A Novel PTH-Based Bone Graft Substitute Demonstrates Noninferiority to Autograft in a Large Phase IIb Study of Tibial Plateau Fractures

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Background/Purpose: A novel formulation containing a modified, covalently linkable parathyroid hormone (TGplPTH1-34) in fibrin with hydroxapatite/tricalcium phosphate

(HA/TCP) granules has been developed for the treatment of tibial plateau fractures (TPFs) following open reduction and internal fixation. Efficacy and safety of the product was compared to the clinical gold standard, cancellous autograft.

Methods: An open-label, controlled, randomized, dose-blinded, phase IIb study was conducted in which patients with TPFs were treated with either cancellous autograft, high concentration (1.0 mg/mL) or low concentration (0.4 mg/mL) of TGplPTH1-34 in fibrin with HA/TCP granules. The primary end point was radiological healing at 16 weeks, as measured by an independent radiology panel. Additional secondary end points included measuring radiographic healing, clinical healing, and maintenance of reduction at both earlier (6 and 12 weeks) and later (6, 12, and 24 months) time points. 183 patients were treated in the study, based on the statistical requirement of showing noninferiority to autograft with a 15% noninferiority margin.

Results: The radiographic healing rate at 16 weeks for patients with the product at the high concentration (83.6%) was demonstrated to be both statistically noninferior to that for autograft (84.5%) and superior to that for the low concentration (66.1%). In the composite end point, which combined CT and clinical outcomes, 72.1% of the patients treated with the high concentration healed compared to 63% of those treated with autograft. Maintenance of reduction was evaluated as well, with minimal loss observed (<1 mm compared to postoperative radiographs) at all time points, out to the end of the study at 24 months. Long-term follow-up demonstrated that essentially all the patients were healed in both the high-dose and autograft groups. Finally, the measured safety parameters further demonstrated that the product was well tolerated.

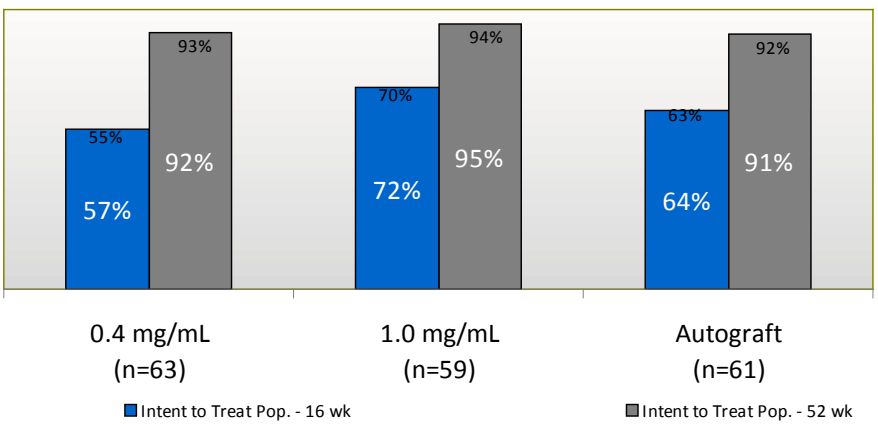

Figure: Outcomes from combined clinical and radiological healing assessment. The combined assessment for the intent to treat population at 16 wks and 52 wks is shown in the blue bars and gray bars respectively. Radiological assessment has been performed by an independent radiology panel while the clinical assessment has been performed by the investigator. At both timepoints, the healing rate following treatment with the high concentration of the PTH based product is higher than that for both patients treated with autograft as well as those treated with the lower concentration of $TGplPTH_{1\text{-}34}$. This trend is confirmed in the per protocol analysis, which is shown in black at the top of each bar.

See pages 47 - 108 for financial disclosure information.

Conclusion: The authors have been developing a novel bone graft substitute based on the local retention of PTH in a fibrin matrix to induce bone healing. While the product has many potential applications, the initial development has been focused on the treatment of TPFs. In this study, it has been demonstrated that healing with the PTH-based product is as robust as that with autograft, throughout the entire healing process, Furthermore, at the early time points, where obtaining healing is more challenging, the product performed even better than autograft. Maintenance of reduction was measured, as this represents an important measure of the clinical outcome. Here, it was observed that the TGplPTH1-34-fibrin-granule composite provided a robust support, with no clinically relevant loss of reduction observed in the study. The combination of these data with the very clean safety profile provides a first clinical demonstration of the efficacy of the PTH-based product as a new powerful tool for fracture healing.