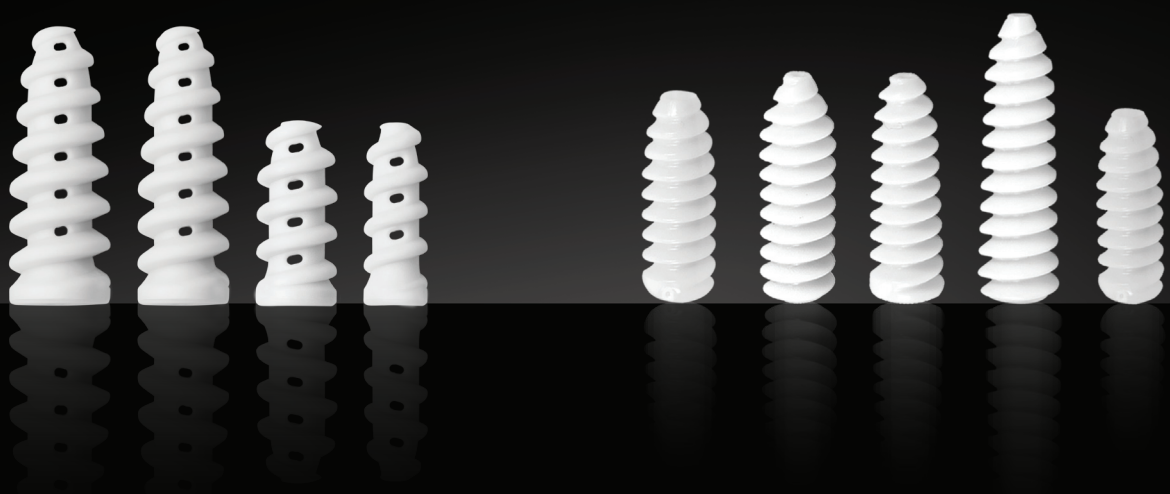
BioComposite Interference Screws

A **STRONGER** Turn in ACL/PCL Reconstruction



Scientific Research and Development

Arthrex
BioComposite Interference Screws for ACL and PCL Reconstruction

Arthrex Research and Development

Introduction

Arthrex has developed a new absorbable composite interference screw for graft fixation in ACL and PCL reconstruction procedures, combining the inherent degradation characteristics of a biocompatible polymer with the bioactivity of a ceramic. The BioComposite Interference Screw is a combination of 70% poly(L-lactide-co-D, L-lactide) (PLDLA) and 30% biphasic calcium phosphate (BCP).

Material Composition

Biodegradable polymeric materials such as polylactide (PLA) and polyglycolide (PGA) have been used in orthopaedic applications since the 1970s, when sutures made from these materials were approved for use by the FDA. Both materials are easily degraded within the body - PLA into lactic acid and PGA into glycolic acid. PLA is a crystalline material with a slow resorption rate, while PGA is amorphous and resorbs much faster. PLA and PGA materials can be combined in different ratios to produce poly(lactide-co-glycolide) (PLGA) polymers with variable degradation rates. PLA exists in two isomeric forms, L-lactide and D-lactide. L-lactide is more commonly found and semi-crystalline, while D-lactide is much less common and amorphous. Even combining just these PLA isomers alone can also alter degradation time and mechanical strength. The 70:30 L:DL ratio in the PLDLA material in our BioComposite Interference Screw results in retention of ½ of its tensile strength after 32 weeks and ½ of its shear strength after 45 weeks *in vitro* [1]. Implanted pins made from 70:30 PLDLA, as in our product, were completely replaced by new bone at 36 months *in vivo* in an osteochondral fracture [2], while complete *in vitro* degradation occurred at about 18 months [3]. Spinal cages made from the same 70:30 PLDLA were completely degraded *in vivo* by 12 months [4]; this can be attributed to the location of the implant in the spine vs. in an osteochondral defect. The degradation of PLDLA falls between poly(L-lactide-co-D-lactide) (PLDA), with a degradation time of 12-16 months, and poly(L-lactide) (PLLA), with a degradation time of 36-60 months [5].

Ceramics such as hydroxyapatite (HA) and Beta-tricalcium phosphate (ß-TCP) are commonly used as bone void filler materials because of their excellent bone biocompatibility and similarity in mineral content to natural bone. However, as seen with polymers, these materials have resorbability issues. HA is crystalline and has a slow resorption rate on the order of years [6], ideal for maintaining structure, but can lead to ingestion of ceramic particulates by surrounding tissues. ß-TCP is amorphous and resorbs quickly, not leaving enough time for new bone to replace the material in the defect site. Combining the resorption rates of HA and ß-TCP would be ideal. A new class of ceramic materials, biphasic calcium phosphates (BCPs) [7], can be created by combining HA and TCP in different ratios, resulting in a range of controllable resorption profiles. Typical commercial BCP formulations can vary in HA:ß-TCP ratio from 60:40 to 20:80. The ratio of calcium to phosphorus (Ca/P) in bone and HA is 1.67, which is considered "optimal". Calcium-deficient BCP has a Ca/P ratio lower than 1.67. This ratio is controlled by the amount of HA to ß-TCP in the base material after sintering it at a high temperature to convert to a mixture of the two ceramics. It has been demonstrated that using a homogeneous calcium-deficient HA powder to form BCP as opposed to physically combining separate HA and ß-TCP powders results in higher compressive strength and less degradation *in vivo* [8]. Physically combining the powders might create voids in the final material, leading to the decrease in strength and increase in degradation. BCP also has the ability to support new bone formation much better than HA or ß-TCP alone, since studies have shown new bone formation without a fibrous tissue layer at earlier timepoints with BCP as opposed to HA or ß-TCP separately [9]. The 60:40 biphasic ratio of HA: ß-TCP in our BioComposite Interference Screw shows good mechanical strength in a rabbit segmental defect model compared to pure HA [10] and shows excellent biocompatibility without a fibrous interface in a rat calvarial defect model [11].

An osteoconductive material supports bone formation, propagation, and growth, and provides suitable mechanical strength when the right cells, growth factors, and other signals are in the vicinity. A study comparing PLDA and PLDA-ß-TCP interference screws to titanium interference screws found that the composite screws had higher pull-out strength and stiffness compared to the metallic screws [12]. Combining HA and BCP ceramics to PLA-urethane materials also results in higher dynamic modulus [13]. As BCP content increases in PLDLA materials, ultimate tensile strength decreases, but is still within range for bone fixation materials [14]. A 70:30 PLDLA spinal cage, containing BCP particles in a 60:40 HA:ß-TCP ratio and combined with adipose-derived stem cells, showed new bone formation and osteoclast activity on the BCP after 4 weeks [15], similar to what studies using these materials separately have found. If the optimal properties of PLDLA and BCP can be combined in a spinal application, as shown above, similar results can be theorized in ACL and PCL reconstruction.

Arthrex vs. Our Competitors' Composite Screws

Table 1 shows the material composition of the Arthrex BioComposite Interference Screw vs. our competitors' composite screws. The ratio of polymer to ceramic in a composite material should be optimized for mechanical strength and material behavior. Either lowering or raising the amount of polymer and/or ceramic material can affect strength at the interface by making the screw brittle or pliable, or possibly increase resorption via acidosis. Polymer degradation that occurs too quickly can lead to a pH drop, therefore increasing the activity of osteoclasts [16] to resorb tissue and screw material and weaken the interface.

Manufacturer	Product Name	Material Composition
Arthrex	***BioComposite Interference Screw***	***70% PLDLA & 30% BCP PLDLA - 70 PLLA/30 PLDA BCP - 60 HA/40 ß-TCP***
DePuy Mitek	Milagro	70% PLGA & 30% ß-TCP PLGA - 85 PLLA/15 PGA
DePuy Mitek	BioCryl	70% PLLA & 30% ß-TCP
Smith & Nephew	BioRCI-HA	95% PLLA & 5% HA
ConMed Linvatec	Matryx	75% self-reinforced (SR) 96/4 PLDA and 25% ß-TCP
Stryker	BiOsteon	75% PLLA and 25% HA
ArthroCare	BiLok	75% PLLA and 25% ß-TCP

Table 1

Controlled Solubility

Studies of the material properties of the BioComposite Interference Screw show that molecular weight (MW, Figure 1a) and inherent viscosity (IV, Figure 1b) drop slowly and uniformly from time 0 up to 12 weeks; however, the mechanical strength at both timepoints is equivalent.

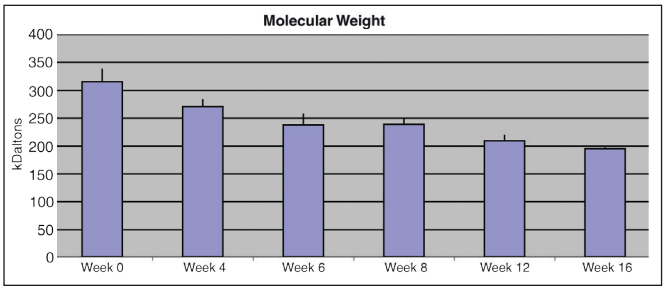


Figure 1a

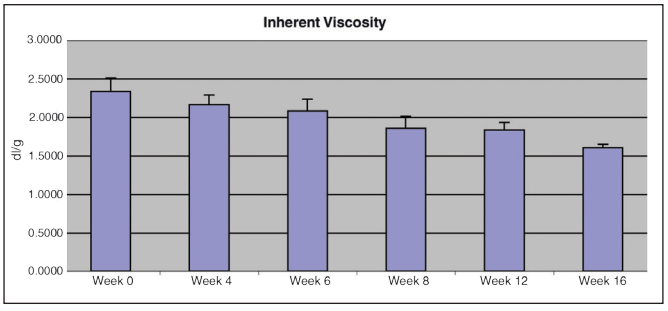


Figure 1b

Imaging characterization of the BioComposite Interference Screw shows uniform dispersion of the ceramic material within the screw structure (Figure 2). The green fluorescent stain represents the inorganic ceramic material within the screw, going from the center cannulated portion of the screw, all the way down to the threads (white arrows).

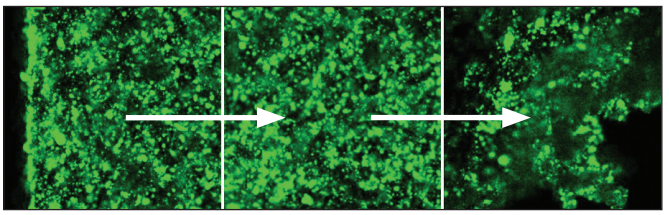


Figure 2

Mechanical Testing

Testing found that 10 mm BioComposite Delta Screws, using a hexalobe driver, had a lower cyclic displacement and higher loads-to-failure compared to Milagro screws (Table 2) with similar insertion torques for both. It is important to note that these screws were not tested side-by-side in the same study. It is also important to note that the number of Milagro screws tested was low, but the initial trend indicates higher insertion torque for Milagro compared to the BioComposite Interference Screws.

	Milagro 10 mm (n=2)	BioComposite Delta 10 mm (n=6)
Insertion Torque (in-lbf)	29 ± 11	28 ± 4
Cyclic Displacement (mm)	4.6 (n=1)	3.5 ± 1.5
Yield Load-to-Failure (N)	728 (n=1)	1053 ± 378
Ultimate Load-to-Failure (N)	877 ± 8	1206 ± 248

Table 2

In Vitro Testing

In vitro studies show similar amounts of human osteoblast adhesion after 24 hours (Figure 3a) and proliferation after 48 hours (Figure 3b) on the BioComposite Interference Screws vs. Milagro screws. Human osteoblasts were seeded onto all surfaces, including tissue culture polystyrene (TCP) as a control, at a density of 20,000 cells/cm^2. Adhesion after 24 hours was determined by counting in a Coulter counter, while proliferation at 48 hours was determined by measuring thymidine incorporation.

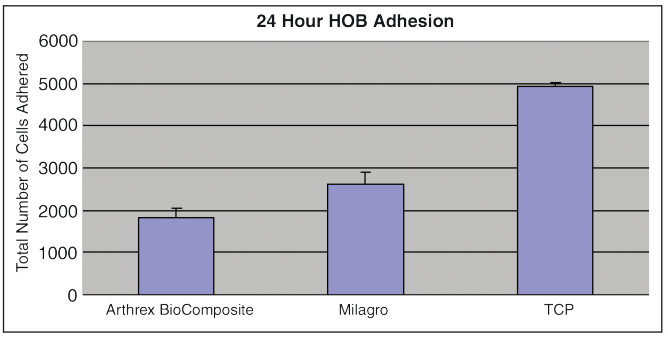


Figure 3a

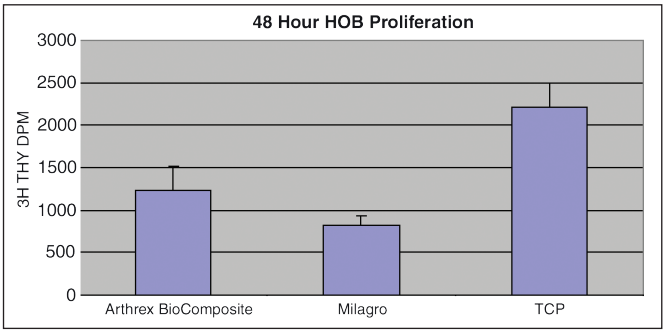


Figure 3b

Animal Testing - 12 Weeks

Computed tomography (CT) data indicate no substantial degradation *in vivo* in an ovine ACL reconstruction model at 12 weeks for either the BioComposite Interference Screw (Figure 4a) or the Milagro screw (Figure 4b) in a tibial insertion site. Hematoxylin and eosin (H&E) histology at 12 weeks shows a minimal inflammatory response for both the BioComposite Interference Screw (Figure 5a) and the Milagro screw (Figure 5b), also in a tibial insertion site.

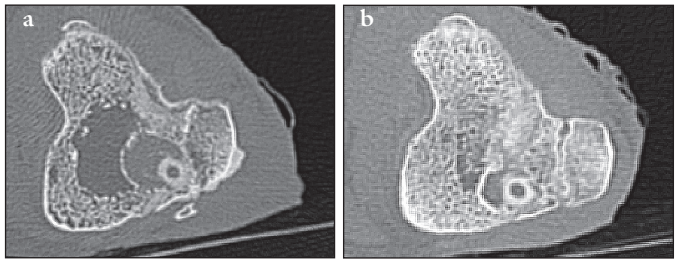


Figure 4

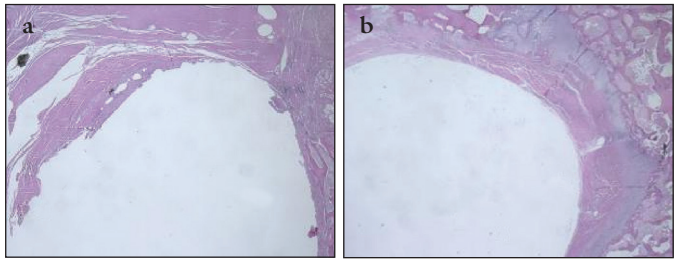


Figure 5

Animal Testing - 26 Weeks

CT data at 26 weeks again shows no significant degradation for either screw type. However, initial bone integration at the tibial insertion site is seen with the BioComposite Interference Screws (Figure 6a), while minimal to no bone integration is seen with the Milagro screws (Figure 6b). Histology of the tendon-bone interface at the tibial insertion site shows Sharpey's fibers (black arrows) between tendon and bone using the BioComposite Interference Screws (Figure 7a), while there was close direct contact without Sharpey's fibers between the tendon and bone using the Milagro screws (Figure 7b). New bone (black arrows) was seen within the tibial screw site of the BioComposite Interference Screws (Figure 7c). The Milagro screws also have some minimal new bone within the tibial screw site (Figure 7d, black arrow). Both screw types also had a layer of fibrous tissue at the screw-tissue interface (not pictured).

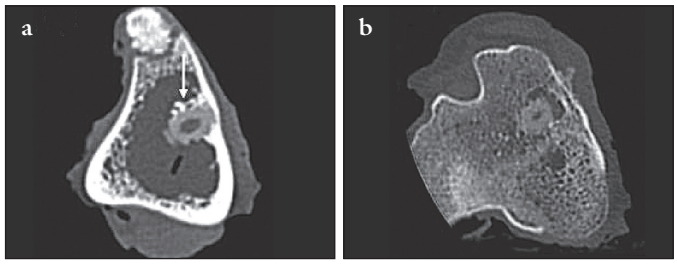


Figure 6

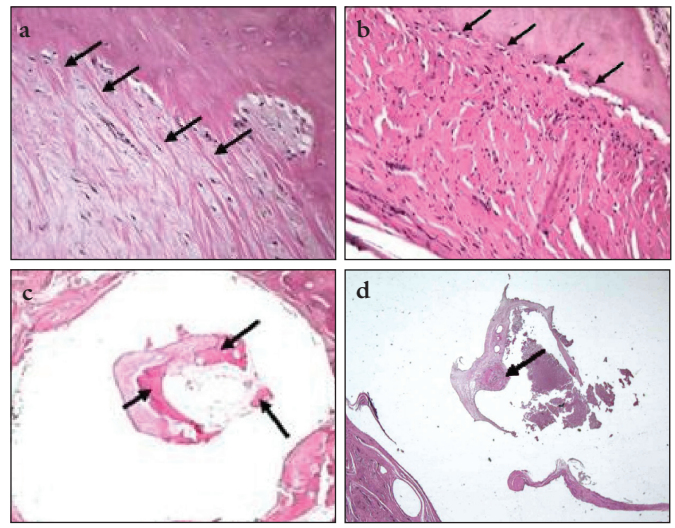


Figure 7

Animal Testing - 52 Weeks

CT data at 52 weeks at the tibial insertion site shows that the BioComposite Interference Screw keeps its shape and is well-integrated into cortical bone (Figure 8a), with some cancellous bone apposition. The Milagro screw (Figure 8b) is starting to lose its shape and does not integrate well with its surrounding bone. Histology at the tibial insertion site shows that the BioComposite Interference Screw has new bone (black arrow) within the screw site (Figure 9a), with some fibrous tissue. The Milagro screw (Figure 9b) also has a thin tract of new bone (black arrow), along with some fibrous tissue, in the screw site. In the femoral tunnel site, the BioComposite Interference Screw (Figure 9c) and the Milagro screw (Figure 9d) both show varying amounts of fibrous tissue at the screw-tissue interface.

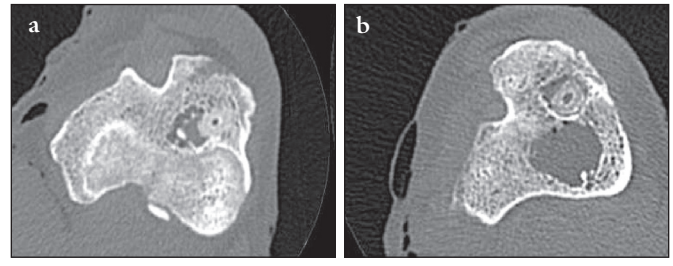


Figure 8

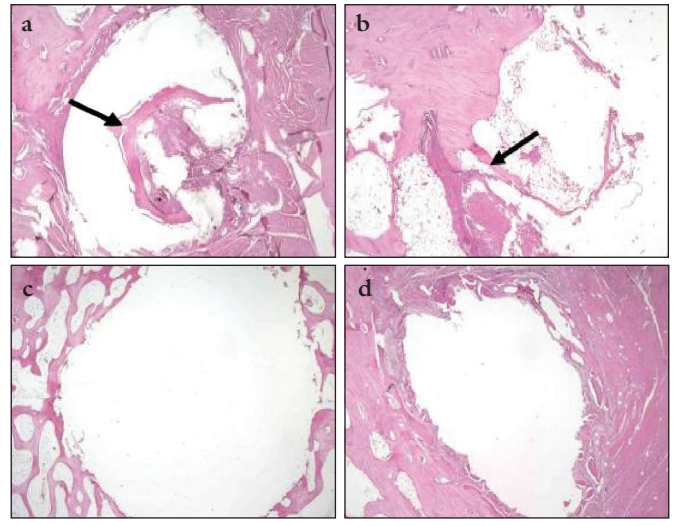


Figure 9

Animal Testing - 104 Weeks

This timepoint showed the most differences in material behavior for the entire study. In Figure 10a, the BioComposite Interference Screw in the tibial insertion site was still easily identified with CT (white arrow), with good bone apposition next to the screw. This was verified with higher resolution of the screw-bone interface with micro CT (Figure 10b). In Figure 10c, the Milagro screw in the tibial insertion site imaged with CT appeared to have degraded and filled in with tissue (white arrow). Figure 10d shows a higher resolution image with micro CT. It showed no evidence of the screw and that most of the void filled in with tissue.

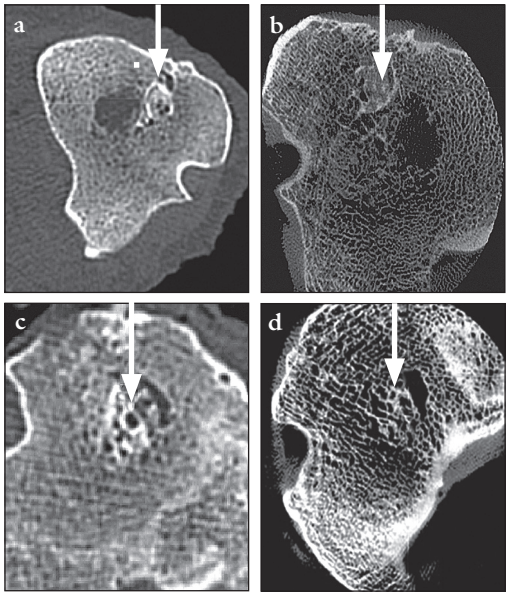


Figure 10

Figure 11a shows the BioComposite Interference Screw in the tibial insertion site. The BioComposite Interference Screw always has a rim of bone completely surrounding the screw void, which is seen in the CT and micro CT images. Small pieces of isolate bone and marrow can be identified within the screw void. The voids are always surrounded by trabecular bone. Some voids were also surrounded by tissue headed towards cartilage or osteoid formation, indicating behavior similar to a fracture callus. However, inflammatory tissue was never identified within the screw site. Histology of the BioComposite Interference Screw appears to be quite predictable, with new bone always surrounding the screw, without a negative inflammatory response.

Figure 11b shows the Milagro screw in the tibial insertion site. A markedly different response is observed. An empty screw void is not visible. Instead, the tissue within the screw void appears to be circular in shape. Presumably, the screw degraded and was replaced by tissue. Some trabecular bone can be identified within the screw void. However, there is much more fibrous tissue within the Milagro screw void compared to the BioComposite Interference Screw void. Some, but not all, of this fibrous tissue is headed towards cartilage or bone formation. The histological response of the Milagro screw appears to show an inflammatory response due to the material degradation, without much new bone formation.

A similar histological response was also seen at the femoral site. Figure 11c shows a ring of bone completely surrounding the screw void in the BioComposite Interference Screw. As before, a large amount of trabecular bone is seen surrounding the screw void. Some isolated bone pieces and marrow are also within the screw void. However, there is no evidence of a significant inflammatory response, similar to the tibial site. Figure 11d shows some new bone and a large amount of fibrous tissue within the Milagro screw void, similar to the tibial site. Again, there is quite a significant inflammatory response here, with tissues heading toward a fibrous, cartilage, or bone lineage, as well as less bone than what is seen in the tibial site.

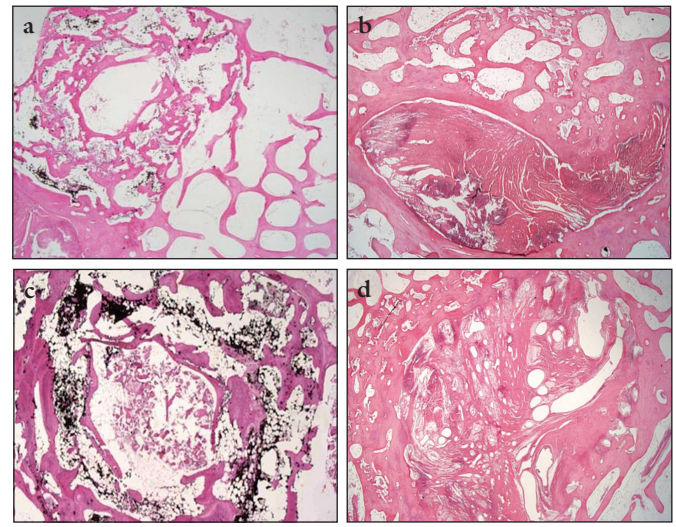


Figure 11

The degradation of the BioComposite Interference Screw is not complete at 2 years. Some new bone is evident, with little to no inflammatory response. The PLDLA in the BioComposite Interference Screws is partially amorphous and presumably degrades between 12 and 36 months, as mentioned above. The 60:40 BCP does not completely degrade by 52 weeks [17]. Therefore, it can be inferred that degradation will not be seen at 2 years.

Complete screw resorption has occurred at 2 years with the Milagro screw, with some new bone and a lot of fibrous tissue. As seen in Table 1, the composition of the amorphous PLGA in the Milagro screw is 85% PLLA and 15% PGA. With this combination, the polymer takes about 5-6 months to degrade completely *in vivo* [5]. Ceramic ß-TCP implants were completely degraded by 86 weeks *in vivo* in minipigs [18]. Therefore, it can be inferred that combining these materials would lead to complete degradation at a timepoint between 24 and 86 weeks. The Milagro 52-week histology shows that some screw degradation has started to occur. At 104 weeks, there is no sign of the screw at all. Therefore, screw degradation occurred between 52 and 104 weeks in this model. However, the tissue replaced with screw degradation contains a lot of fibrous tissue and not too much bone.

Conclusion

This 2-year animal study showed the resorption profiles of the BioComposite Interference Screw vs. the Milagro screw in a sheep model, as well as the screw's ability to support new tissue formation in the tunnel. The BioComposite Interference Screw produced new bone, little to no inflammatory response, and some screw degradation. The Milagro screw produced new bone, as well as fibrous tissue and an inflammatory response. If Milagro produces fibrous tissue without much bone, it would be better to have a more predictable response with the BioComposite Interference Screw.

References:

1. Moser et al, *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 75B: 56–63, 2005.
2. Prokop et al, *Journal of Biomedical Materials Research Part B Applied Biomaterials*, 75B: 304–310, 2005.
3. Ignatius et al, *Journal of Biomaterials Science Polymer Edition*, 12:185-94, 2001.
4. Smit et al, *Journal of Materials Science: Materials in Medicine*, 17:1237–1244, 2006.
5. Middleton and Tipton, *Biomaterials*, 21: 2335-2346, 2000.
6. Itokawa et al, *Biomaterials*, 28: 4922–4927, 2007.
7. LeGeros et al, *Journal of Materials Science: Materials in Medicine*, 14: 201-209, 2003.
8. Gauthier et al, *Journal of Materials Science: Materials in Medicine*, 10: 199-204, 1999.
9. Daculsi et al, *Journal of Materials Science: Materials in Medicine*, 14: 195-200, 2003.
10. Balcik et al, *Acta Biomaterialia* 3: 985–996, 2007.
11. Plachokova et al, *Clinical Oral Implants Research*, 18: 244–251, 2007.
12. Zantop et al, *Arthroscopy*, 22: 1204-1210, 2006.
13. Rich et al, *Journal of Biomedical Materials Research: Applied Biomaterials*, 63: 346–353, 2002.
14. Bleach et al, *Biomaterials*, 23: 1579–1585, 2002.
15. Helder et al, *Tissue Engineering*, 13: 1799-1808, 2007.
16. Komarova et al, *PNAS*, 102: 2643-2648, 2005.
17. Jensen et al, *Journal of Biomedical Materials Research Part B*: Appl Biomater, 90B: 171-181, 2009.
18. Wiltfang et al, *Journal of Biomedical Materials Research* (Appl Biomater), 63: 115-121, 2002.