Morpheus
MOLDABLE
BONE GRAFT SUBSTITUTE

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Morpheus Product Features and Pre-Clinical Evaluation

Morpheus is an advanced bone graft product consisting of a moldable suspension of 1-2mm TrelCor™ granules in a rapidly absorbing, organic binder. Morpheus is moldable, cohesive, mixable with auto-genous bone, and leaves minimal residual material on surgical gloves following handling (**Figure 1**). The binder's resistance to breakdown and irrigation facilitate secure placement and stabilization of the graft mass. It is then rapidly absorbed leaving behind the porous TrelCor granules, which are resorbed, remodeled, and replaced with bone over the next 6-12 months.

The TrelCor bone graft material was specifically engineered to improve the bone regeneration process. It is a next-generation bone graft material that utilizes a nanocrystalline surface, a bone-like mineral composition, and a biomimetic pore architecture to enhance the bone healing response. The combination of multiple characteristics that are beneficial to bone regeneration is the core principle behind the TrelCor technology and is an approach to improving bone grafting that is unique to Biogennix.

Nanostructure Surface
Unlike standard calcium phosphate bone graft products that have a relatively smooth surface, the TrelCor surface found in all Biogennix products has a nanocrystalline structure. This surface structure is evident in the scanning electron microscope (SEM) images in **Figure 2**. This shows a high magnification image of the TrelCor surface where TrelCor has a random assembly of nanoplates. Due to the nanocrystalline surface, the TrelCor granules in Morpheus provide an optimal surface for bone formation. This is based on studies showing that nanocrystalline surfaces positively influence cell proliferation, function, and differentiation.[1,2]

Hydroxycarbanoapatite Composition
The TrelCor granules found in Morpheus are primarily composed of calcium carbonate. However, through

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

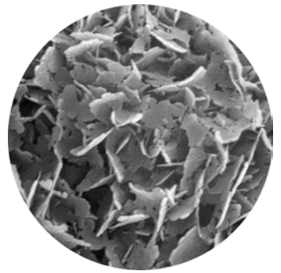

Figure 2. *Magnified image of TrelCor surface.*

Biogennix's proprietary TrelCor manufacturing process, a thin (~4um) outer region of the calcium carbonate surface is chemically converted to a form of carbonated apatite called hydroxycarbanoapatite (HCA). Out of all the calcium phosphate (CaP) materials, HCA is the closest match to the mineral content of human bone. The advantage of HCA over standard calcium phosphate ceramics is that it needs less cellular preparation before bone formation can begin. Studies on HCA have shown that this results in faster bone formation compared to tricalcium phosphate and standard hydroxyaopatite.[3,4]

The HCA region on the TrelCor surface also allows for direct control of the material's resorption properties. Once implanted, calcium carbonate resorbs at a faster rate than calcium phosphate materials like HCA. Due to the TrelCor manufacturing process, the entire calcium carbonate base structure is covered by HCA. Therefore, controlling the thickness of the HCA region allows the resulting resorption to be precisely controlled. This innovative approach to resorption control has allowed Biogennix to determine an HCA thickness that results in an optimal resorption time.

Morpheus STUDY

Biomimetic Pore Architecture
The TrelCor granules used in Morpheus have a unique, biomimetic structure that provides an optimal scaffold for bone formation. With an average pore size of 500 microns (µm) and 100% interconnected porosity, the TrelCor structure closely resembles the natural blueprint of cancellous bone (**Figure 3**).The benefit of the TrelCor pore structure is that the 100% interconnected porosity provides a directly accessible pathway to the interior of the graft site. In combination with a 500µm pore size, bone is able to grow from the periphery of the graft through the entire TrelCor structure.

In addition to functioning as a scaffold for new bone formation, TrelCor's biomimetic structure also provides an optimal combination of strength and porosity. This is especially important for moldable products like Morpheus where the materials are compressed and manipulated during implantation. The TrelCor structure is compression resistant which eliminates crushing during standard intraoperative handling and placement. This is an important feature since the main function of a bone graft is to serve as an osteoconductive scaffold. Porous products with weak structures can be easily crushed or pulverized which can significantly reduce their ability to support bone growth.

Morpheus Pre-Clinical Studies
Blinded side by side studies using Morpheus and Actifuse ABX were completed in the posterolateral spines and critically sized tibial bone defects in skeletally mature rabbits.[3] In the tibial study, Morpheus was implanted alone. In the spine study, Morpheus was combined with autograft. In both studies, bone formation was assessed through radiographic and histological methods. The spine study also assessed fusion measured by manual palpation.

Rabbit Posterolateral Spine Study Results
The histological results from the spine study showed bone formation directly on the surface of the TrelCor granules and growing through the porosity. **Figure 4** illustrates resorption and osteoconduction of a TrelCor granule in Morpheus at twelve weeks in the posterolateral spine. The false color images were created with a scanning electron microscope with backscatter electron emission (SEM-BSE).

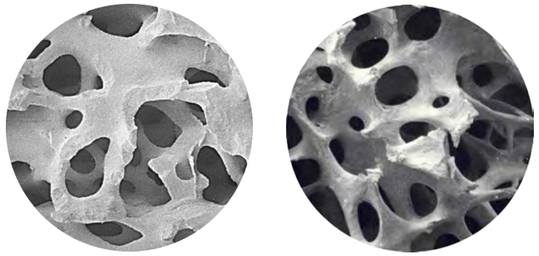

Figure 3.
Comparison of TrelCor (left) and cancellous bone (right)

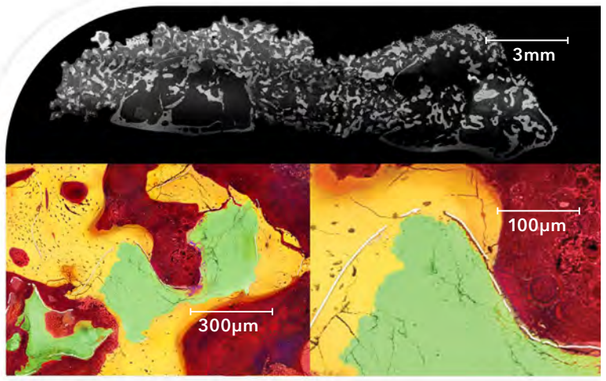

Figure 4.
SEM-BSE image of Morpheus in a spine application.

- *= Bone*
- *= Calcium Carbonate*
- *= HCA layer*
- *= Soft Tissue*

Figure 5.
False colored isometric micro-CT view of Morpheus in rabbit posterolateral spine.

In **Figure 4**, the thin white, wave shaped line starting in the lower left corner of the 100µm image is the HCA region (approximately 4 microns thick) that covers all surfaces of TrelCor granules. As seen in the image, a small breach in the HCA layer near the apex of the wave shape has already allowed bone to rapidly replace a large section of the calcium carbonate base material.

Manual palpation scoring of fusion masses in all posterolateral spine studies showed Morpheus performed equivalently to Actifuse ABX at both 6- and 12-week study intervals. At 12-weeks, the micro-CT images showed an increase in bone formation from 6 weeks images. The 12-week micro-CT also showed that Morpheus consistently showed signs of resorption when compared to Actifuse ABX. **Figure 6** 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.

Rabbit Tibial Study Results
Similar to the spine study, the rabbit tibial study showed that Morpheus was capable of regenerating bone. **Figure 7** 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 micro-CT results improved bone fomration in the Morpheus group compared to the Actifuse group. In **Figure 7**, 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.

The overall results of the pre-clinical testing showed that Morpheus was a highly effective bone graft material capable of regenerating bone in both the rabbit spine and tibia.

1. Zhang J. et al. J. of Tissue Eng. And Regen. Med. 11: pp 3273-3283 (2017)
2. Duan R. et al. ACS Biomater. Sci. Eng. 4: pp 3347-3355 (2018)
3. Spence G. et al. Key Eng. Materials Vols. 309-31: pp 207-210 (2006)
4. Hayashi K. et al. Materials Today Bio. 4: pp. 1-11 (2019)
5. Data on file with Biogennix

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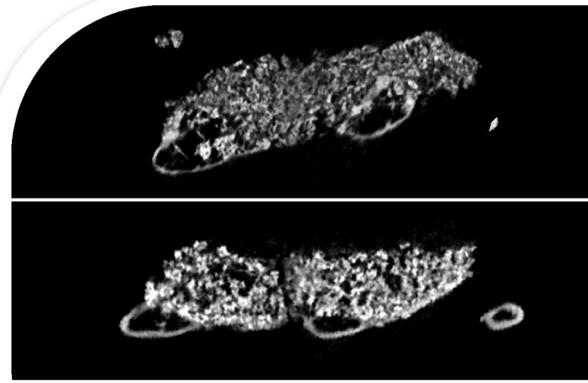

Figure 6. *Micro-CT images (100 µm resolution) of Morpheus (top) and Actifuse ABX (bottom) at twelve weeks in rabbit posterolateral spine.*

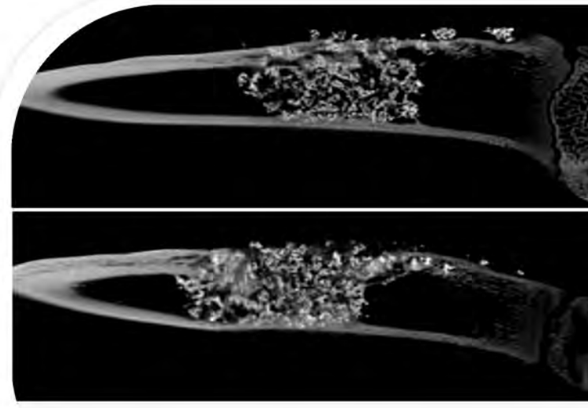

Figure 7*. Micro-CT images (100 µm resolution) of Morpheus (top) and Actifuse ABX (bottom) at six weeks in a critically sized tibial defect.*