Providing an environment conducive to bone growth.

CopiOs®

Bone Void Filler

ZimVie

ZimVie BIOLOGIC SOLUTIONS

The Next Generation in Synthetic Bone Graft Substitutes

Calcium phosphate, dibasic—the unique mineral component of CopiOs Bone Void Filler—is suited to promote bone growth.

Optimal pH Level for Bone Healing

- CopiOs Bone Void Filler is composed of calcium phosphate, dibasic (DICAL) and highly purified Type I bovine collagen
- CopiOs Bone Void Filler provides a moderately acidic environment that promotes solubility of osteoinductive growth factors such as bone morphogenetic proteins (BMPs) **(Table 1)**
- More soluble BMPs may remain available for bone healing processes in the early stages of bone growth[1]
- The concentration of soluble BMPs in calcium salt solution decreases substantially when hydroxyapatite (HA) or beta-tricalcium phosphate (ß-TCP) is present **(Table 1)**

	% BMPs LEFT IN SOLUTION
Control (no mineral)	100
$CaHPO_4$ (DICAL)	76
ß-$Ca_3(PO_4)_2$ (ß-TCP)	23
$Ca_5(PO_4)_3(OH)$ (HA)	15

Table 1. Concentrations of BMPs in various calcium salt solutions[1]

Abundance of Localized Soluble Mineral Ions Promotes Bone Formation

- DICAL provides significantly more calcium and phosphate ions at equilibrium than either ß-TCP or HA **(Table 2)**[2]
- Abundance of localized soluble calcium and phosphate ions promotes bone formation[3]

	SOLUBLE BONE MINERAL CONCENTRATION	
COMPOSITION	$[Ca^{2+}]$ µM	$[Po_4^{3-}]$ µM
$CaHPO_4$ (DICAL)	427.8	427.8
ß-$Ca_3(PO_4)_2$ (ß-TCP)	0.87	0.58
$Ca_5(PO_4)_3(OH)$ (HA)	1.11	0.67

Table 2. Soluble mineral concentrations of various calcium salts at equilibrium based on their solubility product constants[2]

Osteoconductive Scaffolds Provide Key Role in Bone Regeneration

- Three-dimensional collagen scaffold sponge resembles human cancellous bone to aid in bone regeneration
- Sponge structure is approximately 93% porous with interconnecting, multidirectional pores ranging in size from 5 to 1000µm, which allow cell penetration and rapid absorption of autologous fluids **(Figure 1)**
- Paste structure has high void volume **(Figure 2)**
- These osteoconductive attributes allow cellular attachment, nutrient and oxygen infiltration and vascularization throughout the graft material for bone healing

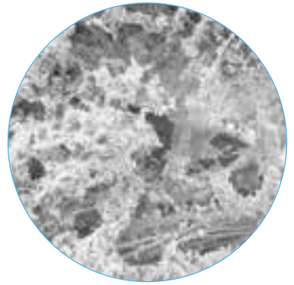


Figure 1. Microscopic view of collagen in CopiOs Sponge (original magnification × 200)

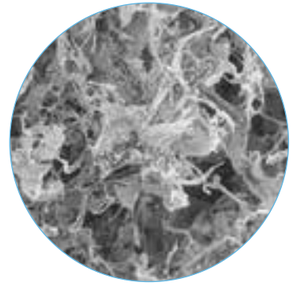
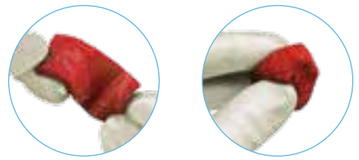


Figure 2. Microscopic view of collagen in CopiOs Paste (original magnification × 100)

A Unique Approach to Bone Growth

At ZimVie Spine, we understand your need for an innovative bone graft substitute. That's why we offer CopiOs Bone Void Filler. Through the use of DICAL, a unique mineral component, this solution creates an environment that is conducive to bone growth. CopiOs Bone Void Filler is another way the people of ZimVie Spine are helping you to improve the lives of your patients.



Additional Benefits

Timely Resorption Concurrent with Bone Growth

- Non–chemically cross-linked collagen provides strength and durability for the scaffold to persist until replaced by new bone
- Scaffold rapidly resorbs as new bone is formed which then remodels by cell-mediated processes **(Figure 3)**
- It resorbs more quickly than hydroxyapatite, which is virtually insoluble[1]

Biocompatible and Safe

- Preclinical studies show CopiOs Bone Void Filler to be biocompatible and nontoxic[1]
- CopiOs Bone Void Filler was nonimmunogenic in animal studies[1]

Autograft Limitations

- Requires a second surgical procedure, which increases costs and is associated with:[4]
    - Longer OR and recovery times
    - Greater blood loss
    - Extended hospital stays
- Limited bone supply and often issues with bone quality, especially in older patients[4]
- Donor site morbidity[4]
- Major complications (25–29%), including disabling chronic pain at the donor site[5]

An Effective Autograft Alternative: CopiOs Bone Void Filler

- CopiOs Bone Void Filler, combined with bone marrow aspirate, provides the three requisite properties for bone healing: osteoinductive growth factors, osteogenic cells and an osteoconductive scaffold
- Preclinical studies of CopiOs Sponge with bone marrow aspirate show bone healing performance equivalent to autograft[1]
- CopiOs Bone Void Filler eliminates the need for a second surgical harvest procedure and associated complications, including donor site morbidity
- CopiOs Bone Void Filler is readily available with consistent quality

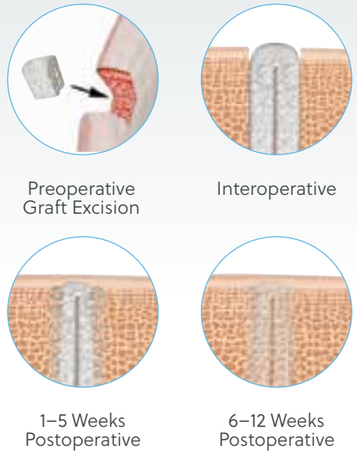


Figure 3.

An Environment Conducive to Bone Growth: Optimized Chemistry[5]

DICAL provides a moderately acidic microenvironment that promotes the solubility of endogenous osteoinductive growth factors such as BMPs.

Study Model

- Female Long-Evans rats (60g–130g)
- Bilateral subcutaneous ectopic implantations (diameter approximately 7mm)
- Mineral compositions with different pH buffering ranges implanted (using a collagen scaffold and osteoinductive protein mixture that contains bovine bone-derived BMPs)
- Histology was compared to assess quality, quantity and maturity of bone formation

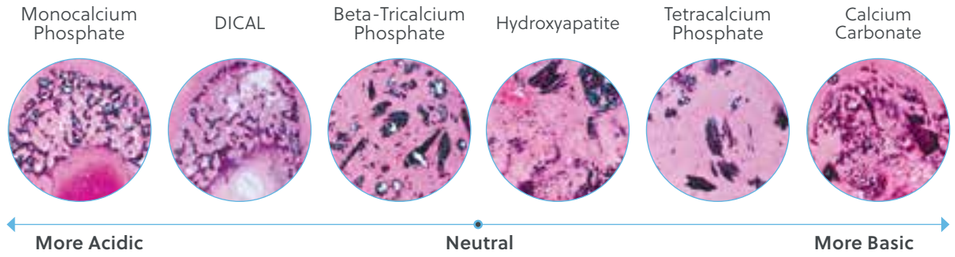


Figure 4. Collagen/mineral composite preclinical product performance comparison (3 weeks)[1].

Conclusions

- The mineral additives had marked effects on the quality, quantity and maturity of bone formed as measured by histological analyses
- The moderately acidic DICAL stimulated the greatest overall amount of bone formation and depth of bone mineralization
- CopiOs Bone Void Filler was the only explant type that showed high-quality cortical rim bone formation
- The explants from supplementation with ß-TCP, hydroxyapatite, tetracalcium phosphate and calcium carbonate resulted in reduced bone formation, even in comparison with the collagen control

Bone Regeneration Clinical Performance: Human Prospective Study

A Prospective Assessment of Bone Regeneration and Pain Following Use of CopiOs Bone Void Filler in the Post-Harvest Iliac Crest[6]

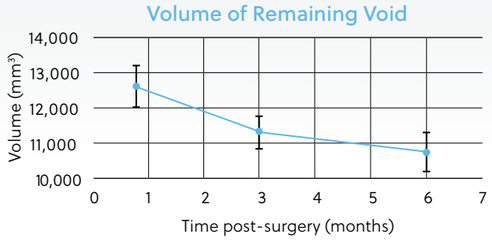
Overview

The purpose of this study was to evaluate the in vivo use of CopiOs Bone Void Filler Sponge (CopiOs Sponge) with respect to bone regeneration and postoperative pain at the donor graft site in the iliac crest. This single site provided preoperative and postoperative evaluations of subjects undergoing spinal fusion (L2–S1) with autogenous bone graft in which the CopiOs Sponge was used as a bone void filler in the post-harvest site of the iliac crest.

Study Model

- This was a prospective, nonblinded, nonrandomized case series of CopiOs Sponge involving bone grafting and rigid fixation techniques for stabilizing bone voids
- Thirty-five subjects were enrolled in the study, with 30 (15 men and 15 women) undergoing the surgical procedure; all subjects were over 18 and deemed appropriate candidates by meeting the inclusion/exclusion criteria for iliac crest graft harvest as part of their spinal procedures
- Serial CT scans were obtained at 3 time points using 3-mm slice thickness from the top of the iliac crest to the symphysis pubis; the scans were analyzed for volume of the defect site, measured in Hounsfield units; statistical analysis (t test, assuming equal variance) was performed comparing the 3-week and 6-month estimates for volume of the void
- Subject variables, surgical information and radiographic results were quantified in the form of frequency distributions and means

Clinical Outcomes



	3-WEEK FOLLOW-UP	3-MONTH FOLLOW-UP	6-MONTH FOLLOW-UP*
N	29	28	29
Mean (mm^3)	12,641	11,352	10,770
SEM†	632.5	512.9	590.1

*$p < .05$
†SEM, standard error of the mean.

Figure 5.

Radiographic Iliac Crest Void Measurements

The 3-week and the 6-month estimates for volume of the remaining void were compared using a t test analysis assuming equal variance. A statistically significant decrease in the volume of the void was reported between the 3-week and the 6-month postoperative evaluations ($p < .05$). These results are reported in **Figure 5**, which shows the decrease in the volume of the remaining bony void over the course of the study.

Patients enrolled in this study were assessed for iliac crest pain preoperatively and at 3 weeks, 3 months and 6 months postoperatively. Preoperatively, a mean numeric rating scale (NRS) score of 0.0, indicating "no pain," was reported.

Numeric Rating Scale Results

	MEAN ± SD*	N
Preoperative	0.0 ± 0.0	30
3 weeks	0.7 ± 1.4	30
3 months	0.8 ± 2.5	30
6 months	0.4 ± 1.7	30

*SD, standard deviation using a pain rating scale from 1–10.

Mean NRS Scores Reported Postoperatively

	MEAN
3 weeks	0.7
3 months	0.8
6 months	0.4

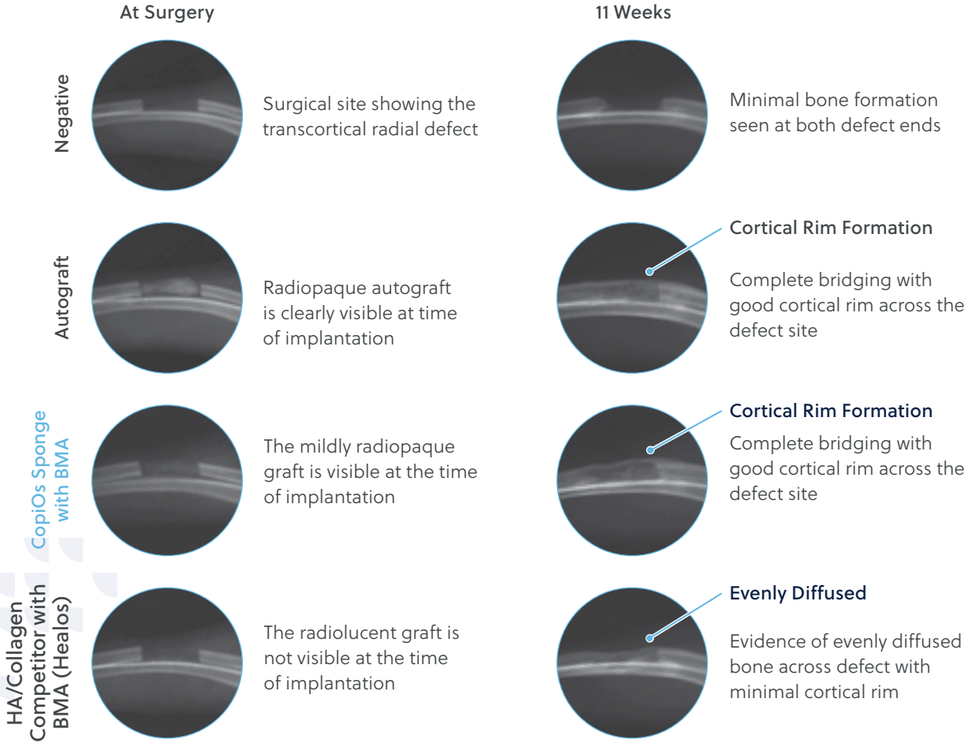
Figure 4. Collagen/mineral composite preclinical product performance comparison (3 weeks)[1].

Preclinical Performance

Study Model

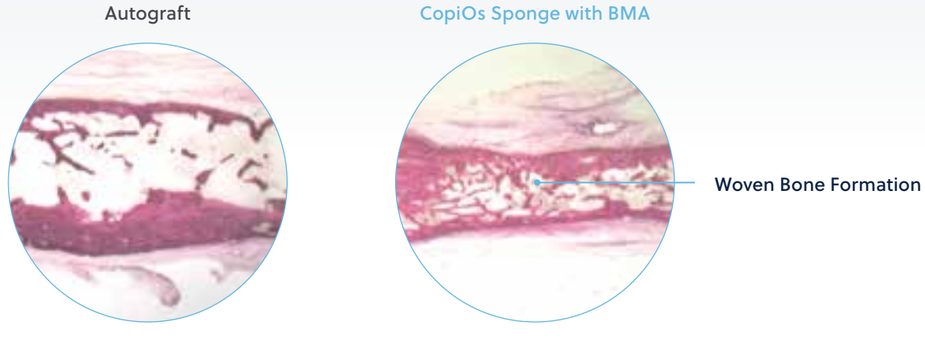
- Skeletally mature New Zealand white rabbits (approximately 6 months old, 3kg–5kg)
- Radial critical-size segmental defect model (15mm length)
- Evaluated use of autograft, CopiOs Sponge with bone marrow aspirate (BMA) and DePuy's Healos® Bone Graft Substitute with bone marrow aspirate; an unfilled defect was the negative control, and the contralateral limb was the control for mechanical strength
- Mechanical, radiographic and histologic evaluations were performed

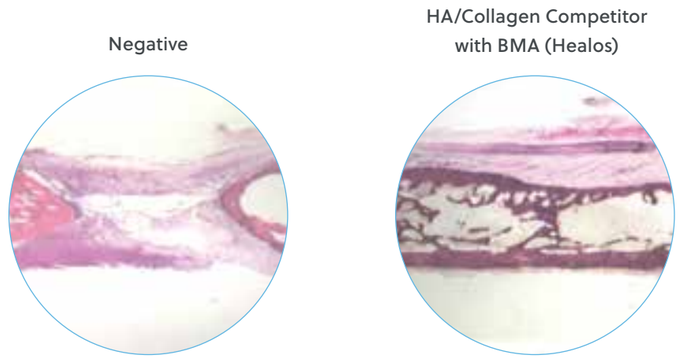
CopiOs Sponge with BMA Was Equivalent to Autograft Showing Cortical Rim Formation at 11 Weeks



Radiographic Analysis: 11 Weeks[1]

CopiOs Sponge with BMA Shows Trabecular Bone Formation at 12 Weeks Equivalent to Autograft





Histologic analysis at 12 weeks, original magnification × 6[1]

Defect site filled with large marrow space and minimal trabecular bone; thin cortical bridge seen across the defect site

Conclusions

- CopiOs Bone Void Filler performed equivalent to autograft in promoting bone healing in this model
- The evidence of healing at 12 weeks demonstrates that CopiOs Sponge is superior to Healos in the amount and quality of new bone formed

Two Convenient Forms for Interoperative Flexibility

SPONGE SIZE	PART NUMBER
1cc (1 cm × 2 cm × 0.5 cm)	07.00582.001
5cc (2 cm × 5 cm × 0.5 cm)	07.00582.003
10cc (2 cm × 5 cm × 0.5 cm) × 2	07.00582.004

PASTE VOLUMES (WHEN HYDRATED)	PART NUMBER
1cc	00-1103-020-01
5cc	00-1103-020-05
10cc	00-1103-020-10

DESCRIPTION	PART NUMBER
Bone Marrow Aspiration Needle*	00-1103-007-00

*Currently only available in the United States.

Excellent Handling and Easy to Use

CopiOs Sponge Is:

- Pliant when hydrated, so it can be easily molded into irregularly shaped defects
- Easy to shape and cut
- Stable in a fluid environment
- Mildly radiopaque, permitting visualization of graft placement immediately after surgery without interfering with visualization of the healing process

CopiOs Paste Provides:

- Ease of graft placement in difficult-to-reach defects
- Handling properties of a putty/paste formulation

CopiOs Sponge

CopiOs Paste

Surgical Technique

CopiOs Sponge and CopiOs Paste should be used in the OR in an aseptic surgical field. The bone void site should be prepared adequately to expose healthy, bleeding bone to help promote future bone growth.

1. Determine the volume of the bone defect.
2. Select and open appropriate number of packages of CopiOs Bone Void Filler based on product volume/size to best fill the defect while providing maximal contact with the bone surface. CopiOs Sponges can be cut to size with surgical scissors or a scalpel.
3. Aspirate or obtain locally autologous blood, bone marrow or other blood product in the following volume recommendations.

   For CopiOs Sponge, obtain a volume of blood or bone marrow equal to the volume of the defect.

   For CopiOs Paste, use the volumes in the table below to achieve a putty-like consistency.

PRODUCT SIZE	FLUID VOLUME
1cc	0.6cc
5cc	4.0cc
10cc	8.5cc

4. Hydrate CopiOs Bone Void Filler with the blood product obtained.

   For CopiOs Sponge, place sponge(s) into a sterile mixing bowl and add the blood product to saturate.For CopiOs Paste, transfer the compressed powder disk into the bowl and add the blood product. Add slightly more or less fluid to achieve desired putty handling characteristics. Mix thoroughly for 1–2 minutes until there are no dry spots.

5. Thoroughly irrigate the site of the bone defect.
6. Gently mold CopiOs Bone Void Filler into the defect. Avoid compressing the structure of the graft. As an alternative, CopiOs Paste can be loaded into the barrel of an appropriately sized sterile syringe and then extruded.
7. Secure the filled defect with surrounding soft tissue and perform rigid fixation of the bone void as needed. Optimal management of fractures or defects requires adequate alignment and stability.

   CopiOs Bone Void Filler will resorb during the course of the healing process.

References:

1. Data on File. Findings from an animal model are not necessarily predictive of human clinical results.
2. Fernandez E, Gil FJ, Ginebra MP, Driessens FC, Planell JA, Best SM. Calcium phosphate bone cements for clinical applications, part I: solution chemistry. *J Mater Sci Mater Med.*1999;10(3):169–176.
3. LeGeros RZ. Biodegradation and bioresorption of calcium phosphate ceramics. *Clin Mater.* 1993;14(1):65–88.
4. Betz RR. Limitations of autograft and allograft: new synthetic solutions. *Orthopedics.* May 2002;25(5 suppl): S561–S570.
5. Szpalski M, Gunzburg R. Applications of calcium phosphate-based cancellous bone void fillers in trauma surgery. *Orthopedics.* May 2002;25(5 suppl):S601–S609.
6. Dennis MD, Menzie AM, Garrett R. A prospective assessment of bone regeneration and pain following use of CopiOS Bone Void Filler in the post-harvest iliac crest. (White paper L1562 Rev. A) Zimmer Spine, Minneapolis, MN; 2010.

For more information, visit ZimVie.com

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