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# Local Sustained Delivery of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)

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*Abstract*— **Local delivery of recombinant human bone morphogenetic protein-2 (rhBMP-2) as a bone graft substitute in spinal fusion was Food and Drug Administration approved on July 2, 2002. Its commercial trade name is INFUSE Bone Graft. It was cleared as a combination biologic device after petitioning the FDA in the early 1990s with the argument that rhBMP-2's effects were only local and not systemic. The protein is applied to a type I collagen sponge at the time of surgery. After a minimum of 15 minutes to allow binding, the collagen sponge is rolled up and placed into a titanium spinal fusion cage. Two of the rhBMP-2 loaded cages are implanted into an intervertebral spinal disc space to promote bone growth across the disc, i.e., spinal fusion. Fusion stops motion at the treated level and ultimately reduces back pain originating from the degenerated disc. This same product was FDA approved for a tibia long bone fresh fracture bone grafting application in August 2004, and for sinus elevation and alveolar defects associated with extraction sockets in March 2007. In addition, a new carrier is under clinical evaluation that will offer longer rhBMP-2 sustained release and compression resistance, further expanding the clinical utility of rhBMP-2.**

## I. INTRODUCTION

THE recent commercial success of INFUSE® Bone Graft was the culmination of a long history of research and development. Early basic bone research by Marshall Urist, MD, in the mid-1960s led to the discovery that some bone "protein extracts" had the ability to induce new bone formation. He discovered this by dissolving the mineral away from bones and implanting the protein extract in a rat subcutaneous implant site, away from any bone. Within a few weeks the extracted protein formed a small nodule of new bone. Urist never isolated the individual proteins responsible for the new bone formation, but first coined the term "bone morphogenetic protein." It wasn't until the mid-1980s that scientists at Genetics Institute identified the specific proteins in this bone protein extract that were actually responsible for this new bone formation. A family of proteins were identified and numbered sequentially. One of the more prevalent and potent bone- producing proteins discovered was BMP-2, which was cloned and produced recombinantly. A commercial product could now be contemplated.


Since BMP-2 clears from the bloodstream so rapidly (within minutes), it cannot be delivered systemically in bone grafting applications and must to be implanted at the site of desired bone formation. Several years were spent investigating the optimal rhBMP-2 concentration, dose, and carrier to consistently form new bone in the desired quantity and shape. These carriers had to have good handling properties for implantation by the surgeon, had to act as a scaffold on which new bone could form, and most importantly, had to deliver the rhBMP-2 over a sufficient length of time to ensure efficacy.

An earlier carrier made of bioerodable beads was found ineffective in a pilot clinical trial, showing that the carrier is just as important as the protein. The type I collagen sponge used in subsequent clinical trials has been found to be effective. The collagen sponge proved to be a good carrier for BMP because it has the inherent ability to bind rhBMP-2. After application of the rhBMP-2 solution to the collagen sponge and a minimum of 15 minutes soak time, approximately 95% of the BMP is bound to the collagen sponge. This binding approaches 97% at a soak time of 2 hours. Once the BMP soaked sponge is implanted, it releases the BMP over about a 2-week period, with a half-life of only 2-3 days. It appears that this early release of rhBMP-2 over the first 2-3 days is important in initiating the bone formation process. rhBMP-2 is chemotactic for stem cells and induces their differentiation into osteoblasts. Osteoblasts are responsible for the new bone formation. The rhBMP-2 is completely metabolized and removed from the surgical site within about 2 weeks. The bone initiation process occurs relatively quickly, and the body continues to lay down new bone naturally over several weeks to heal the bone defect.

INFUSE Bone Graft was approved in the spinal fusion indication after a 279-patient prospective, randomized, clinical trial in which autograft bone harvested from the patients' own iliac crest was the control. Sixteen clinical sites enrolled patients into this trial. Harvesting autograft from the iliac crest was the standard of care up to this point, requiring a separate surgical incision over the iliac crest to harvest bone to transplant to the site requiring bone graft. This procedure can result in several complications and post operative pain for months or even years. At two years post surgery, 32% of these autograft control patients reported some pain from the iliac crest harvest site. The fusion success rate in this clinical trial was 94.5 vs. 88.7%, respectively, for the investigational and autograft control group. The long bone fresh fracture clinical trial was also a prospective, randomized, clinical trial comparing rhBMP-2

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to the standard of care. Four hundred and fifty patients were enrolled at 49 clinical sites around the world. This study demonstrated a 41% reduction in the need for a second surgical procedure. The rhBMP-2 patients in this study also clinically healed faster than the control patients. The oral/ maxillofacial clinical trial involved a procedure called a sinus lift elevation, in which a window is created in the posterior maxilla to open the sinus space, which is filled with either autograft or rhBMP-2 on the absorbable collagen sponge (ACS). The objective of the procedure is to fill the base of the sinus with new bone so that after a few months, a dental implant and prosthesis can be inserted and functionally loaded. This was a prospective, randomized, clinical trial comparing rhBMP-2 to autograft iliac crest bone. One hundred and sixty patients were enrolled at 21 different clinical sites. Sixteen weeks postsurgery, 8mm of new bone was formed in the base of the sinus from the rhBMP-2. Overall, an equivalent number of dental implants were retained in the rhBMP-2 treated patients as in the autograft control patients (87%). Additional clinical trials are also being conducted to expand the approved indications of INFUSE Bone Graft.

To date, the INFUSE Bone Graft product with the absorbable collagen sponge carrier is the only commercially available rhBMP-2 product. There are some clinical bone grafting applications in which a carrier needs to be able to resist surrounding muscle forces and compression. If the carrier is compressed, then some of the BMP could be squeezed out or only a thin piece of new bone is formed. The first FDA-cleared spinal fusion application involved placing the collagen sponge inside a metal fusion device and protecting it from compressive forces. There is another common fusion technique called a posterolateral fusion, in which the surrounding muscles do apply pressure on the carrier. In order to offer the surgeon a new carrier with different handling properties and some compression resistance, a new carrier is being clinically investigated. This new carrier, known as a compression-resistant matrix (CRM), consists of a collagen sponge with calcium phosphate granules impregnated throughout its structure. The granules give the carrier some bulk resistance to compression and slowly degrade over a period of 6-9 months. The granules consist of a biphasic composition of 15% hydroxyapatite and 85% tricalcium phosphate. Preclinical work has demonstrated that tricalcium phosphates resorb too quickly, limiting reproducible bone formation and hydroxyapatite degrades much too slowly, making it difficult for radiographic assessment of fusion and complete remodeling of the graft into new bone. Therefore, this particular biphasic composition was designed to support new bone formation while slowly degrading to allow new bone to form throughout its structure. Calcium phosphate is an excellent carrier for BMP because it also inherently binds BMP. Once bound to the CRM, the BMP is released much slower than from collagen alone after it is implanted. The BMP half-life on the CRM is approximately 8 days (4 times longer than collagen) and the protein is released over a period of approximately 4 weeks (2 times longer than collagen alone).

This combination of rhBMP-2 and the CRM carrier will be called AMPLIFYTM rhBMP-2 Matrix. Enrollment of 463 patients has been completed in a prospective, randomized clinical trial comparing iliac crest autograft to AMPLIFYTM rhBMP-2 Matrix in a single-level instrumented posterolateral fusion indication. This will be followed by a putty formulation carrier, rounding out a complete portfolio of carriers that can be offered to surgeons.

INFUSE Bone Graft is an example of a commercially successful combination device. It is the result of years of research and development by many people, and represents only the first generation, with many new carriers and clinical indication approvals to come.