Dexcel Pharma Technologies Ltd.

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

Summary of Protocol Changes

Protocol Number:	CLI/016P
NCT Number	NCT02080403
EudraCT Number:	2013-000383-28
Sponsor:	Dexcel Pharma Technologies Ltd.
Date:	13/April/2021

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Dexcel Pharma Technologies Ltd

Protocol No.: CLI/016P
Protocol Title: The Efficacy and Safety of Chlorhexidine Gluconate Chip (PerioChip®) in Therapy of Peri-Implantitis

Clinicaltrial.gov Identifier: NCT02080403
EudraCT Number: 2013-00038-28

Summary of changes from version 1 dated 02 Nov. 2013 to version 2 dated 22 Jan. 2014		
Page/Section	**Original Text (version 1)**	**Amended Text (version 2)**
All through the protocol	Number of subjects that are expected to be randomized to the study 230 (115 at each study group)	Number of subjects that are expected to be randomized to the study 246 (123 at each study group)
All through the protocol	Number of subjects that are expected to be screened to the study 288	Number of subjects that are expected to be screened to the study 336
All through the protocol	Study expected power 80% and statistical significance level 4% for all statistical analysis and comparisons	Study expected power 85% and statistical significance level 5% for all statistical analysis and comparisons
Page 22 - Study Design and Duration	The duration of patient follow-up will be 25-28 weeks (including Screening), with interim visits at 0, 2, 4, 6, 8, 10, 12, 16 and 24 weeks	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
Page 40 - Randomization Code	The randomization will be performed with stratification to study sites smoking habits and Baseline PD measurement in balanced blocks, each block containing 6 subjects. A total number of 48 blocks will be prepared for a total of 288 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). This number already includes 10 blocks for spare.	The randomization will be performed with stratification to ~~study sites~~ 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). A total number of 56 blocks will be prepared for a total of 336 subjects. 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. This number already includes 10 blocks for spare.
Page 41 – Sample size	Statistical significance level was set to 4% since an Interim Analysis, that will use 1% of the total significance level, is planned.	Statistical significance level for all statistical analysis was set to ~~4% since an Interim Analysis that will use 1% of the total significance level, is planned~~ 5.
Page 42 - Analysis 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 all safety evaluations	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

Page 44 - Efficacy analysis and statistical models	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 analysed by a Chi-square test or Fisher's exact test as is appropriate	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 analysed by a Chi-square test or Fisher's exact test as is appropriate
Page 11- Protocol synopsis and Page 46 - Interim Analysis	An interim analysis is planned when 30 patients in each group have completed 24 weeks of therapy. Interim analysis will include primary efficacy endpoint and safety assessment. The purpose of the interim analysis is to achieve a primary assessment for the study safety and efficacy endpoints. The primary efficacy endpoint will be tested using a 0.01 significance level. 1% (0.01) of the overall type 1 error for this study of 5% will be used in the interim analysis. The final analyses will be tested with statistical significance level of 4% (0.04). The levels of significance will maintain an overall P value of 0.05 (Peto, Pike, Armitage, Breslow, Cox, Howard, et al. 1976	~~An interim analysis is planned when 30 patients in each group have completed 24 weeks of therapy. Interim analysis will include primary efficacy endpoint and safety assessment. The purpose of the interim analysis is to achieve a primary assessment for the study safety and efficacy endpoints. The primary efficacy endpoint will be tested using a 0.01 significance level. 1% (0.01) of the overall type 1 error for this study of 5% will be used in the interim analysis. The final analyses will be tested with statistical significance level of 4% (0.04). The levels of significance will maintain an overall P value of 0.05 (Peto, Pike, Armitage, Breslow, Cox, Howard, et al. 1976~~
Summary of changes from version 2 dated 22 Jan. 2014 to version 3 dated 13 July 2014		
Page/Section	**Original Text (version 2)**	**Amended Text (version 3)**
Page 20 - Study Design and Duration		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.
Page 39 - Statistical methods		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 (periimplantitis) and treatment regimen (frequent chip insertion) as appear in the current protocol

Page 58 - Reference List		23. Perio Products.I. Clinical effects following subgingival administration of Chlorhexidine gluconate (2.5 mg) in a cross-linked gelatin matrix (PerioChip) in patients with periodontal disease (study 91-011). *Clinical Study Report* 24. Perio Products. II. Clinical effects following subgingival administration of Chlorhexidine gluconate (2.5 mg) in a cross-linked gelatin matrix (PerioChip) in patients with periodontal disease (study 91-013). *Clinical Study Report*
Summary of changes from version 3 dated 13 July2014 to version 4 dated 16 Nov. 2014		
Page/Section	**Original Text (version 3)**	**Amended Text (version 4)**
Page 7 - Protocol Synopsis; Page 22 - Inclusion Criteria	Inclusion Criteria 1 "Signed and dated informed consent"	Inclusion Criteria 1 "Signed and dated informed consent. *The patient is of age and is capable of understanding the nature, significance and implications of the clinical trial and to form a rational intention in the light of the facts*."
Page 8 – Protocol synopsis; Page 24 - Exclusion Criteria	Exclusion Criteria 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."	Exclusion Criteria 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. *In case the investigator advises the patient that antibiotic therapy is required during the course of the study, the patient should be excluded from further participation*."
Page 25 - Patient Discontinuation/ Withdrawal Criteria	"Patient receives emergency dental treatment which may interfere with the assessment of study endpoints."	"Patient receives emergency dental treatment *including target implant explanation* which may interfere with the assessment of study endpoints. *Paragraph was added: "Despite participating in the study, patient, who in the opinion of the investigator displays an inadequate response to subgingival debridement and chemical disinfection during the study period, may be entitled to surgical therapy of peri-implantitis."*
Page 26 - Concomitant Medication Treatment	Patients will be instructed to refrain from: "Any use of Chlorhexidine oral rinses/mouthwashes during the study"	Patients will be instructed to refrain from: "Any use of Chlorhexidine oral rinses/mouthwashes during the study *without consulting the Investigator in advance.*"
Summary of changes from version 3 dated 13 July2014 to version 5 dated 07 Oct. 2015		
Page/Section	**Original Text (version 3)**	**Amended Text (version 5)**
Page 7 - Protocol Synopsis	Number of clinical sites "5 clinical sites" to "at least 5 clinical sites"	Number of clinical sites "at least 7 clinical sites"
Page 13; Page 28; Page 37 - Study Schedule	Last visit number "visit 9" The allowance (window)of final visit “90 ±10 days from previous visit”	Last visit number "visit 10" The allowance (window)of final visit “56±10 days from previous visit (8 weeks)”

Summary of changes from version 4 dated 16 Nov. 2014 to version 6 dated 07 Oct. 2015		
Page/Section	**Original Text (version 4)**	**Amended Text (version 6)**
Page 7 - Protocol Synopsis	Number of clinical sites "5 clinical sites" to "at least 5 clinical sites"	Number of clinical sites "at least 7 clinical sites"
Page 13;Page 29; Page 38 -Study Schedule	Last visit number "visit 9" The allowance (window)of final visit "90 ±10 days from previous visit"	Last visit number "visit 10" The allowance (window)of final visit "56±10 days from previous visit (8 weeks)"
Summary of changes from version 5 dated 07 Oct. 2015 to version 7 dated 20 July 2017		
Lines	**Original Text (version 5)**	**Amended Text (version 7)**
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8 - 9	**Date :** 07 October 2015	**Date :** 02 August 2017
8 - 9	**Version :** 5	**Version :** 7
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141-146	10. page 48; 10.1 page 48;	10. page 49; 10.1 page 49;
Clinical Study Protocol - Overview		
203	**Date :** 07 October 2015	**Date :** 02 August 2017
Protocol Synopsis - Number of patients		
221-224	A total of 246 patients in at least five clinical sites will be randomized. 123 patients for the Subgingival debridement + PerioChip® arm, and 123 patients for Subgingival debridement alone arm	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%
Protocol Synopsis - Inclusion Criteria #5		

248-254	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.	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.
Protocol Synopsis - Exclusion Criteria #10		
273-276	Patients chronically (i.e. two weeks or more) treated with non-steroidal anti-inflammatory drugs (NSAIDs) or any medications know to affect soft tissue condition (excluding treatment of Acetylsalicylic acid ≤ 100 mg/day).	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.
Protocol Synopsis - Exclusion Criteria #11 *(New)*		
277-283		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.
Protocol Synopsis - Exclusion Criterias 12 - 16		
284-285	11. Patients with uncontrolled diabetes, of any type, and/or patients with HbA1c test value >7.5% dated 3 months prior to the screening visit.	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.
286-287	12. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.	13. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.
288-289	13. 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.	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.
290	14. Drug and alcohol abuse.	15. Drug and alcohol abuse.
291-292	15. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.	16. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.
Protocol Synopsis – Statistical Methods – Sample Size		
315-321	A total of 246 patients will be randomized, 123 patients for the	A total of up to 290 patients will be randomized. At least 123 patients

	Subgingival Debridement + PerioChip® arm and 123 patients for the Subgingival Debridement alone arm. 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 336 patients will be screened in order to randomize 246 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.
Abbreviations		
401-402	4 abbreviations regarding pocket aspects were not listed	MB - Mesio-Buccal; MiB - Mid-Buccal; DB -Disto-Buccal; MiL-Mid-Lingual
Study Schedule		
404-413	**Evaluations/Activity Column**: "dental Radiography **SuperScript #1:** Dental Radiography evaluation dated within 1 (one) year prior the Screening visit **SuperScript #2:** In case chips are pop-out recurrently in visits 3, 5 and 7 a pocket examination will be conducted by the designated examiner to verify PD ≥ 5 mm **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip and which pocket depth at those visits is ≥ 5 mm and which pocket depth at those visits is ≥5 mm" was removed	**Evaluations/Activity Column**: "Periapical dental Radiography **SuperScript #1:** "Periapical Dental Radiography evaluation dated within 1 (one) year prior the Screening visit. **SuperScript #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 **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip and which pocket depth at those visits is ≥ 5 mm
Study Design and Duration		
621	The same examiner will perform all the measurements during the study.	Calibrated examiners will perform all the measurements during the study.
5.1 Number of Patients		
649-657	A total of 246 patients, with symptoms of peri-implantitis, will be randomized, into one of the study arms; 123 patients for the Subgingival debridement + PerioChip® arm and 123 patients for the Subgingival debridement arm alone.	A total of 290 patients, with symptoms of peri-implantitis, will be randomized into one of the study arms; 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%
658-663	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 336 patients will be screened in order to randomize 246 patients.	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.
5.2.2 Exclusion Criteria – Exclusion Criteria #10		
708-713	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).	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
Protocol Exclusion Criteria #11 *(New)*		
714-721		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.
Protocol Synopsis - Exclusion Criterias 12 - 16		
722-724	11. Patients with uncontrolled diabetes, of any type, and/or patients with HbA1c test value >7.5% dated 3 months prior to the screening visit.	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.
725-726	12. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.	13. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.
727-729	13. 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.	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.
730	14. Drug and alcohol abuse.	15. Drug and alcohol abuse.
731-732	15. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.	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		
744	Serious Adverse Events (SAEs) which are still ongoing at the end of the study period must be followed up to determine the final outcome.	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.
5.4 Concomitant Medication Treatment		
782-785	Any use of toothpicks and/or floss around the treated implant/s in the 24 hours following the chip insertion**.**	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.
6. Study Plan - Treatment 1: (PerioChip®)		

804-807	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).	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).
6.1 Study Schedule		
826-834	**Evaluations/Activity Column**: "dental Radiography **SuperScript #1:** Dental Radiography evaluation dated within 1 (one) year prior the Screening visit **SuperScript #2:** In case chips are pop-out recurrently in visits 3, 5 and 7 a pocket examination will be conducted by the designated examiner to verify PD ≥ 5 mm **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip and which pocket depth at those visits is ≥ 5 mm	**Evaluations/Activity Column**: "Periapical dental Radiography. **SuperScript #1:** "Periapical Dental Radiography evaluation dated within 1 (one) year prior the Screening visit. **SuperScript #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 **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip
6.2.1 Screening Visit and Hygienic Phase Therapy (Weeks (-3 to -1))		
850-860	radiographic evaluation dated within 1 (one) year prior the Screening visit	periapical radiographic evaluation dated within 1 (one) year prior the Screening visit
6.2.2 Baseline Visit (Week 0)		
955-961	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 ultrasonic management and irrigation with Chlorhexidine ("blasting" cleaning is prohibited).	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).
980-987	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 in the 24 hours following the chip insertion.	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.
990-991		The period between Baseline visit and Visit 3 should not exceed 14 ± 4 days
6.2.3 Visits 3, 4, 5, 6, 7 and 8 (Weeks 2, 4, 6, 8, 10 and 12)		
1010	Supragingival Scaling (at week 12 only)	Supragingival Scaling (at week 12 (Visit 8) only).
1012-1013	Pocket examination and measurements (i.e. PD, R and BOP) only for	Pocket examination and measurements (i.e. PD, R and BOP) only for

	the target implant/s (only at weeks: 8 and 12)	the target implant/s (only at weeks: 8 and 12 (visits 6 and 8)).
1015-1017	Subgingival debridement will be carried out for all the chosen target implant/s, regardless of the study arm randomization, (at week 12 only).	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)**.**
1018-1029	Chip/s insertion only in those target pockets which had previously received a chip and which pocket depth is ≥ 5 mm. In case chips are pop-out recurrently in visits 3, 4, 5 and 7 a pocket examination will conducted by the designated examiner to verify PD ≥ 5 mm. The examiner will then declare "please try to restore again" if PD≥ 5 mm or "do not proceed with the 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 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".
1030-1037	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 in the 24 hours following the chip insertion.	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.
6.2.4 Visits 9 (Week 16)		
1058-1059		The allowed window for visit 9 should not exceed **28 ± 4 days** from the previous visit.
6.3.1 Calibration of Examiners		
1076-1078	PD and R measurement procedures will be standardized between medical centres and investigators prior to study initiation, consistent with Good Clinical Practice (GCP).	PD and R measurement procedures will be standardized between investigators within each medical centre prior to study initiation, consistent with Good Clinical Practice (GCP).
7.2 Randomization Codes		
1107-1108	A total number of 56 blocks will be prepared for a total of 336 subjects.	Line removed
1113	This number already includes 10 blocks for spare	Line removed
7.3 Blinding		
1118-1122	Subgingival debridement only	Subgingival debridement alone
8.1 Sample Size		
1133-1140	A total of 246 patients will be randomized, 123 patients for the Subgingival debridement + PerioChip® arm and 123 patients for the Subgingival debridement alone arm. Based on previous phase IIa studies, the expected drop-out rate in this study will be between 20%-25%. Thus, it is estimated that	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%.

	approximately 336 patients will be screened in order to randomize 246 patients.	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.
Summary of changes from version 6 dated 07 Oct. 2015 to version 8 dated 29 Aug. 2017		
Lines	**Original Text (version 6)**	**Amended Text (version 8)**
Headline (First Page)		
8 - 9	**Date :** 07 October 2015	**Date :** 29 August 2017
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Clinical Study Protocol – Overview		
130	**Date :** October 7th 2015	**Date :** August 29th 2017
Protocol Synopsis - Number of patients		
148-151	A total of 246 patients in at least five clinical sites will be randomized. 123 patients for the Subgingival debridement + PerioChip® arm, and 123 patients for Subgingival debridement alone arm	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%
Protocol Synopsis - Inclusion Criteria #5		
177-183	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.	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.

Protocol Synopsis - Exclusion Criteria #10		
204-207	Patients chronically (i.e. two weeks or more) treated with non-steroidal anti-inflammatory drugs (NSAIDs)or any medications know to affect soft tissue condition (excluding treatment of Acetylsalicylic acid ≤ 100 mg/day).	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.
Protocol Synopsis - Exclusion Criteria #11 *(New)*		
208-213		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.
Protocol Synopsis - Exclusion Criterias 12 – 16		
214-215	11. Patients with uncontrolled diabetes, of any type, and/or patients with HbA1c test value >7.5% dated 3 months prior to the screening visit.	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.
216-217	12. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.	13. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.
218-219	13. 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.	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.
220	14. Drug and alcohol abuse.	15. Drug and alcohol abuse.
221-222	15. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.	16. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.
Protocol Synopsis – Statistical Methods – Sample Size		
245-252	A total of 246 patients will be randomized, 123 patients for the Subgingival Debridement + PerioChip® arm and 123 patients for the Subgingival Debridement alone arm. 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 336 patients will be screened in order to randomize 246 patients.	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.
Abbreviations		
332-333	4 abbreviations regarding pocket aspects were not listed	MB - Mesio-Buccal; MiB - Mid-Buccal; DB -Disto-Buccal; MiL-Mid-Lingual
Study Schedule		
336-344	**Evaluations/Activity Column**: "dental Radiography **SuperScript #1:** Dental Radiography evaluation dated within 1 (one) year prior the Screening visit **SuperScript #2:** In case chips are pop-out recurrently in visits 3, 5 and 7 a pocket examination will be conducted by the designated examiner to verify PD ≥ 5 mm **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip and which pocket depth at those visits is ≥ 5 mm	**Evaluations/Activity Column**: "Periapical dental Radiography **SuperScript #1:** "Periapical Dental Radiography evaluation dated within 1 (one) year prior the Screening visit. **SuperScript #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 **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip and which pocket depth at those visits is ≥ 5 mm
Study Design and Duration		
522	The same examiner will perform all the measurements during the study.	Calibrated examiners will perform all the measurements during the study.
5.1 Number of Patients		
580-584	A total of 246 patients, with symptoms of peri-implantitis, will be randomized, into one of the study arms; 123 patients for the Subgingival debridement + PerioChip® arm and 123 patients for the Subgingival debridement arm alone.	A total of 290 patients, with symptoms of peri-implantitis, will be randomized into one of the study arms; 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%
585-590	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 336 patients will be screened in order to randomize 246 patients.	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.
5.2.2 Exclusion Criteria – Exclusion Criteria #10		
640-645	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).	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
Protocol Exclusion Criteria #11 *(New)*		
646-654		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.
Protocol Synopsis - Exclusion Criterias 12 – 16		
655-657	11. Patients with uncontrolled diabetes, of any type, and/or patients with HbA1c test value >7.5% dated 3 months prior to the screening visit.	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.
658-659	12. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.	13. Patients receiving radiation therapy to the head and neck area and/or receiving immunosuppressive therapy.
660-662	13. 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.	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.
663	14. Drug and alcohol abuse.	15. Drug and alcohol abuse.
664-665	15. Patient participates in any other clinical study 30 days prior to the start of the study and throughout the study duration.	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		
677	Serious Adverse Events (SAEs) which are still ongoing at the end of the study period must be followed up to determine the final outcome.	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.
5.4 Concomitant Medication Treatment		
721-723	Any use of toothpicks and/or floss around the treated implant/s in the 24 hours following the chip insertion**.**	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.
6. Study Plan - Treatment 1: (PerioChip®)		
742-745	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).	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).
6.1 Study Schedule		
764-772	**Evaluations/Activity Column**: "dental Radiography **SuperScript #1:** Dental Radiography evaluation dated within 1 (one) year prior the Screening visit **SuperScript #2:** In case chips are pop-out recurrently in visits 3, 5 and 7 a pocket examination will be conducted by the designated examiner to	**Evaluations/Activity Column**: "Periapical dental Radiography. **SuperScript #1:** "Periapical Dental Radiography evaluation dated within 1 (one) year prior the Screening visit. **SuperScript #2:** In case chips are pop-out recurrently in visits 3, 4, 5 and 7 a pocket examination will be conducted by the designated

	verify PD ≥ 5 mm **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip and which pocket depth at those visits is ≥ 5 mm	examiner to verify PD ≥ 5 mm **SuperScript #6**: Chip/s will be inserted only in target implant/s which had previously received a chip
6.2.1 Screening Visit and Hygienic Phase Therapy (Weeks (-3 to -1))		
788-798	radiographic evaluation dated within 1 (one) year prior the Screening visit	periapical radiographic evaluation dated within 1 (one) year prior the Screening visit
6.2.2 Baseline Visit (Week 0)		
893-899	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 ultrasonic management and irrigation with Chlorhexidine ("blasting" cleaning is prohibited).	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).
918-925	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 in the 24 hours following the chip insertion.	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.
928-929		The period between Baseline visit and Visit 3 should not exceed 14 ± 4 days
6.2.3 Visits 3, 4, 5, 6, 7 and 8 (Weeks 2, 4, 6, 8, 10 and 12)		
949	Supragingival Scaling (at week 12 only)	Supragingival Scaling (at week 12 (Visit 8) only).
951-952	Pocket examination and measurements (i.e. PD, R and BOP) only for the target implant/s (only at weeks: 8 and 12)	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)).
954-956	Subgingival debridement will be carried out for all the chosen target implant/s, regardless of the study arm randomization, (at week 12 only).	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).
957-966	Chip/s insertion only in those target pockets which had previously received a chip and which pocket depth is ≥ 5 mm. In case chips are pop-out recurrently in visits 3, 4, 5 and 7 a pocket examination will conducted by the designated examiner to verify PD ≥ 5 mm. The examiner will then declare "please try to restore again" if PD≥ 5 mm or "do not proceed with the 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 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".
967-974	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 in the 24 hours following the chip insertion.	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.
6.2.4 Visits 9 (Week 16)		
995-996		The allowed window for visit 9 should not exceed **28 ± 4 days** from the previous visit.
6.3.1 Calibration of Examiners		
1013-1015	PD and R measurement procedures will be standardized between medical centres and investigators prior to study initiation, consistent with Good Clinical Practice (GCP).	PD and R measurement procedures will be standardized between investigators within each medical centre prior to study initiation, consistent with Good Clinical Practice (GCP).
7.2 Randomization Codes		
1044-1045	A total number of 56 blocks will be prepared for a total of 336 subjects.	Line removed
1050	This number already includes 10 blocks for spare	Line removed
7.3 Blinding		
1055-1059	Subgingival debridement only	Subgingival debridement alone
8.1 Sample Size		
1070-11077	A total of 246 patients will be randomized, 123 patients for the Subgingival debridement + PerioChip® arm and 123 patients for the Subgingival debridement alone arm. 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 336 patients will be screened in order to randomize 246 patients.	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.