChip® therapy group or the Subgingival debridement therapy only group. The randomization will be done according to a predetermined computer-generated randomization by block table.
- PerioChip® insertion - Chip/s will be inserted only into the chosen target implant/s in the patients randomize to the Subgingival debridement + PerioChip® therapy group. Up to 2 chips will be inserted for each implant's site which pocket depth is 5-8.

  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.
- Safety assessment including AEs, pregnancy assessment by questioning the patient (where applicable), recording of concomitant medications changes and dental treatment.

- Oral Hygiene instructions - The Investigator or designee will remind the patient of the importance of good hygiene of the mouth (if necessary) and of the restriction of use of Chlorhexidine oral rinses/mouthwashes. In addition the patient will be instructed to refrain from use of toothpicks and/ or floss at least for the 24 hours following the chip insertion, and advised to use such interproximal cleaning devices only to negotiate food impaction for the following 6 days.

- Patients will be instructed to notify the Investigator if they feel that the chip has been dislodged.

- The period between Baseline visit and Visit 3 should not exceed **14 ± 4 days**

6.2.2.1 Gingival Index (GI)

Gingival inflammation is assessed using a modification of Löe Silness Gingival Index (GI) as described by Löe (1967), 4 sites per tooth/ implant will be assessed as follows:

0 = No bleeding; 1 = BOP spontaneous or on probing pressure

6.2.2.2 Plaque Index (PI)

Plaque is assessed using a modification of O'Leary plaque control record as described by O'Leary, et.al. (1972). For each of the 4 sites per tooth/ implant a +/- marked is assign. The (-) sign indicating accumulation of plaque and the (+) sign indicating "No plaque". The percent of (-) signs from the total number of sites is computed.

6.2.3 Visits 3, 4, 5, 6, 7 and 8 (Weeks 2, 4, 6, 8, 10 and 12)

At weeks 2, 4, 6, 8, 10 and 12, the patients will return to the clinic for the following procedures:

- Safety assessment including AEs, pregnancy assessment by questioning the patient (where applicable), recording of concomitant

medications changes and dental treatment.

- Oral inspection.
- Supragingival Scaling (at week 12 (Visit 8) only).
- Supragingival plaque removal - only on target implant/s.
- Pocket examination and measurements (i.e. PD, R and BOP) only for the target implant/s (only at weeks: 8 and 12 (visits 6 and 8)).
- Gingival and Plaque inspection for the target implant/s.
- Subgingival debridement will be carried out for all the chosen target implant/s, regardless of the study arm randomization, (at week 12 (Visit 8) only).
- PerioChip® insertion –
    - Chip/s insertion only in those target pockets which had previously received a chip.
    - For visits 6 and 8, chip insertion will follow pocket depth verification of ≥ 5 mm as measured during the visit.
    - For visits 3, 4, 5 and 7, in case chips pop-out recurrently in a pocket examination will be conducted by the designated examiner to verify PD ≥ 5 mm. The examiner will then declare "please try to insert again" if PD≥ 5 mm or "do not proceed with the insertion".
- Oral Hygiene instructions - The Investigator or designee will remind the patient of the importance of good hygiene of the mouth (if necessary), and to refrain from use of Chlorhexidine oral rinses/mouthwashes. In addition the patient will be instructed to refrain from use of toothpicks and/ or floss at least for the 24 hours following the chip insertion and advised to use such interproximal cleaning devices only to negotiate food impaction for the following 6 days.Patients will be instructed to notify the Investigator if they feel

that the chip has been dislodged.

In cases where the target pocket depths increased by more than 2 mm the patient will be withdrawn from the study.

The allowed window for visits 3, 4, 5, 6, 7 and 8 should not exceed **14 ± 4 days** from the previous visit.

6.2.4 Visits 9 (Week 16)

At week 16, the patients will return to the clinic for the following procedures:

- Safety assessment including AEs, pregnancy assessment by questioning the patient (where applicable), recording of concomitant medications changes and dental treatment
- Oral inspection.
- Pocket examination and measurements (i.e. PD, R and BOP) only for the target implant/s
- Gingival and Plaque inspection for the target implant/s
- Oral Hygiene instructions - The Investigator or designee will remind the patient of the importance of good hygiene of the mouth (if necessary), and to refrain from use of Chlorhexidine oral rinses/mouthwashes.
- The allowed window for visit 9 should not exceed **28 ± 4 days** from the previous visit

6.2.5 Last Visit/ Early Withdrawal Visit (Week 24)

At Last Visit/ Early Withdrawal Visit (week 24), the patients will return to the clinic for the following procedures:

- Safety assessment including AEs, pregnancy assessment by questioning the patient (where applicable), recording of concomitant medications changes and dental treatment.

- Oral inspection.
- Full mouth Plaque and Gingival inspection and recording.
- Pocket examination and measurements (i.e. PD, R and BOP) for the target implant/s only.
- Oral Hygiene instructions - The Investigator or designee will remind the patient of the importance of good hygiene of the mouth.

The allowed window for visit 10 is **56 ± 10 days** from the previous visit.

6.3 Other Study Considerations

6.3.1 Calibration of Examiners

PD and R measurement procedures will be standardized between investigators within each medical centre prior to study initiation, consistent with Good Clinical Practice (GCP).

6.3.2 Dental Treatment during Study

If extensive crown and bridge work is planned, the Investigator should be notified to make sure that no periodontal landmark measurements are affected.

6.3.3 Post-study Periodontal Therapy

Upon completion of the study, patients requiring traditional methods of periodontal therapy will be referred for appropriate treatment.

7. RANDOMIZATION AND BLINDING

7.1 Patient Assignment

The patients accepted for the screening visit will be assigned Screening Number XXX, where XXX is a number beginning from 001. For each patient, the Investigator will add the relevant Screening Number to the labels of the assigned medication.

In addition each medical center will have a site ID which will be used as an aid

in differentiating between patient screening numbers.

7.2 Randomization Codes

Eligible patients at Baseline visit will be assigned a randomization number. The order will start from: 101

Each randomization number will be randomly assigned to one of the two letters A or B; each letter will be assigned randomly to one of the two treatments Subgingival debridement + PerioChip® or Subgingival debridement alone.

The randomization will be generated using a computerized algorithm of random numbers by the data management Statistician using the SAS® program, prior to the study start.

The randomization will be performed with stratification to smoking habits and Baseline PD measurement in balanced blocks, each block containing 6 subjects (3 per treatment Subgingival debridement + PerioChip® and 3 per treatment Subgingival debridement alone). Randomization blocks will be sent to the sites by the study data management Statistician. Each site will receive 4 types of lists by the defined stratification (smokers with PD 5 mm, smokers with PD 6-8 mm, non-smokers with PD 5 mm and non-smokers with PD 6-8 mm). Additional blocks will be provided to the sites according to the recruitment rate.

One hundred and twenty three (123) chip packages, each containing 60 chips for one patient will be prepared for the Subgingival debridement + PerioChip® treatment.

7.3 Blinding

At the Baseline visit the patient will start receiving one of the two treatments (Subgingival debridement followed by insertion of PerioChip® or Subgingival debridement alone), since only the examiner who conducts the measurements is blinded to the study treatments the masking is considered "single blinding".

In order to maintain the study blinding condition, in each visit prior to evaluation, the examiner will instruct the patients to refrain of bringing up

whether they did or did not received a PerioChip® in the previous visits.

One set of sealed envelopes will be provided to the Investigator containing individual randomization codes and will be kept at the investigational site.

7.4 Maintenance of the Randomization Code List

The master randomization list will be kept with the Sponsor and with the study data management Statistician.

8. STATISTICAL METHODS

8.1 Sample Size

A total of up to 290 patients will be randomized, in order to analyse at least 123 patients in the Subgingival debridement + PerioChip® arm and at least 123 patients in the Subgingival debridement alone arm, considering expected patient drop-out rate estimation of 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, of which 246 patients will complete all required study visits.The sample size is determined based on relevant literature (Machtei et al. 2012) and previous phase IIa study (CLI/013P) in peri-implantitis patients that demonstrated substantial improvement (trend toward significant, p = 0.07) in PD reduction between PerioChip® and Placebo chip.

The rational 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%.

It is worth noting that although parameters used in the above calculation are derived from a placebo-controlled design, it is reasonable to assume this calculation is more conservative than if the parameter used were taken from previous studies where the study design included a treatment arm with no chip assigned, in Periodontitis patients.

In other words, the sample size calculation is based on sound data derived from a study design which used the same indication (peri-implantitis) and treatment regimen (frequent chip insertion) as appear in the current protocol.

8.2 Analysis Population

Three study populations will be defined for data analysis:

1. 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.
2. 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.
3. Per Protocol (PP) population – all patients in the ITT population who completed the study according to the protocol and with no major protocol violations.

8.3 Efficacy Endpoints

8.3.1 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.

8.3.2 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.

8.3.3 Exploratory Endpoints

- 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.

8.4 Efficacy Analysis and Statistical Models

All statistical analysis and consideration will be conducted in respect to a detailed Statistical Analysis Plan (SAP).

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

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.

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.

The change in efficacy parameters, PD, R and RAL during the 24 week treatment, will be modelled using a linear-mixed model (SAS® 9.2 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% 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, 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.

A hierarchical model will be used for analysing the secondary endpoints.

The secondary 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.

All treatment comparison will be two-sided at the 0.05 level of significance. The primary time-point for all analyses will be at 24 weeks.

The data will be analyzed using the SAS® version 9.2 (SAS Institute, Cary

North Carolina) or higher version.

8.5 Safety Evaluation

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.

8.6 Handling of Missing data

Missing data will be handled for imputation the primary endpoint data.

The MMRM model (Mixed-effect Model for Repeated Measures), which is based on MAR (missing at random) assumption will be applied to all ITT subjects.

Sensitivity analyses will be applied for testing the effect of the imputation on the treatment effect. This will show the influence of the imputation on the study results.

9. HANDALING ADVERSE EVENTS

9.1 Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. New inter current illnesses or injuries after a patient signs the study Informed Consent Form should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal,
- is associated with clinical signs or symptoms,
- leads to treatment or further diagnostic tests, or
- is considered by the Investigator to be of clinical significance.

AEs are classified as either serious or non-serious. A Serious Adverse Event (SAE) is any event that results in any of the following outcomes:

- death,
- are life threatening,
- hospitalization or prolongation of existing hospitalization,

- persistent or significant disability or incapacity,
- a congenital anomaly or birth defect, or malignancy
- other important medical event.

All AEs that do not meet any of the criteria for serious should be regarded as non-SAEs.

The study period for the purpose of AE reporting is defined as the period from the initiation of study to the end of the follow-up period. Although not considered a serious adverse event, it is the responsibility of the Investigator, or his designee, to report any pregnancy (spontaneously reported to them), which begins during the course of the study. At that time, all study-related medication should be stopped and the patient discontinued from the study. All patients who become pregnant must be followed up until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant) must also be reported by telephone to one of the individuals listed in this protocol.

9.2 Recording of Adverse Events

At each contact with the patient, the Investigator must seek information on AEs by specific questioning, and as appropriate, by examination. Information on all AEs should be recorded in the SD and immediately on the CRF AE Form.

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause.

9.3 Reporting of Serious Adverse Events

All SAEs during the study period, whether or not considered to be related to study treatment are to be reported immediately to the Sponsor within 24 hours of the Investigator's first knowledge of the event. The report should be made to one of the Sponsor's representatives as detailed in the CRF SAE Form.

SAEs which are still ongoing at the end of the study period must be followed

up to determine the final outcome.

The Investigator must complete the CRF SAE Form with as much information as is available at the time of completion. All clearly related signs, symptoms and abnormal diagnostic procedures for an event should be grouped together and recorded as a single diagnosis on the CRF SAE Form.

The Investigator must complete a written follow-up report on the CRF SAE Form within 72 hours after receiving any additional information about the SAE and/or when all parameters, including laboratory values, have returned to normal or are otherwise explained.

In addition, it is the responsibility of the Investigator to report SAEs to the IEC in accordance with the applicable local regulatory requirements and the ICH-GCP guideline.

9.4 Patient Removal from Study due to Adverse Events

1. Any patient who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. If the AE may relate to overdose of study treatment, the Investigator Brochure should be consulted for details of any specific actions to be taken. In the event where a patient requires discontinuation due to an AE, the Sponsor must be notified as soon as possible.
2. Pre-treatment event or AE(s). If in the period between Screening visit and Baseline visit the subject has experienced a pre-treatment event or AE, where continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pre-treatment event or AE, the subject may be terminated early.
3. Implant losses PD - In cases where the target pocket depths increased by more than 2 mm the patient will be withdrawn from the study.
4. The clinical course of AE(s) occurring during the study should be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause.

10. STUDY MEDICATION

10.1 Labelling and Packaging

For each randomized patient an individual chip package will be allocated. Each chip package will contain 6 aluminium blister trays containing 10 chips each. The blister packs will be stored in room temperature not above 30°C (storage temperature adequacy will be constantly monitored by the sponsor).

The Chlorhexidine chip will be manufactured and packaged by Dexcel Pharma Technologies (DPT) Ltd, Israel. Each chip package and blister will be labelled in accordance with the current ICH-GCP guideline, Volume 4 EU guidelines to GMP Annex 13: Manufacture of investigational medicinal products, CFR 21 part 312 and the local regulatory requirements.

For Israel: Each chip package will include the following information in English and the wording "For Clinical Trial Use Only" in the following languages: English, Hebrew and Arabic:

Protocol No.: CLI/016P
60 chips of 2.5 mg Chlorhexidine Gluconate
For Insertion into Periodontal Pocket Only
For instruction for administration, please refer to the study protocol.
Investigator Name:_____Investigator Site No.: ____
Randomization No.:_____Screening No.:_____Initials:____
Storage condition: Not above 30°C
Batch No.: XXXXX Expiry date: MM/ 20YY
Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel
Telephone No.: 972-4-636400 (ext. 246)
For Clinical Trial Use Only
לשימוש בניסוי רפואי בלבד
يس ت ع م ل ف ق ط ل ت ج ا ر ب ل ي ط ي ة

Each chip blister will include the following information in English only and the wording "For Clinical Trial Use Only" in English, Hebrew and Arabic:

Protocol No.: CLI/016P
10 chips of 2.5 mg Chlorhexidine Gluconate
For Insertion into Periodontal Pocket
Investigator Name:_____Investigator Site No.:____
Randomization No.:_____Screening No.:_____Initials:____
Batch No.: XXXXX Expiry date: MM/ 20YY
Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel
For Clinical Trial Use Only
לשימוש בניסוי רפואי בלבד
يس ت ع م ل ف ق ط ل ت ج ا ر ب ل ي ط ي ة

For the United States of America:

Protocol No.: CLI/016P
60 chips of 2.5 mg Chlorhexidine Gluconate
For Insertion into Periodontal Pocket Only
For instruction for administration, please refer to the study protocol.
Investigator Name:_____Investigator Site No.:____
Randomization No.:_____Screening No.:_____Initials: ____
Storage condition: Store between 20-25°C (68-77°F) with excursion between 15-30°C (59-86°F)
Batch No.: XXXXX Expiry date: MM/ 20YY
Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel
Telephone No.: 972-4-636400 (ext. 246)
Caution: New Drug--Limited by Federal (or United States) law to investigational use.

Each of the immediate chip blisters will include the following information:

Protocol No.: CLI/016P
10 chips of 2.5 mg Chlorhexidine Gluconate
For Insertion into Periodontal Pocket
Randomization No.:_____Screening No.:_____Initials:____
Storage condition: Store between 20-25°C (68-77°F) with excursion between 15-30°C (59-86°F)
Batch No.: XXXXX Expiry date: MM/ 20YY
Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel
Caution: New Drug--Limited by Federal (or United States) law to investigational use.

For Germany:

EudraCT Nr.: 2013-000383-28 Protokoll Nr.: CLI/016P
60 Chips mit 2,5 mg Chlorhexidin(D-gluconat)
Nur zum Einbringen in Parodontaltaschen
For instruction for administration, please refer to the study protocol.
Name des Forschers:_____ Studienort Nr:____
Randomisierungs-Nr.:_____Screening Nr.:____ Kürzel:____
Lagerbedingungen: Nicht über 30 °C

Batch Nr.: XXXXX Verwendbar bis: MM/ 20YY Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel Telefon Nr.: 972-4-636400 (Durchwahl: 246) **For Clinical Trial Use Only** **zur klinischen Prüfung bestimmt**

Each of the immediate chip blisters will include the following information:

EudraCT Nr.: 2013-000383-28 Protokoll Nr.: CLI/016P 10 Chips mit 2,5 mg Chlorhexidin(D-gluconat) **Nur zum Einbringen in Parodontaltaschen** Randomisierungs-Nr.:_____Screening Nr.:____ Kürzel:____ Lagerbedingungen: Nicht über 30 °C Batch Nr.: XXXXX Verwendbar bis: MM/ 20YY Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel **For Clinical Trial Use Only** **zur klinischen Prüfung bestimmt**

For the United Kingdom:

EudraCT No.: 2013-000383-28 Protocol No.: CLI/016P
60 chips of 2.5 mg Chlorhexidine Gluconate
For Insertion into Periodontal Pocket Only
For instruction for administration, please refer to the study protocol.
Investigator Name:_____Investigator Site No.:____
Randomization No.:_____Screening No.:_____Initials: ____
Storage condition: Not above 30°C
Batch No.: XXXXX Expiry date: MM/ 20YY
Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel
Telephone No.: 972-4-636400 (ext. 246)
For Clinical Trial Use Only

Each of the immediate chip blisters will include the following information:

EudraCT No.: 2013-000383-28 Protocol No.: CLI/016P
10 chips of 2.5 mg Chlorhexidine Gluconate
For Insertion into Periodontal Pocket
Investigator Name:_____Investigator Site No.:____
Randomization No.:_____Screening No.:_____Initials:____
Batch No.: XXXXX Expiry date: MM/ 20YY
Dexcel Pharma Technologies Ltd. 10 Hakidma Street Yokneam, Israel
For Clinical Trial Use Only

In addition, 21 identical labels (3 for each visit) for weeks 0, 2, 4, 6, 8, 10 and 12 will be prepared and attached at each visit to each of the CRF pages (original page and two copy pages) with information of the following in English:

Protocol #: CLI/0016P
2.5 mg Chlorhexidine Gluconate
Visit No.: _____
Randomization No.:_____
Screening No.:_____ Initials:_____
Number of chips inserted: _____
Storage condition: Not above 30°C
Expiry date: MM/20YY
Dexcel Pharma Technologies Ltd.
For Clinical Trial Use Only

10.2 Dosage Regimen of Study Drug

The following procedure will be utilized for the insertion of the PerioChip® into peri-implant pockets assigned to this treatment.

Using a pair of college forceps, a chip assigned to that pocket will be picked up so that the tapered end points are away from the forceps. The chip will then be carried to the pocket, which has been isolated and dried, and will be rapidly inserted into the pocket to its maximum depth and released. The chip can then be further maneuvered into position using the tips of the forceps or a flat plastic instrument.

10.3 Disposition of Study Drug

The Sponsor has ultimate responsibility for the inventory and disposition of study drugs. The Investigator shall keep complete records of the chips, which were received and used in the study, and if possible, shall return all unused or damaged chips and inventory records to the Sponsor upon study completion. The study drugs, under the supervision of the Investigator, will be stored in a secure, locked area 15-30°C. The Investigator is not permitted to destroy any of the chips.

11. ADMINISTRATIVE OBLIGATIONS

11.1 Source Data

Where SDs (such as laboratory reports, medical records or Electrocardiogram (ECG) or laboratory databases) exist, all relevant data will be transcribed into the CRF, transferred electronically to the study database or entered into the study database directly from SDs. Where no SDs exists, data will be written directly into the CRF.

The Investigator/Institution will permit study-related monitoring, audits/inspections, IEC review and regulatory inspection providing direct access to SDs.

11.2 Language

CRFs will be in English. Generic or active ingredient or the International Nonproprietary Name- INN for concomitant medications should be recorded in the CRF whenever possible. All written material to be used by patients must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

11.3 Data Collection

All CRFs will be completed using a black ballpoint pen, and entries must be legible. Errors should be crossed by a single line but not obliterated, the correction inserted, and the change initialled and dated by the Investigator or an authorised member of the investigational site team. The Investigator will sign and date at the indicated places of the CRF. This signature will indicate a thorough inspection of the data on the CRF has been made, and it will certify the contents of the form.

All laboratory reports (if applicable) will be reviewed, signed and dated by the Investigator.

11.4 Data Entry

The CRFs will be logged and the data will be entered into the study database using double data entry with verification upon second entry. Independent persons will enter data into the database system, while the first entry is blind to the second operator to minimize bias.

The two data entries will be compared to see if they are identical using "proc compare" by SAS®.

Two data entry files are independently produced and are compared and corrected until they are identical by the use of a computer verification process.

The data base will include automatic header information of the protocol number, the site number, subject number and initials and visit number.

Text items/comments will be entered once and checked manually against the

CRFs.

Subsequent electronic review of the data may result in queries being generated that will be forwarded simultaneously to the investigator or designee for prompt resolution. Resolutions will be sent back to the DMC in a timely fashion. All data modifications resulting from review or querying of the data will be electronically tracked.

Any errors detected by either the study monitor or the investigator after query, resolution should be documented in CRF data change forms.

In all cases the signature of an investigator or designee and of the study monitor will be required.

11.5 Monitoring

It is understood that the study monitors may contact and visit the Investigator, and that they will be allowed to inspect the various records of the study on request (CRFs and other relevant data), provided that patient confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to the local regulatory requirements and ICH-GCP guideline.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

11.6 Study Documentation and Data Storage

The Investigator should maintain the essential study documents as specified by Section 8 of the ICH-GCP guideline for no less than 15 years after the study completion, and should take measures to prevent accidental and premature destruction of these documents.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the

study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.7 Quality Control and Quality Assurance

Quality Control will be performed according to Dexcel Pharma SOPs. All necessary data and documents will be made available for inspection.

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