Morpheus
MOLDABLE
BONE GRAFT SUBSTITUTE

BIOGENNIX™
SHAPING FUSION

1641 McGaw Avenue, Irvine, CA, 92614 T 949.253.0994 F 949.266.5800 biogennix.com

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Morpheus Product Features and Pre-Clinical Evaluation

Figure 1. *Morpheus extruded from syringe and molded.*

Figure 2. *Magnified image of TrelCor granule.*

Morpheus moldable bone graft substitute was found substantially equivalent to osteoSPAN™ granules for use in the extremities and pelvis (FDA K132377) and additionally as a bone graft extender in the posterolateral spine (K142828).

Morpheus is a moldable form of the original osteoSPAN product. It is composed of 1-2mm proprietary TrelCor™ granules suspended in a rapidly absorbable organic binder to facilitate placement and containment of the implant. Once this binder is absorbed in-situ, only the TrelCor granules are left behind without affecting their natural osteoconductive or resorbable properties.

The synthetic polymer binder added to the TrelCor granules in Morpheus provides improved intraoperative handling characteristics over granules alone and does not interfere with the osteoconductive properties of the TrelCor granules. This family of polymers has been used in countless pharmaceutical formulations and medical applications for decades, including bone graft substitutes classified in FDA product code MQV by Allosource (K071849 & K103036), Apatech (Actifuse products K071206 & K080736), Integra (K103742), Isotis Orthobiologics (K040419, K050642, K050690 & K070751), Therics (K053228) and others.

Biogennix proprietary TrelCor technology creates the ideal environment for bone regeneration through its architecture and chemistry. The architecture of TrelCor technology is an osteoconductive scaffold of true interconnected porosity, with 65% porosity and an average pore size of 500 microns. TrelCor chemistry is a composite of calcium carbonate and calcium phosphate in a ratio engineered to be ideal for bone growth. All surfaces throughout the porosity are completely coated with a thin layer, approximately 4 microns, of calcium phosphate, the primary mineral content of bone.

TrelCor granules are biocompatible, osteoconductive, resorbable, and radiographically opaque. Once implanted next to viable bone and stabilized, new bone and soft connective tissue will begin to grow throughout the pores of the material. Within months osteoclasts dissolve the calcium phosphate surface layer to expose the more rapidly resorbable calcium carbonate base material while osteoblasts replace the implant material with new bone. This implant biodegradability is a key attribute of TrelCor technology and plays an important role in tissue engineering applications. Through normal physiological remodeling processes the material's radio-opacity is systematically decreased as new bone density is increased.

Bone scaffolds that are designed to degrade over time in synchrony with tissue regrowth rates may provide a more effective therapy than materials that do not degrade.[1] Clinical outcomes are much easier to assess using standard x-ray and CT analysis methods when biodegradable materials are used since these types of materials gradually disappear over time and do not mask the progression of natural tissues.

The phase purity, phase composition and crystallinity of TrelCor technology has been compared to Actifuse granules using x-ray powder diffraction methods. TrelCor granules are more than 95% crystalline and nominally contain 8% calcium phosphate with the remaining balance being calcium carbonate; conversely, Actifuse granules are also more than 95% crystalline but are almost entirely hydroxyapatite (95%), making this material much less likely to degrade over time.

Blinded side by side studies using Morpheus and Actifuse ABX were completed in critically sized tibial bone defects and posterolateral spines of skeletally mature rabbits. [2] Figure 3 illustrates resorption and osteoconduction of a TrelCor granule in Morpheus at twelve weeks in the posterolateral spine. The false color images are non-decalcified histology, viewed under a scanning electron microscope with backscatter electron emission (SEM-BSE). The thin white, wave shaped line starting in the lower left corner of the 100µm image is the calcium phosphate layer (approximately 4 microns thick) that covers all surfaces of TrelCor granules. As can be seen here, a small breach in the calcium phosphate coating near the apex of the wave shape has already allowed bone to rapidly replace a large section of the calcium carbonate base material.

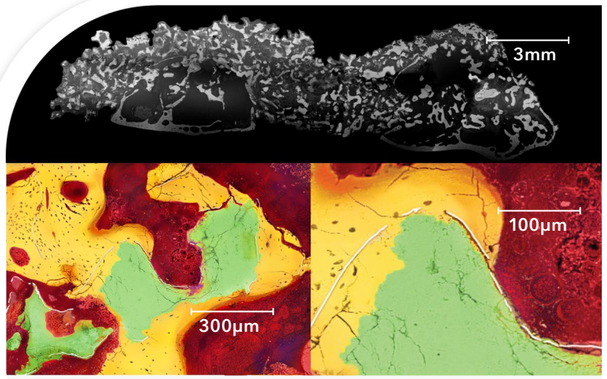

Figure 3. *SEM-BSE image of Morpheus in a spine application.*

- = *Bone*
- = *Calcium Carbonate*
- = Calcium phosphate
- = *Soft Tissue*

Figure 4. *False colored isometric micro-CT view of Morpheus in rabbit posterolateral spine.*

Additionally, Morpheus has been qualitatively judged to have excellent handling characteristics during pre-clinical studies and actual clinical usage. Morpheus easily integrates autogenous materials without losing its molding and handling capabilities. Also, the binder in Morpheus leaves less residual material on surgical gloves, making it easier for the surgeon to hold surgical instruments.

Multivariable assessments were conducted in each preclinical study using Morpheus to fully assess study outcomes.[2] Morpheus passed biocompatibility tests for cytotoxicity, endotoxicity, genotoxicity, acute systemic injection, intramuscular implantation, long term implantation and intracutaneous reactivity. Manual palpation scoring of fusion masses in all posterolateral spine studies showed Morpheus performed equivalently to Actifuse ABX and osteoSPAN granules at both six and twelve week study intervals. At twelve weeks Morpheus consistently showed signs of resorption on micro-CT images when compared to Actifuse ABX. Figure 5 contains exemplary images of a transverse micro-CT view of each implant in the posterolateral spine. The ovoid shaped segments on both ends of the fusion mass in each image are adjacent transverse processes that have been connected by a bridge of implant material. The Actifuse ABX implant (bottom) has distinctly more pronounced radio-opacity than Morpheus, providing a clear indication that Morpheus is gradually being remodeled and replaced by natural tissue.

Figure 6 contains coronal micro-CT images of the critical sized tibia defect at six weeks. These images illustrate how the entire transcortical defect and intramedullary canal were packed with implant materials. The image on the top shows new bone has almost entirely replaced the Morpheus implant along the cortical surface; conversely, the lower image demonstrates how difficult it is to see any cortical regeneration in the Actifuse ABX implant at the same time interval.

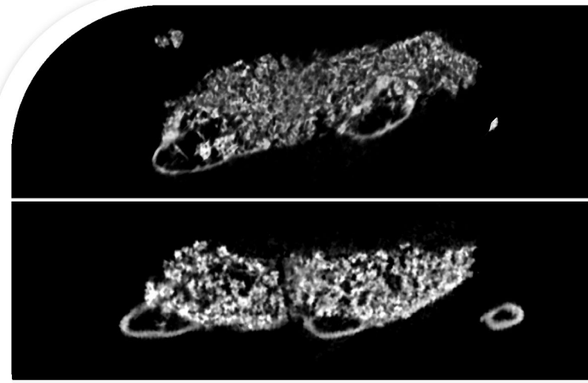

Figure 5. *Micro-CT images (100 µm resolution) of Morpheus (top) and Actifuse ABX (bottom) at twelve weeks in rabbit posterolateral spine.*

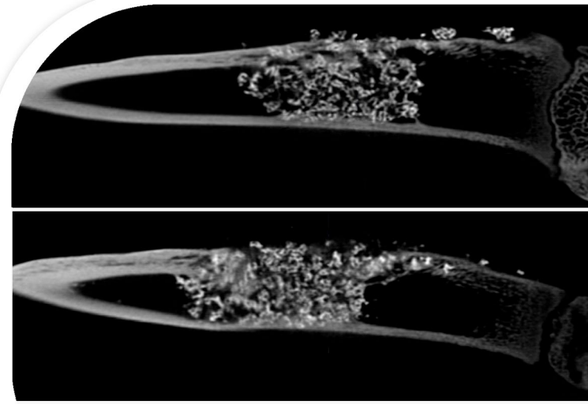

Figure 6. *Micro-CT images (100 µm resolution) of Morpheus (top) and Actifuse ABX (bottom) at six weeks in a critically sized tibial defect.*

[1]Ericka M. Bueno and Julie Glowacki. 2011. Biologic Foundations for Skeletal Tissue Engineering (Synthesis Lectures on Tissue Engineering). Morgan & Claypool Publishers. [2] Data on file at Biogennix.