Platelet-Derived Growth Factor Promotes Periodontal Regeneration in Localized Osseous Defects: 36-Month Extension Results From a Randomized, Controlled, Double-Masked Clinical Trial

Myron Nevins,* Richard T. Kao,† Michael K. McGuire,‡ Pamela K. McClain,§ James E. Hinrichs,‖ Bradley S. McAllister,¶ Michael S. Reddy,# Marc L. Nevins,* Robert J. Genco,** Samuel E. Lynch,†† and William V. Giannobile‡‡

Background: Recombinant human platelet-derived growth factor (rhPDGF) is safe and effective for the treatment of periodontal defects in short-term studies up to 6 months in duration. We now provide results from a 36-month extension study of a multicenter, randomized, controlled clinical trial evaluating the effect and long-term stability of PDGF-BB treatment in patients with localized severe periodontal osseous defects.

Methods: A total of 135 participants were enrolled from six clinical centers for an extension trial. Eighty-three individuals completed the study at 36 months and were included in the analysis. The study investigated the local application of β-tricalcium phosphate scaffold matrix with or without two different dose levels of PDGF (0.3 or 1.0 mg/mL PDGF-BB) in patients possessing one localized periodontal osseous defect. Composite analysis for clinical and radiographic evidence of treatment success was defined as percentage of cases with clinical attachment level (CAL) ≥2.7 mm and linear bone growth (LBG) ≥1.1 mm.

Results: The participants exceeding this composite outcome benchmark in the 0.3 mg/mL rhPDGF-BB group went from 62.2% at 12 months, 75.9% at 24 months, to 87.0% at 36 months compared with 39.5%, 48.3%, and 53.8%, respectively, in the scaffold control group at these same time points ($P<0.05$). Although there were no significant increases in CAL and LBG at 36 months among all groups, there were continued increases in CAL gain, LBG, and percentage bone fill over time, suggesting overall stability of the regenerative response.

Conclusion: PDGF-BB in a synthetic scaffold matrix promotes long-term stable clinical and radiographic improvements as measured by composite outcomes for CAL gain and LBG for patients possessing localized periodontal defects (ClinicalTrials.gov no. CT01530126). *J Periodontol 2013;84:456-464.*

KEY WORDS

Bone regeneration; periodontics; platelet-derived growth factor; randomized controlled trial; regenerative medicine; tissue engineering.

* Division of Periodontology, Department of Oral Medicine, Infection, and Immunity, Harvard School of Dental Medicine, Boston, MA.
† Private practice, Cupertino, CA.
‡ Private practice, Houston, TX.
§ Private practice, Aurora, CO.
‖ School of Dentistry, University of Minnesota, Minneapolis, MN.
¶ Private practice, Tigard, OR.
# Department of Periodontology, University of Alabama, Birmingham, AL.
** University at Buffalo, Buffalo, NY.
†† Biomimetic Therapeutics, Franklin, TN.
‡‡ Michigan Center for Oral Health Research and Department of Periodontics and Oral Medicine, University of Michigan, Ann Arbor, MI.

Platelet-derived growth factor (PDGF) is a thoroughly studied growth factor in clinical periodontics for the treatment of localized periodontal osseous and soft tissue defects.[1-3] Since PDGF was first discovered to promote the regeneration of bone, cementum, and periodontal ligament (PDL),[4] nearly 100 investigations have been published on its effect on PDL and alveolar bone and on the regeneration of the periodontium preclinically and clinically.[5-9] A number of studies have clearly demonstrated the presence of cell surface receptors for PDGF on PDL and alveolar bone cells and elucidated the stimulatory effect of PDGFs on the proliferation and chemotaxis of these cells.[10,11] Recombinant human PDGF (rhPDGF-BB) promotes the regeneration of periodontal tissue, including bone, cementum, and PDL in vivo.[6,12-17] A clinical trial studying the application of 0.15 mg/mL rhPDGF-BB and 0.15 mg/mL recombinant human insulin-like growth factor I to local periodontal defects resulted in a significant improvement in bone fill compared with conventional surgery plus a vehicle control.[18] Furthermore, rhPDGF-BB (becaplermin) has been clinically available for >10 years for the treatment of chronic neuropathic and diabetic cutaneous ulcers.[19,20]

A proof-of-principal case series demonstrated the capability of satisfying the definition of periodontal regeneration for both infrabony and Class II furcation defects. The treatment used rhPDGF with a matrix of bone allograft with the biopsy harvest of the tooth, and supporting periodontium after 6 months showed clear evidence of the stimulation of new bone, cementum, and PDL.[21]

The growth-factor-enhanced matrix system is a fully synthetic bone regeneration system composed of a purified recombinant PDGF§§ and a synthetic calcium phosphate matrix.[9]‖‖ This combination therapy has received Food and Drug Administration (FDA) clearance for its use in the treatment of osseous defects, to act physically as a filler and provide a biocompatible, osteoconductive, three-dimensional matrix to facilitate new bone formation.[22] The original clinical trial from which this long-term evaluation was derived evaluated the application of the matrix with buffer alone and buffer containing one of two concentrations, 0.3 or 1.0 mg/mL rhPDGF-BB. This pivotal trial enrolled 180 patients with infrabony defects, 77% of which included a component of 1- and 2-wall morphologies.[9] The 6-month follow-up evaluation demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of periodontal osseous defects. A similar study was recently published by an independent research team who corroborated the findings in a randomized clinical trial of 54 human participants (Clinicaltrials.gov no. NCT00496847).[7]

To evaluate the long-term stability of the improved radiographic and clinical parameters resulting from the use of scaffold + rhPDGF-BB, an extension study to the pivotal clinical trial was performed. Endpoints included changes in clinical attachment level (CAL), probing depth (PD), linear bone growth (LBG), percentage bone fill (%BF), and composite outcome of bone and CAL with evaluations at 12, 24, and 36 months from a subset of six of the original 11 centers that participated in the pivotal trial.

MATERIALS AND METHODS

This long-term study was an extension of the pivotal trial by Nevins et al.[9] and included clinical and radiographic evaluations at 12, 24, and 36 months after implantation of the study device (Fig. 1A). All participants provided written informed consent in accordance with the Institutional Review Board of each participating center. The pivotal study was conducted at 11 centers, enrolling a total of 180 participants with advanced periodontal defects (Fig. 1B). The initial study population was randomized into three treatment groups of 60 participants each: 1) β-tricalcium phosphate (β-TCP) (scaffold) with sodium acetate buffer alone; 2) β-TCP with sodium acetate buffer containing 0.3 mg/mL rhPDGF-BB; and 3) β-TCP with sodium acetate buffer containing 1.0 mg/mL rhPDGF-BB.

All participants who completed the treatment and follow-up phases (visits 1 through 13) were eligible for entry into the extension study. Postoperative visits were scheduled for the extension period (visits 14 through 17) from a total of six of the 11 centers involved in pivotal trial (the centers of WVG, JEH, RTK, BSM, PKM, and MKM).[9] Centers withdrew from the study principally because patients returned to their primary dentist for maintenance care.

The effectiveness measures consisted of CAL gain, PD reduction (PDR), gingival recession (GR), radiographic LBG, and radiographic %BF, as described previously.[9] Additional analyses were performed, comparing the percentage of participants (test treatments compared to active control) meeting combined historical benchmarks of effectiveness for CAL gain and radiographic LBG and CAL gain and radiographic %BF to determine the percentage of participants having a successful outcome at 12, 24, and 36 months after treatment from 2001 to 2006.[23]

The expected duration of participant involvement in the extended study was 36 months after implantation of the study device. Study follow-up visits, including clinical and radiographic evaluation, represent the standard of care for participants receiving

§§ BioMimetic Therapeutics, Franklin, TN.
‖‖ Gem 21S, Osteohealth, Shirley, NY.
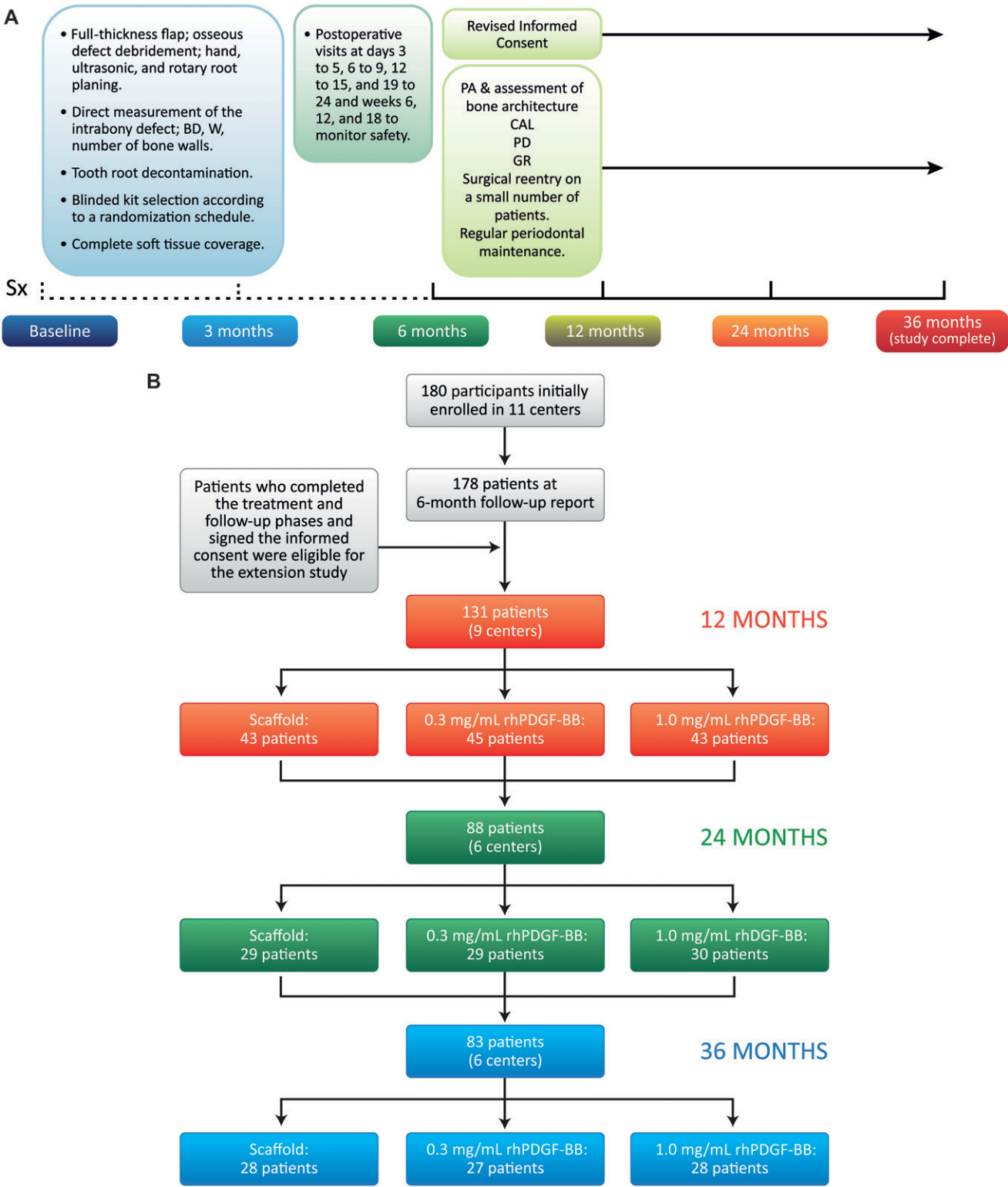
Figure 1.
A) Study timeline of the extension investigation. Patients were randomized at baseline and followed up at 3, 6, 12, 24, and 36 months after surgery and device delivery. BD = bone depth; W = width; GR = gingival recession; Sx = surgery. B) Patient disposition Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients from initial entry and 6, 12, 24, and 36 months after therapy.
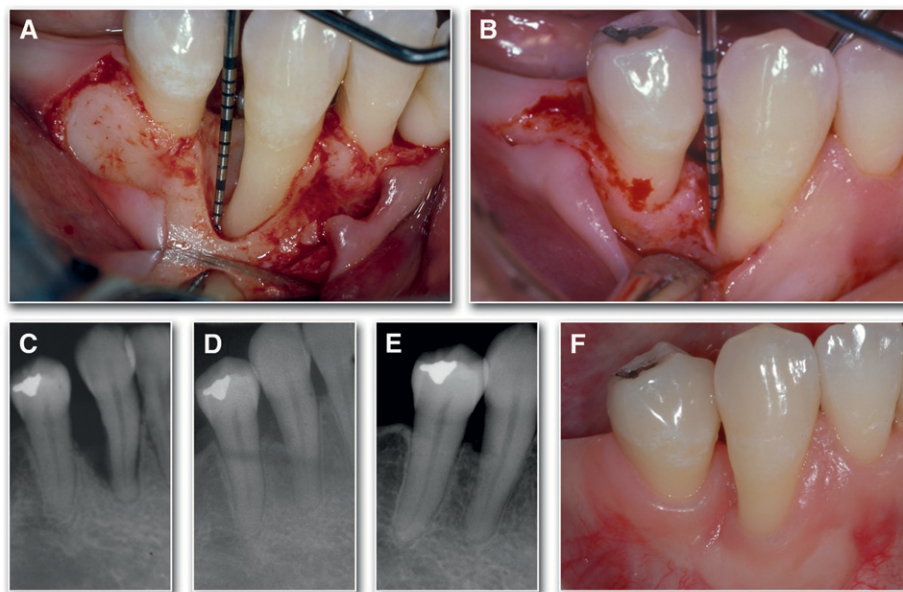
Figure 2.
PDGF promotes periodontal bone repair. A patient with a localized bony defect as initially described in the original study cohort[9] is shown. The baseline defect (A), the 1-year reentry (B), the baseline radiograph (C), the 3-year postoperative radiograph (D), and the 10-year postoperative radiograph (E) and clinical photograph (F), demonstrating periodontal repair and stability of the result.
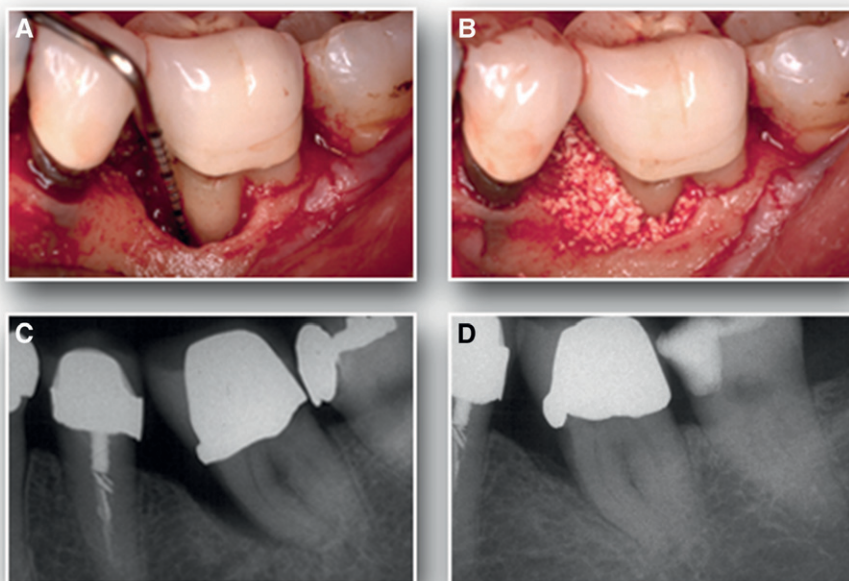
Figure 3.
PDGF promotes periodontal wound repair. A localized osseous defect (A) has PDGF-BB delivered to the defect in the scaffold matrix (B). Radiographs at baseline (C) and 3 years postoperative (D).

regular dental care and provided nothing in addition to what is provided in routine patient management care.

Participants were discontinued from the study if 1) the participant requested to be withdrawn from the study or 2) the principal investigator decided that it was in the participant's best interest to discontinue participation in the study (e.g., more efficient for patient to go to general dentist for maintenance care). Five of the original study centers decided not to participate in the extension study.

An Internet-based remote data entry system¶¶ was used to collect clinical trial data at the investigational sites. The system complied with FDA Title 21 Code of Federal Regulations Part II and was used to enter, modify, maintain, archive, retrieve, and transmit data. The study was conducted in accordance with good clinical practice (GCP) standards in that all collected data were supported by complete and thorough source documentation as verified by the study monitors.

An interexaminer quality assurance procedure was conducted using a masked periodontist to independently evaluate the radiographs and identify potential discrepancies of ≥20% in bone fill for reassessment by the radiologic technician. The potential discrepancies were queried by the periodontist conducting the review and were reassessed and verified or corrected by the radiographic technician and the study director. Corrections and revisions were documented in conformance with GCPs.

Effectiveness data were examined and summarized by descriptive statistics. Categorical measurements were

¶¶ Target e*CRF, Target Health, New York, NY.
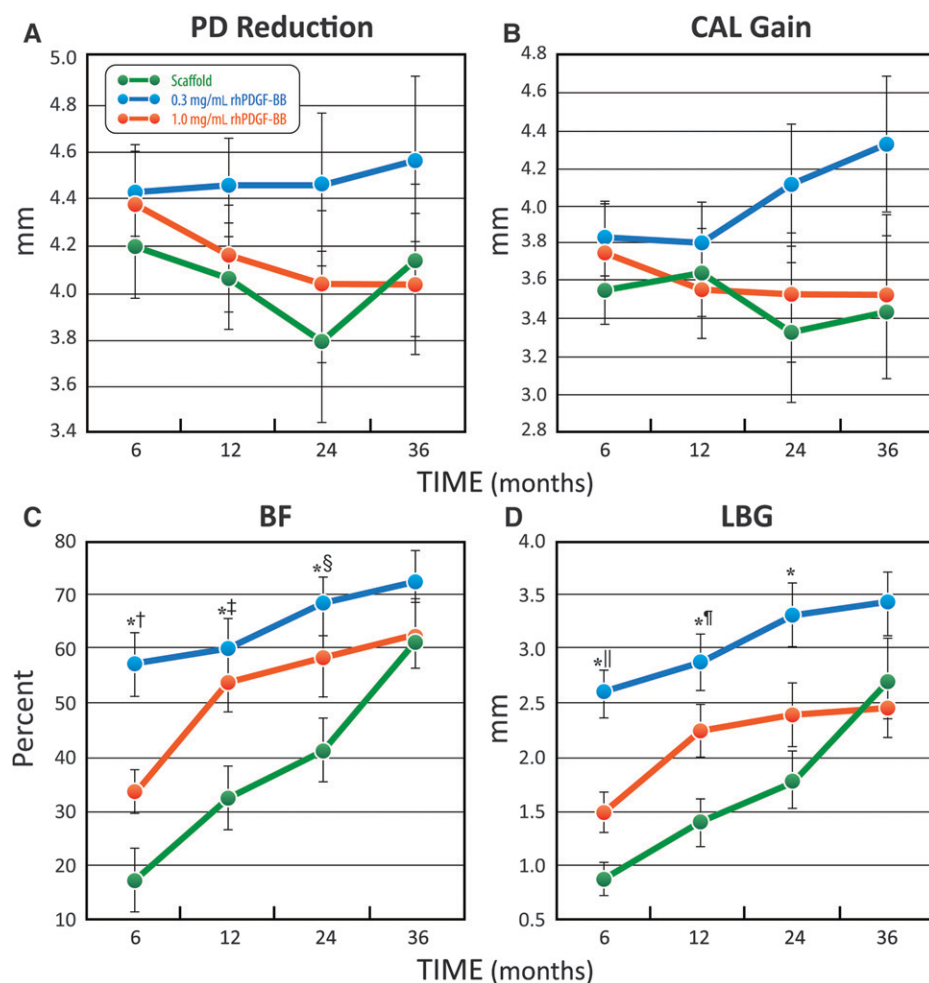
Figure 4.
PDGF delivery promotes CAL gain, PDR, and bone gain. A) PDR over time among groups. B) CAL gain. C) %BF. D) LBG. n = 83 to 178 participants per group (for details, see Fig. 1B). Bars show mean ± SD. *P <0.001 for scaffold vs. 0.3 mg/mL rhPDGF-BB; †P = 0.019, ‡P <0.007, §P = 0.022, ‖P = 0.021, ¶P = 0.008 for scaffold vs. 1.0 mg/mL rhPDGF-BB.

fectiveness for change in CAL (2.7 mm) and LBG (1.1 mm) as described previously.[23] An additional survivor analysis was performed to show that the baseline data from the survivor population of the extension study is representative of the results from the population of the original study cohort at baseline.[9] The study was designed and powered for the 6-month endpoint, and, given that there was a reduction in study centers for the extension study, there was a reduction in statistical power. "Survivors" are defined as those participants from the original 6-month study that participated in the 12-, 24-, and/or 36-month extension study. The smoking status and defect classification at baseline, clinical (CAL gain, PDR, and GR change) and radiographic (LBG and %BF) assessments at 6 months were examined for the 12-, 24-, and 36-month survivors and non-survivors. The statistical comparisons for these assessments, between survivors and non-survivors, at the three time points (12, 24, and 36 months) were made using a χ^2 test for the categorical measurements and ANOVA for the continuous measurements.

displayed as counts and percentages, and continuous variables were displayed as means, medians, standard deviations, and ranges. Statistical comparisons between the test product treatment groups (0.3 and 1.0 mg/mL PDGF in carrier) and the scaffold alone were made using χ^2 or Fisher exact test for categorical variables and t tests or analysis of variance methods (ANOVA) for continuous variables. In addition, an analysis of covariance model included the baseline covariates of defect class, and current smoking status was applied to control for covariates when estimating the treatment effect.

Comparisons among treatment groups for ordinal variables were made using Cochran-Mantel-Haenszel methods. $P \leq 0.05$ (one-sided) was considered to be statistically significant for CAL, LBG, and %BF. Composite endpoint analyses used literature reference means to identify historical benchmarks of ef-

RESULTS

A survivor analysis was performed to establish that participants involved in the 12-, 24-, and 36-month extension study ("survivors") for each treatment group were not statistically significantly different from the participants not participating in the extension study ("non-survivors") with regard to baseline defect characteristics and participant demographics, as well as 6-month clinical and radiographic results. Overall, there were no statistically significant differences observed among the survivor and non-survivor populations for all parameters tested at baseline (except for defect characteristics at the coronal portion of the lesions for the 36-month population), confirming the ability to evaluate for changes in clinical and radiographic parameters at 12, 24, and 36 months from baseline and the original 6-month conclusion of the

COMPOSITE OUTCOME ANALYSIS
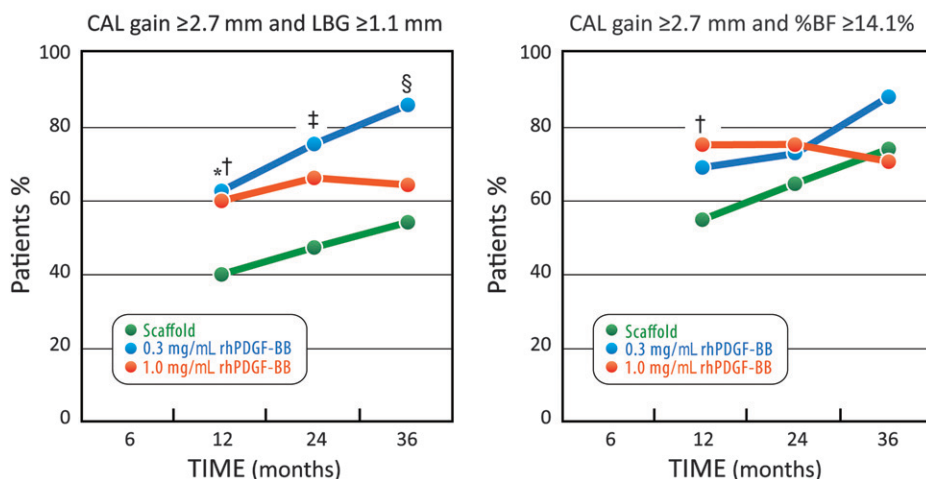
Figure 5.
Composite outcome analysis of CAL and LBG shows 0.3 mg/mL PDGF stimulates periodontal regeneration.
***A)** The percentage of participants demonstrating CAL > 2.7 mm and LBG > 1.1 mm. **B)** Composite outcome of CAL and %BF. *P = 0.017 for scaffold vs. 0.3 mg/mL rhPDGF-BB; †P <0.03 for scaffold vs. 1.0 mg/mL PDGF-BB; ‡P = 0.015, §P = 0.006 for scaffold vs. 0.3 mg/mL PDGF-BB.*

trial. Some examples of cases treated in the trial for ≥3 years are shown in Figures 2 and 3.

The clinical improvements observed 6 months after surgery for both rhPDGF-BB treatment groups persisted throughout the 12-, 24-, and 36-month visits and are shown in Figure 4. Similarly to the original report, the 0.3 mg/mL rhPDGF-BB + scaffold group showed the greatest improvement in CAL gain and PDR throughout the 36-month study (Fig. 4).

The 0.3 mg/mL rhPDGF-BB + scaffold treatment demonstrated a statistically significant increase from baseline compared with treatment with scaffold alone in radiographic LBG (mm) and radiographic %BF in participants at the 12-month (LBG, 2.88 versus 1.42; %BF, 60.5 versus 32.6; $P \leq 0.001$) and the 24-month (LBG, 3.32 versus 1.81; %BF, 68.3 versus 41.5; $P \leq 0.001$) postoperative visits. The 1.0 mg/mL rhPDGF-BB + scaffold treatment also demonstrated a statistically significant increase in LBG and %BF from baseline compared with the scaffold control (LBG, 2.25 versus 1.42, $P = 0.008$; %BF, 53.7 versus 32.6, $P <0.007$) in participants who completed the 12-month postoperative visit and in %BF (57.3 versus 41.5, $P = 0.022$) in participants who completed the 24-month postoperative visit. These improvements persisted throughout the 36-month follow-up period, although they were not significant. At the 6-month postoperative visit, both the 0.3 mg/mL rhPDGF-BB + scaffold and 1.0 mg/mL rhPDGF-BB treatment demonstrated a statistically significant increase in LBG and improvement in %BF compared with the control ($P \leq 0.001$).

To assess the cumulative beneficial effect for clinical and radiographic outcomes, a composite analysis was performed to determine the percentage of participants with a successful outcome as defined by CAL ≥2.7 mm and LBG ≥1.1 mm or by CAL ≥2.7 mm and %BF ≥14.1% at 12, 24, and 36 months (Fig. 5).

At the 12-month postoperative visit, 62.2% of the 0.3 mg/mL rhPDGF-BB group and 60.5% of the 1.0 mg/mL rhPDGF-BB group exceeded the composite benchmark for success compared to 39.5% of the scaffold group, resulting in a statistically significant benefit in CAL ≥2.7 mm and LBG ≥1.1 mm ($P = 0.017$ and 0.026, respectively). For the composite analysis of CAL and %BF, the only difference was at 12 months for the 1.0 mg/mL dose of PDGF versus the scaffold ($P <0.05$).

At the 24-month postoperative visit, 75.9% of the 0.3 mg/mL rhPDGF-BB group exceeded the composite benchmark for success compared with 48.3% of scaffold group participants, resulting in a statistically significant benefit in CAL ≥2.7 mm and LBG ≥1.1 mm ($P = 0.015$). The results of the 3-year long-term extension study demonstrate statistically significant composite CAL and LBG benefits for both rhPDGF-BB treatment groups (0.3 and 1.0 mg/mL rhPDGF-BB + scaffold) compared with scaffold alone based on historical benchmarks of effectiveness.

The influence of smoking and defect type are shown in Figure 6. It was noted that the greatest responses in LBG and %BF were for defects treated with 0.3 mg/mL PDGF in the scaffold matrix (data not shown for the 1.0 mg/mL PDGF-BB dose). However, these differences were not significant at the 12-, 24-, and 36-month time points for all of the clinical measures when comparing the 0.3 mg/mL PDGF dose to matrix alone or matrix plus 1.0 mg/mL PDGF (Figs. 2 through 4). For 1- to 2-wall defects versus 3-wall/circumferential defects, all groups demonstrated increases over time, but no differences were shown when the defects were stratified in this manner by 36 months (Fig. 6).

DISCUSSION

The optimal goal of periodontal treatment regimens is to restore periodontal health and to retain the result over a significant time frame. Periodontal regeneration
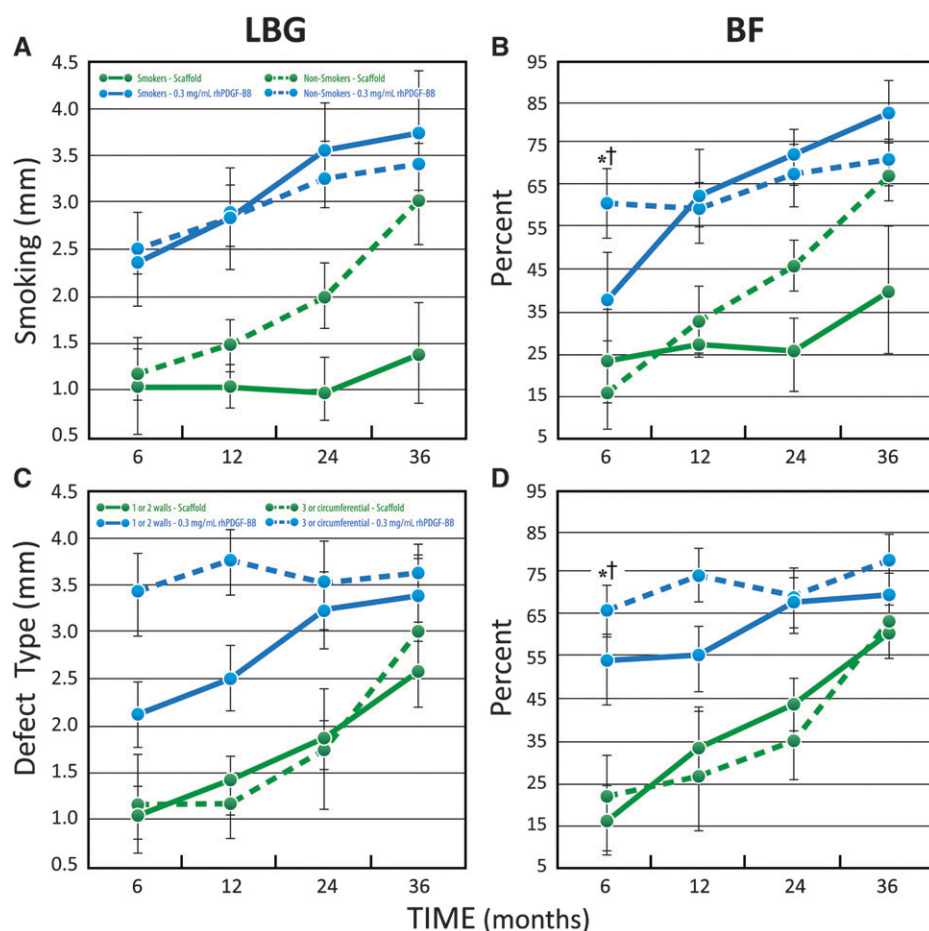
Figure 6.
*Effect of smoking (**A** and **B**) and defect type (**C** and **D**) on LBG (A and C) and %BF (B and D). Bars show mean ± SD (for details, see Fig. 1B). *P <0.001 for scaffold vs. 0.3 mg/mL rhPDGF-BB; †P <0.03 for scaffold vs. 1.0 mg/mL PDGF-BB (data not shown).*

is defined as providing new cementum, new bone, and a new PDL on a tooth surface previously exposed to disease.[24] This should improve the prognosis of the tooth by making the area amenable to patient and therapist debridement procedures. Over the past years, there have been significant interest and encouraging outcomes in the development of growth factor–based therapies to stimulate periodontal regeneration,[25,26] with the recent publication of several important randomized controlled clinical trials and case series using growth factors, such as PDGF-BB,[7,27] fibroblast growth factor-2,[28] and growth and differentiation-5.[29] These trials highlight the continued investigation of the field of growth factor biology and bioengineering technologies to promote regeneration of periodontal osseous defects. As such, it is important to extend these studies to the long term to identify how well these regenerative strategies support long-term success. Furthermore, when comparing these findings to more well-studied regenerative biomaterials as summarized in meta-analyses

of guided tissue regeneration[30,31] and enamel matrix derivative,[32] these results compare favorably for CAL gain, bone height, and bone fill in short-term and long-term trials.[33]

The use of 0.3 mg/mL rhPDGF-BB + scaffold for the treatment of periodontal osseous defects resulted in the greatest CAL gain and PDR, with significantly greater increases in radiographic LBG and %BF from baseline compared with sites treated with scaffold alone through 24 months. At 36 months, the effect was sustained but no longer statistically significant, which may have been attributable to the lessened power because the original power calculation was performed on the 6-month endpoint for FDA clearance.[9] The clinical significance of these results is further confirmed by comparison to historical controls.

Descriptive subgroup analyses (no *P* values) were performed to determine baseline characteristic trends that could influence effectiveness outcomes (data not shown). The radiographic LBG and %BF measurements at the 6-, 12-, 24-, and 36-month postoperative follow-up visits, for participants who completed the entire follow-up continuation study, by smoking status, bone defect depth, and defect class overall, showed limited differences as a result of stratifications of the overall small sample sizes per group (27 to 28 participants per group) (Fig. 1B). The trends demonstrated overall lessened responses in effectiveness attributable to smoking on the effectiveness for all therapies, consistent with the impact of smoking on regeneration and the cellular response.[34,35] Of interest, it appeared that there was an enhanced effect of PDGF on promoting healing in smokers compared with non-smokers. It is not clear as to this mechanism, but it has been noted that activation of nicotine receptors via smoking leads to increased transcription and expression of PDGF-β receptors (the most responsive receptors to PDGF protein).[36] As such, there could be a process that allows this heightened response, but this result should be interpreted with caution given the

small sample size. In addition, the influence of bony defect type on the regenerative outcomes was also in alignment with other studies on regeneration, suggesting a greater impact on regeneration with a greater number of bony walls.[37] Although not significant, the trend still favored the addition of PDGF at the 0.3-mg/mL dose on the regenerative response compared with scaffold alone or scaffold + 1.0 mg/mL PDGF (Fig. 6). In both this study and the initial report at 6 months, 0.3 mg/mL PDGF is favored over the 1.0-mg/mL dose. The reasons are not completely clear, but it is likely that there is a feedback regulation of receptor expression because of the very high dosing of PDGF locally.[11]

rhPDGF-BB at 0.3 mg/mL is a bone regeneration system comprising a wound-healing agent and a biocompatible, osteoconductive, three-dimensional scaffold (β-TCP). This extension study report is based on 12-, 24-, and 36-month postoperative data available for clinical and radiographic measurements as summarized below.

rhPDGF-BB at 0.3 mg/mL was found to be an effective treatment for the restoration of soft tissue attachment level and bone as shown by the following: 1) a consistent improvement in CAL gain from baseline through 6, 12, 24, and 36 months after treatment; 2) significantly improved radiographic LBG and %BF compared with the scaffold control, between baseline and 6, 12, 24, and 36 months after treatment; and 3) significantly improved composite outcomes, combining hard- and soft- tissue measurements based on historical benchmarks of effectiveness (CAL and LBG) compared with the scaffold control.

CONCLUSION

rhPDGF-BB at 0.3 mg/mL was shown to result in significantly greater composite clinical and radiographic improvements, from baseline throughout the 36-month observation period, in moderate-to-severe 2- and 3-wall periodontal infrabony defects.

ACKNOWLEDGMENTS

REFERENCES

1. Kaigler D, Avila G, Wisner-Lynch L, et al. Platelet-derived growth factor applications in periodontal and peri-implant bone regeneration. *Expert Opin Biol Ther* 2011;11:375-385.
2. Hollinger JO, Hart CE, Hirsch SN, Lynch S, Friedlaender GE. Recombinant human platelet-derived growth factor: Biology and clinical applications. *J Bone Joint Surg Am* 2008;90(Suppl. 1):48-54.
3. Schilephake H. Bone growth factors in maxillofacial skeletal reconstruction. *Int J Oral Maxillofac Surg* 2002;31:469-484.
4. Lynch SE, Williams RC, Polson AM, et al. A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. *J Clin Periodontol* 1989;16:545-548.
5. Giannobile WV, Finkelman RD, Lynch SE. Comparison of canine and non-human primate animal models for periodontal regenerative therapy: Results following a single administration of PDGF/IGF-I. *J Periodontol* 1994;65:1158-1168.
6. Giannobile WV, Hernandez RA, Finkelman RD, et al. Comparative effects of platelet-derived growth factor-BB and insulin-like growth factor-I, individually and in combination, on periodontal regeneration in *Macaca fascicularis. J Periodontal Res* 1996;31:301-312.
7. Jayakumar A, Rajababu P, Rohini S, et al. Multi-centre, randomized clinical trial on the efficacy and safety of recombinant human platelet-derived growth factor with β-tricalcium phosphate in human intra-osseous periodontal defects. *J Clin Periodontol* 2011;38:163-172.
8. Nevins M, Camelo M, Nevins ML, Schenk RK, Lynch SE. Periodontal regeneration in humans using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and allogenic bone. *J Periodontol* 2003;74:1282-1292.
9. Nevins M, Giannobile WV, McGuire MK, et al. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: Results of a large multicenter randomized controlled trial. *J Periodontol* 2005;76:2205-2215.
10. Matsuda N, Lin WL, Kumar NM, Cho MI, Genco RJ. Mitogenic, chemotactic, and synthetic responses of rat periodontal ligament fibroblastic cells to polypeptide growth factors in vitro. *J Periodontol* 1992;63:515-525.
11. Yu X, Hsieh SC, Bao W, Graves DT. Temporal expression of PDGF receptors and PDGF regulatory effects on osteoblastic cells in mineralizing cultures. *Am J Physiol* 1997;272:C1709-C1716.
12. Cho MI, Lin WL, Genco RJ. Platelet-derived growth factor-modulated guided tissue regenerative therapy. *J Periodontol* 1995;66:522-530.

13. Lynch SE. The role of growth factors in periodontal repair and regeneration. In: Polson AM (ed.). Periodontal regeneration: Current status and directions. Berlin: Quintessenz; 1994:179-198.

14. Lynch SE, Genco R, Marx R. *Tissue Engineering: Applications in Maxillofacial Surgery and Periodontics.* Chicago: Quintessence; 1999:xi-xviii.

15. Lynch SE, de Castilla GR, Williams RC, et al. The effects of short-term application of a combination of platelet-derived and insulin-like growth factors on periodontal wound healing. *J Periodontol* 1991;62:458-467.

16. Park JB, Matsuura M, Han KY, et al. Periodontal regeneration in class III furcation defects of beagle dogs using guided tissue regenerative therapy with platelet-derived growth factor. *J Periodontol* 1995;66:462-477.

17. Rutherford RB, Niekrash CE, Kennedy JE, Charette MF. Platelet-derived and insulin-like growth factors stimulate regeneration of periodontal attachment in monkeys. *J Periodontal Res* 1992;27:285-290.

18. Howell TH, Fiorellini JP, Paquette DW, Offenbacher S, Giannobile WV, Lynch SE. A phase I/II clinical trial to evaluate a combination of recombinant human platelet-derived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. *J Periodontol* 1997;68:1186-1193.

19. Smiell JM; Becaplermin Studies Group. Clinical safety of becaplermin (rhPDGF-BB) gel. *Am J Surg* 1998;176 (Suppl. 2A):68S-73S.

20. Knight EV, Oldham JW, Mohler MA, Liu S, Dooley J. A review of nonclinical toxicology studies of becaplermin (rhPDGF-BB). *Am J Surg* 1998;176(Suppl. 2A):55S-60S.

21. Camelo M, Nevins ML, Schenk RK, Lynch SE, Nevins M. Periodontal regeneration in human Class II furcations using purified recombinant human platelet-derived growth factor-BB (rhPDGF-BB) with bone allograft. *Int J Periodontics Restorative Dent* 2003;23: 213-225.

22. U.S. Food and Drug Administration. GEM 21S (Growth-Factor Enhanced Matrix)-P040013. 2005. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078383.htm. Accessed April 29, 2012.

23. Lynch SE, Lavin PT, Genco RJ, Beasley WG, Wisner-Lynch LA. New composite endpoints to assess efficacy in periodontal therapy clinical trials. *J Periodontol* 2006;77:1314-1322.

24. Kao DW, Fiorellini JP. Regenerative periodontal therapy. *Front Oral Biol* 2012;15:149-159.

25. Giannobile WV, Hollister SJ, Ma PX. Future prospects for periodontal bioengineering using growth factors. *Clin Adv Periodontol* 2011;1:88-94.

26. Somerman M. Growth factors and periodontal engineering: Where next? *J Dent Res* 2011;90:7-8.

27. McGuire MK, Kao RT, Nevins M, Lynch SE. rhPDGF-BB promotes healing of periodontal defects: 24-month clinical and radiographic observations. *Int J Periodontics Restorative Dent* 2006;26:223-231.

28. Kitamura M, Akamatsu M, Machigashira M, et al. FGF-2 stimulates periodontal regeneration: Results of a multi-center randomized clinical trial. *J Dent Res* 2011;90:35-40.

29. Stavropoulos A, Windisch P, Gera I, Capsius B, Sculean A, Wikesjö UM. A phase IIa randomized controlled clinical and histological pilot study evaluating rhGDF-5/β-TCP for periodontal regeneration. *J Clin Periodontol* 2011;38:1044-1054.

30. Huynh-Ba G, Kuonen P, Hofer D, Schmid J, Lang NP, Salvi GE. The effect of periodontal therapy on the survival rate and incidence of complications of multi-rooted teeth with furcation involvement after an observation period of at least 5 years: A systematic review. *J Clin Periodontol* 2009;36:164-176.

31. Trombelli L, Heitz-Mayfield LJ, Needleman I, Moles D, Scabbia A. A systematic review of graft materials and biological agents for periodontal intraosseous defects. *J Clin Periodontol* 2002;29(Suppl. 3):117-135, discussion 160-162.

32. Koop R, Merheb J, Quirynen M. Periodontal regeneration with enamel matrix derivative (EMD) in reconstructive periodontal therapy. A systematic review. *J Periodontol* 2012;83:707-720.

33. Ramseier CA, Rasperini G, Batia S, Giannobile WV. Advanced reconstructive technologies for periodontal tissue repair. *Periodontol 2000* 2012;59:185-202.

34. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: Cellular and molecular mechanisms. *J Dent Res* 2012;91:142-149.

35. Patel RA, Wilson RF, Palmer RM. The effect of smoking on periodontal bone regeneration: A systematic review and meta-analysis. *J Periodontol* 2012;83:143-155.

36. Pestana IA, Vazquez-Padron RI, Aitouche A, Pham SM. Nicotinic and PDGF-receptor function are essential for nicotine-stimulated mitogenesis in human vascular smooth muscle cells. *J Cell Biochem* 2005;96:986-995.

37. Cortellini P, Bowers GM. Periodontal regeneration of intrabony defects: An evidence-based treatment approach. *Int J Periodontics Restorative Dent* 1995;15:128-145.

Correspondence: Dr. Myron Nevins, 90 Humphrey St., Swampscott, MA 01907. E-mail: nevinsperimp@aol.com.