2 SYNOPSIS

Sponsor: Dexcel Pharma Technologies Ltd. (hereafter referred to as DPT)

Name of Investigational Product: PerioChip® (chlorhexidine gluconate chip; hereafter referred to as PerioChip)

Study Number: CLI/016P

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

Investigators: Ten investigators participated in the study.

Study Centers and Countries: This study was performed at 10 study sites in Germany (1 site), Israel (2 sites), the United Kingdom (1 site), and the United States (6 sites).

Publication: Machtei EE, Romanos G, Kang P, Travan S, Schmidt S, Papathanasiou E, et al. Repeated delivery of chlorhexidine chips for the treatment of periimplantitis: A multicenter, randomized, comparative clinical trial. J Periodontol. 2020 Oct 28. doi: 10.1002/JPER.20-0353.

Phase: 3

Initiation Date (first patient screened): 19 August 2014

Completion Date (last patient last visit): 28 June 2018

Previous Reports for This Study: Not applicable

Objectives: The primary objective of the study was to compare the mean probing pocket depth (PD) reductions (absolute change) for the selected target implant(s) at Week 24 compared to Baseline. Secondary objectives were as follows: PD measurement at Week 24 compared to Baseline in patients with Baseline PD measurement of 6 to 8 mm (inclusive), bleeding on probing (BOP) measurements at Weeks 16 and 24 compared to Baseline, and PD measurement at Week 16 compared to Baseline.

METHODS

Design: This study was a Phase 3, multicenter, randomized, single-blind masking, parallel, 2-arm clinical study designed to examine the efficacy and safety of the PerioChip versus subgingival debridement in adult patients with peri-implantitis.

Adult male and female patients aged ≥18 years with peri-implantitis who satisfied the inclusion and exclusion criteria were eligible for enrollment in the study. Randomization of approximately 290 patients was planned to permit analysis of at least 246 patients.

The study consisted of a Screening/Hygienic Phase (Weeks -3 through -1), Treatment Phase (Weeks 0 through 12), and Follow-up Phase (Weeks 16 through 24). After completion of the Screening/Hygienic Phase, patients underwent selection of the deepest periodontal pockets from at least 1 and not more than 2 implants at Baseline (Week 0). Eligible patients were randomized equally to 1 of the following 2 treatment arms:

- PerioChip + subgingival debridement: For each target pocket (5 to 8 mm PD), patients underwent PerioChip insertion every 2 weeks from Baseline through Week 12 along with subgingival debridement at Baseline and Week 12.
- Subgingival debridement: For each target pocket, patients underwent subgingival debridement at Baseline and Week 12.

During the Treatment Phase, patients received their assigned treatment at each target pocket during each visit. Implants that were not selected as targets were treated per the investigator's discretion as long as treatment was consistent with the study inclusion/exclusion criteria.

Study assessments included pocket examination and measurements (ie, PD, BOP, recession, and relative attachment level) at each target implant/pocket along with standard safety evaluations and other oral inspection parameters. Calibrated examiners performed all measurements during the study.

The study used a single-blind masking design, in which patients and clinicians responsible for administering treatment (ie, placing PerioChips in the periodontal pockets and/or performing subgingival debridement) were aware of treatment arm assignments but separate clinicians who were not aware of treatment arm assignments were responsible for performing the other study assessments. All pocket measurements and chip insertions were completed in the same order at each study visit.

Patients were provided toothpaste and toothbrushes for exclusive use during the study and instructed regarding the importance of good oral hygiene. Use of chlorhexidine oral rinses/mouthwashes was restricted during study participation.

The total duration of patient participation in the study, including the Screening/Hygienic Phase, was 25 to 28 weeks.

Number of Patients (planned, enrolled, and analyzed):

- Planned: Randomization of approximately 290 patients was planned to permit analysis of at least 246 patients.
- Enrolled: Out of a total of 370 patients screened for the study, 290 patients were enrolled: 146 patients in the PerioChip + subgingival debridement arm and 144 patients in the subgingival debridement arm.
- Analyzed: All 290 enrolled patients were included in the Intent-to-Treat (ITT) population used for efficacy and safety analyses. Numbers of patients analyzed in the supportive Modified ITT (mITT), Per Protocol (PP), and Additional PP (PP2) populations are presented in the body of the report.

Diagnosis and Main Criteria for Inclusion: Adult patients with peri-implantitis were eligible for enrollment. Patients must have had at least 1 implant in the oral cavity with clinical and radiographical signs of peri-implantitis, as evidenced by at least 1 of the 4 aspects measured (mesiobuccal, midbuccal, distobuccal, and midlingual) showing radiographic evidence of bone loss of at least 3 mm from the implant shoulder (with at least 2 mm distal and mesial supporting bone left from the apex to the coronal direction), bleeding and/or suppuration on probing, and a peri-implant PD of 5 to 8 mm. Patients who used chlorhexidine oral rinses/mouthwashes on a regular basis, who had a history of allergic reaction to chlorhexidine, or who had technical and/or other limitations that could have precluded study procedures were excluded from the study.

Investigational Products, Dose and Mode of Administration, Batch Number: PerioChips were manufactured by DPT (Israel) according to the approved manufacturing process. Each chip contained 2.5 mg of chlorhexidine gluconate formulated in a biodegradable, crosslinked gelatin matrix. Patients receiving PerioChip + subgingival treatment received treatment every 2 weeks from Baseline (Week 0) to Week 12. Patients may have received up to 2 PerioChips (5 mg chlorhexidine gluconate) per target implant and up to 4 PerioChips (10 mg chlorhexidine gluconate) total across all implants, with the dose of chlorhexidine gluconate administered to each implant determined by the number of chips inserted into a single implant and being a function of the implant's pocket width. Batch numbers used in this study were as follows: BY011013, BY150714, BY310716, and BY201216. Patients receiving subgingival debridement underwent the treatment procedure at Baseline (Week 0) and at Week 12.

Duration of Treatment: 12 weeks

Endpoints: The primary endpoint was the mean PD reduction (absolute change) for the selected target implant(s) at Week 24 compared to Baseline. Secondary endpoints were PD measurement at Week 24 compared to Baseline in patients with a Baseline PD measurement of 6 to 8 mm (inclusive), BOP measurements at Weeks 16 and 24 compared to Baseline, and PD measurement at Week 16 compared to Baseline.

Statistical Methods:

Statistical analyses were done using SAS® (SAS Institute, Cary, North Carolina) version 9.3 or higher. All treatment comparisons were 2-sided and used a significance level of 0.05. All measured variables and derived parameters were listed individually and, if appropriate, tabulated by descriptive statistics.

Efficacy Analyses

For the primary endpoint, the change in PD over 24 weeks at the target pocket was modelled using a mixed linear model with treatment as a fixed factor and patient and pocket as random effects. Interactions between treatment and selected covariates were tested and added to the model if they achieved statistical significance of ≤5%. The analysis was adjusted for covariates, and the adequacy of the mixed model was checked. Contrasts with 95% confidence intervals for the difference between the changes by week were computed.

A paired t-test or signed rank test for 2 means (paired observations) was applied to test the significance of the PD reduction at each time point within each treatment arm. A 2-sample t-test or nonparametric median test for independent samples was applied to test the significance of the difference in the percent PD reduction from Baseline between treatment arms. Logistic regression was applied to assess categorical changes at Week 24, with adjustment for Baseline measurement, age, sex, site, and smoking status (where applicable). Interactions between treatment and covariates were tested and added to the model if they were statistically significant. An analysis of covariance, with adjustment for Baseline measurement, age, sex, site, and smoking status (where applicable), was used to assess the PD change at Weeks 8, 12, 16, and 24. Interactions between treatment and covariates were tested and added to the model if they were statistically significant.

Changes in secondary and exploratory efficacy parameters during the study were modeled using a mixed linear model similar to that used for the primary endpoint. An ordered testing paradigm was used for the assessment of secondary efficacy endpoints.

Safety Analyses

The primary safety evaluation compared the number of treatment-emergent adverse events (TEAEs) reported for each treatment arm. In addition, treatment arms were compared to detect any treatment-related differences the number of dental-related TEAEs (eg, dental or gingival pain) and observed changes in the clinical appearance of the tissues at each oral inspection relative to Baseline. The time of first occurrence of dental-related TEAEs was also evaluated to assess the association of these events with chip insertion. Chi-square and Fisher's exact tests were applied to detect differences in safety parameters between treatment arms.

RESULTS

Patient Disposition:

The rate of premature withdrawal from the study was low and similar between treatment arms, with the most frequent (>25% of withdrawn patients in either treatment arm) reasons for premature withdrawal

being protocol violation, adverse events (AEs), and withdrawal by patient. The overall study completion rate was 90.7%.

Baseline Demographics:

The majority of patients were female, white, and not Hispanic or Latino, with a mean (standard deviation) age of 62.6 (11.38) years. Demographic and Baseline characteristics were well balanced between treatment arms, and there were no noteworthy differences between treatment arms for any pocket examination characteristics at any aspect assessed at the Screening or Baseline Visits.

Efficacy Results:

Overall, the study met its primary endpoint, which assessed PD reduction from Baseline to Week 24. By-pocket and by-patient analyses of the primary endpoint demonstrated that PD decreased significantly from Baseline to Week 24 for both treatment arms, with the magnitude of the PD reduction and the percentage of implants/patients with large (≥2 mm) reductions being numerically greater for the PerioChip + subgingival debridement arm than subgingival debridement arm. Although univariate analyses of the ITT population did not reveal significant differences between treatment arms, results of the mixed linear model in this population suggested greater PD reductions from Baseline to Week 24 among the PerioChip + subgingival debridement arm than subgingival debridement arm. Further, univariate and adjusted analyses of the mITT and PP2 populations demonstrated substantially greater efficacy in the PerioChip + subgingival debridement arm than subgingival debridement arm. The timing of the PD reduction was distinct between treatment arms, with reductions tending to occur slowly and consistently throughout the 24-week observation period for the PerioChip + subgingival debridement arm versus rapidly early in observation for the subgingival debridement arm. Together, these results demonstrate that PerioChip as an adjunct to subgingival debridement resulted in a greater PD reduction from Baseline to Week 24 than subgingival debridement alone.

Analyses of the secondary endpoints did not reveal significant differences between treatment arms. Among implants with a Baseline PD of 6 to 8 mm, PD decreased significantly from Baseline to Week 24 in both treatment arms, with the magnitude of the mean PD reduction and the percentage of implants with large reductions again being numerically greater for the PerioChip + subgingival debridement arm than subgingival debridement arm. However, with the exception of analyses conducted on the PP2 population, differences between treatment arms were not statistically significant. Given the lack of a significant difference between treatment arms for this secondary endpoint, significance testing was not conducted for the remaining efficacy endpoints. Analyses of BOP revealed improvement in bleeding over the course of the study. At Baseline, the majority of the target pockets selected for treatment had BOP, whereas approximately half had BOP at Week 24. BOP improvements were also reflected in the proportion of implants with shifts in BOP status (ie, from bleeding to no bleeding) from Baseline to Week 24. The magnitude of the PD reduction and the percentage of implants with large reductions from Baseline to Week 16 were similar between treatment arms.

Safety Results:

Overall, study treatment was well tolerated in both treatment arms. Although a substantial minority of patients (PerioChip + subgingival debridement: 41.1%, subgingival debridement: 34.0%) reported TEAEs during the study, most patients reporting TEAEs had events that were mild in severity. Dental-related TEAEs accounted for a notable fraction of TEAEs reported during the study and were more common among patients receiving PerioChip + subgingival debridement (26.7%) than subgingival debridement alone (13.9%). The most commonly reported TEAE preferred terms across all patients were implant site pain, nasopharyngitis, and post procedural discomfort. The incidences of treatment-related TEAEs and dental-related, treatment-related TEAEs were higher among patients receiving PerioChip + subgingival debridement (12.3% and 11.6%, respectively) than subgingival debridement

alone (1.4% and 0.7%, respectively), with treatment-related events reported for at least 2 patients overall being implant site pain, post procedural discomfort, and implant site swelling.

Two patients, both in the subgingival debridement treatment arm, had TEAEs resulting in death during the study. The TEAEs were not considered related to study treatment. The incidence of serious TEAEs was low for both treatment arms (PerioChip + subgingival debridement arm: 2.7%, subgingival debridement arm: 2.1%), and no individual serious TEAE preferred terms were reported for more than a single patient. No dental-related serious TEAEs were reported during the study. TEAEs leading to study withdrawal were infrequent in both treatment arms, and no individual preferred term led to withdrawal of more than 1 patient. The only dental-related TEAEs leading to study withdrawal were implant site exfoliation and medical device removal.

Results of other safety examinations (eg, oral inspections, plaque and gingival examinations, and dental changes since the prior visit) revealed no safety concerns during the study.

CONCLUSIONS:

Overall, the results of this study demonstrated favorable efficacy and safety results for PerioChip + subgingival debridement in the treatment of patients with peri-implantitis. The study met its primary endpoint, with the magnitude of the mean PD reduction and the percentage of implants with large PD reductions being numerically greater for the PerioChip + subgingival debridement arm than subgingival debridement arm at Week 24 and selected adjusted analyses confirming greater PD reductions from Baseline to Week 24 among the PerioChip + subgingival debridement arm. Analyses of secondary efficacy endpoints did not reveal significant differences between treatment arms. Treatment with PerioChip + subgingival debridement was well tolerated, with no unexpected safety findings.

Date of Report: 13 April 2021