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REGENESORB
Absorbable Biocomposite Material
A Unique Formulation of Materials with Long Histories of Clinical Use

Summary

The REGENESORB material is a new absorbable biocomposite material developed by Smith & Nephew designed to improve upon currently marketed absorbable materials. This document is intended to provide an overview of the REGENESORB component materials, their history of clinical use, and their activity in the body. In addition, the results of pre-clinical testing conducted during the development of REGENESORB are presented, demonstrating that the REGENESORB material is absorbed faster than poly l-lactic acid hydroxyapatite (PLLA-HA) and is replaced by bone within 24 months (Smith & Nephew Report Nos. 15001194 and 15000897).

Material Overview

The REGENESORB material is a new bioabsorbable biocomposite material comprised of the co-polymer PLGA (poly (l-lactide co-glycolide)) combined with two fillers, calcium sulfate and Beta-tricalcium phosphate (ß-TCP) in a ratio of 65:20:15, respectively. Both calcium-based fillers have been individually demonstrated to be osteoconductive.[8, 10] Calcium sulfate and ß-TCP each have very different absorption rates in the body and act during a different stage in the healing process as well as through different mechanisms of action.[7, 11, 14] All of these compounds have long histories of clinical use, with PLGA clinically used since the 1970s, calcium sulfate since the 1890s, and ß-TCP since the 1920s.[1, 2, 3]

The REGENESORB mixture produces a biocomposite material designed to remain mechanically stable for a minimum of six months before subsequently being absorbed and replaced by bone within 24 months.

POLY (L-LACTIDE CO-GLYCOLIDE) POLYMER (PLGA)

The REGENESORB biocomposite material is primarily composed of the co-polymer PLGA, which is a mixture of two polymers, poly l-lactic acid (PLLA), and polyglycolic acid (PGA), both with long histories of clinical use in implanted surgical devices. Both are absorbable and are comprised of naturally occurring compounds, lactic acid (lactide) and glycolic acid (glycolide), respectively.[4] These polymers are members of the class of biodegradable linear aliphatic polyesters that are the earliest and most frequently used bioabsorbable polymeric biomaterials, originally used in absorbable sutures for wound closure in the early 1970s.[1] The glycolide-lactide co-polymers are the most studied co-polymers in this family of polyesters and have a wide range of properties, depending on the ratio of lactide to glycolide and the choice of the optical isomer of lactic acid (poly D-lactic acid, PDLA, or poly L-lactic acid, PLLA). 50:50 ratios of PLLA:PGA degrade the fastest, while increased proportions of PLLA in the composition decrease the rate of absorption.[4] The REGENESORB biocomposite material is comprised of an 85:15 ratio of PLLA to PGA, producing a polymeric mixture that is bioabsorbable within two years based on pre-clinical testing (Smith & Nephew Report No. 15000897).

Table 1. Polymer Nomenclature

PLLA	poly l-lactic acid or poly l-lactide
PGA	poly glycolic acid or poly glycolide
PLGA	poly l-lactic acid co-glycolic acid or ploy l-lactide co-glycolide (polymer used in REGENESORB material)

Note: The lactide or glycolide forms are the salts of the lactic and glycolic acids respectively.

BETA-TRICALCIUM PHOSPHATE (ß-TCP)

Beta-tricalcium phosphate (ß-TCP) is a member of the larger family of calcium orthophosphates. Calcium phosphate fillers are considered the most biocompatible synthetic substances for use in hard tissue repair and have over 40 years of clinical history.[2, 5] This high degree of biocompatibility is a feature of calcium phosphates of varying chemical compositions and is largely attributable to their similarity to natural calcified tissue.[5] The first successful repair of a bony defect using these materials was described by Albee in 1920.[2] Major academic groups progressed this technology toward commercialization in the 1970s[1] leading to the large number of calcium phosphate-based products currently on the market. Published studies on ß-TCP use in bone graft substitutes have demonstrated that ß-TCP is osteoconductive and enhances new bone formation and infill into bony defects.[6, 8, 10] Calcium phosphates are also often used in biocomposite implants due to their ability to promote implant integration.[6] Exposed calcium phosphate at the implant surface supports increased local osteoblast adhesion and new bone accrual leading to a concomitant increase in device stability.[6] Two predominant forms of calcium phosphate used clinically in orthopedics are hydroxyapatite (HA) and Beta-tricalcium phosphate (ß-TCP). Of these two forms of calcium phosphate, ß-TCP is bioabsorbed in the body more rapidly, typically within 18 months, while HA can take multiple years for complete absorption.[7] This rate of bioabsorption is more in line with PLGA degradation and thus acts as a longer-term osteoconductive filler, which is one of the primary reasons ß-TCP is included in the REGENESORB biocomposite formulation.[6, 8, 10]

CALCIUM SULFATE

Calcium sulfate is a calcium salt that has a long history of clinical use for the treatment of musculoskeletal injuries. Calcium sulfate is one of the oldest bone graft substitutes, with its first reported use dating back to 1892.[3] Contemporary commercial use of calcium sulfate as a bone void filler began in 1996[8]. Attributes of calcium sulfate include a 4–12 week rate of absorption in the body, indicating that this filler works primarily in the early stages of bone healing.[7]

Benefits of calcium sulfate include a compressive strength similar to that of cancellous bone,[9] release of calcium ions as it is bioabsorbed,[9] and the ability to improve the rate of new bone formation as reported in the peer reviewed literature.[8, 10] For example, in 1957 Peltier and Lilo reported the results of a study on the implantation of calcium sulfate cylinders into critical size defects (i.e., defects not spontaneously healed) in the radii of dogs.[3] Complete regeneration of bone occurred within 3 months. Based on this study and others, calcium sulfate is widely considered to be osteoconductive.[3, 8, 10] A separate study examining the mechanism of action of calcium sulfate demonstrated that calcium sulfate bone graft substitutes are associated with increased levels of local growth factors compared to non-treated defects, indicating that calcium sulfate promotes new bone formation in part through a growth factor-mediated mechanism.[11] Specifically, Walsh et al. reported in 2003 on the in vivo response to calcium sulfate pellets implanted into a bilateral critical size distal femoral defect in an adult sheep model. Robust new bone formation was observed in the defects filled with calcium sulfate pellets, and increased immunostaining for the growth factors BMP-2, BMP-7, TGFß-1 and PDGF was seen in defects filled with calcium sulfate pellets alone as compared to untreated control defects.[11]

PROPRIETARY MANUFACTURING PROCESS FOR HOMOGENOUS DISTRIBUTION OF MATERIAL

The REGENESORB biocomposite material is made by compounding the PLGA polymer with the ß-TCP and calcium sulfate fillers using a proprietary compounding process designed to ensure homogeneous micro-particle distribution of osteoconductive fillers throughout the polymer matrix. In addition, implants undergo a special heat treatment process after molding to minimize implant deformation during sterilization and shipping.

Figure 1. Micro-CT image of filler micro-particle distribution throughout the REGENESORB material.

Pre-clinical Testing

During the development of the REGENESORB material, Smith & Nephew conducted four separate pre-clinical studies on this material in adult sheep. Studies lasted from a minimum of 12 weeks up to two years and included two long term compatibility and absorption studies, one 18 months in duration and the second 24 months. In addition, two independent 12-week studies were conducted using tendon to bone repair models, including a patellar tendon re-attachment study to model rotator cuff repair and an ACL reconstruction study. A total of 82 sheep were implanted with REGENESORB-based devices in the course of these studies with no adverse events related to the implants observed. Functionally the REGENESORB-based implant performance was found to be mechanically equivalent to PLLA-HA based implants in both the patellar tendon re-attachment model and the ACL reconstruction model at 12 weeks (Smith & Nephew validation report Nos. 15000919 and 15000921, respectively). Two specific claims regarding the bioabsorption of the REGENESORB material can be made based on the outcome of these studies:

- REGENESORB material is replaced by bone within 24 months (Smith & Nephew Report No. 15000897)
- REGENESORB material is absorbed and replaced by bone faster than PLLA-HA (Smith & Nephew Report No. 15001194)

IN PRE-CLINICAL STUDIES, REGENESORB IS REPLACED BY BONE WITHIN 24 MONTHS

(Smith & Nephew Report No. 15000897)

The predominant reason for the use of bioabsorbable implants is to allow the body to eventually absorb and replace the implant with native tissue. Biocomposite materials are specifically designed to provide clinically sufficient fixation during the critical healing period of the repair site and then for some period thereafter before being absorbed and replaced with native tissue. For bone implants, e.g. suture anchors and interference screws, this native tissue is new bone. Newer biocomposites are being developed to reduce the period of absorption and replacement, leading to more rapid restoration of the native tissue structure and function. Data from our pre-clinical study conducted in an ovine bone implantation model (distal femur or proximal tibia bone implantation) using a 9x10 mm interference screw design implant molded in our new biocomposite material, REGENESORB, demonstrates that the REGENESORB material is absorbed and replaced by native bone within 24 months (Figure 2). Specifically, histological evaluation of interference screws implanted in bone at 6, 12, 18, and 24 months post-implantation shows a completely intact device at 6 months. By 18 months the material has begun to be actively bioabsorbed and newly formed bone is visible between the remaining material fragments. New bone formation progresses through the 24-month time point at which the material appears to be completely absorbed and replaced by new bone.

9x10 mm REGENESORB Interference Screw evaluated in direct-in-bone sheep model

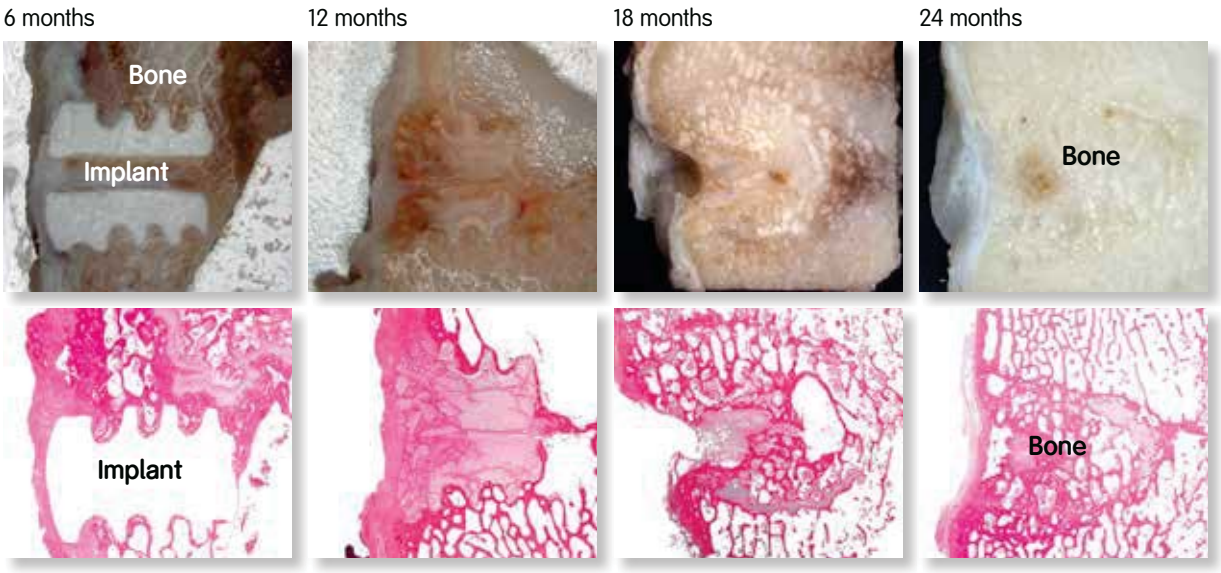

Figure 2. Representative histological images of 9x10 mm interference screws molded in REGENESORB material after 6, 12, 18, and 24 months post-implantation in bone (distal femur or proximal tibia) in adult sheep. The top row displays gross images of bisected implant in bone. The bottom row shows sections of the same samples stained with Hematoxylin and Eosin (H&E).

**In vivo animal testing has demonstrated that REGENESORB material is bioabsorbable and is replaced by bone. Implants (9x10 mm) were implanted in ovine cancellous bone and compared to an empty defect (9x10 mm) at 6, 12, 18, and 24 months (n=6). Micro-CT analysis demonstrated that by 24 months, bone in-growth into this material (289.5 mm^3) was significantly greater ($p<0.05$) than bone in-growth into an empty defect (170.2 mm^3) and reaches a bone volume not statistically different from intact bone (188.2 mm^3). Results of in vivo simulation have not been shown to quantitatively predict clinical performance. Data on file at Smith & Nephew in Report No. 15000897.*

IN PRE-CLINICAL STUDIES, REGENESORB IS ABSORBED AND REPLACED BY BONE FASTER THAN PLLA-HA

(Smith & Nephew Report No. 15001194)

A goal of newer biocomposite materials is to reduce the duration of time the implant remains in the body in order to more closely match material absorption with bony replacement. Materials such as PLLA have previously been demonstrated to remain inert for a long time (4–7 years) and frequently are not replaced by bone.[12, 13] One theory is that the body only maintains the ability to restore the bony site for a limited period of time.[12, 13] The creation of PLLA composite materials containing fillers (e.g., HA) has, in part, reduced the occurrence of this phenomenon by reducing the degradation time closer to 3 years in order to be more conducive to eventual bone replacement. Data from our pre-clinical study comparing suture anchors in two different composite materials (PLLA-HA vs. REGENESORB) conducted in an ovine bone implantation model (distal femur or proximal tibia bone implantation) demonstrate that the REGENESORB material-based implant begins visible bulk degradation around 12 months post-implantation. By 18 months the implant displays a fragmented appearance typical of the absorption of biocomposite implants combined with bone ingrowth between and around these fragments (Figure 3). Higher magnification histology demonstrates significant new bone ingrowth into the implant as well as the formation of organized collagen structures visible under polarized light, indicating more mature lamellar bone. In contrast, PLLA-HA anchors display no visible signs of absorption histologically 18 months post-implantation.

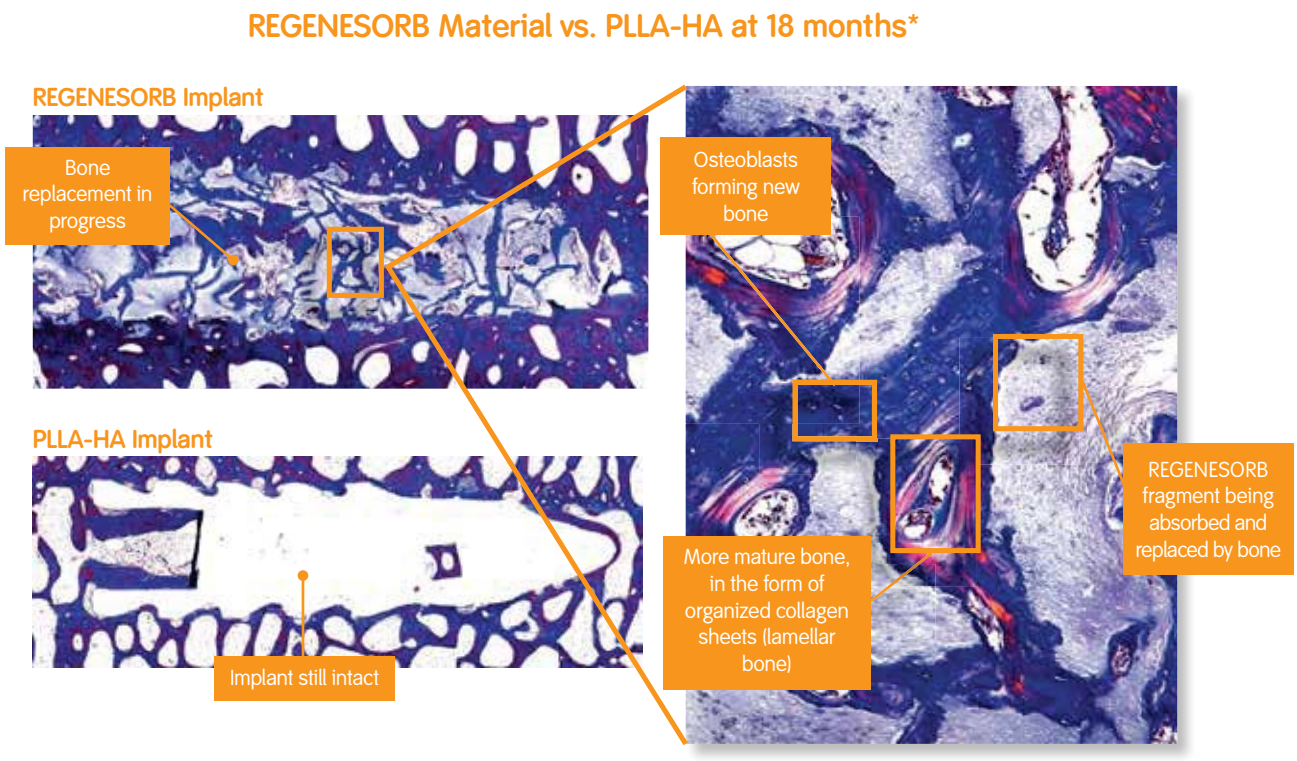

Figure 3. Representative histological images of 2.3 mm suture anchors molded in either REGENESORB material or PLLA-HA after 18 months implantation in bone (distal femur or proximal tibia) in an adult sheep. Higher magnification of boxed area in the REGENESORB anchor (left panel) using polarized light shows remaining REGENESORB material fragments, osteoblasts forming new bone, and organized collagen structures of more mature bone between the REGENESORB fragments at 18 months post-implantation.

**In vivo animal testing has demonstrated that the composite material is bioabsorbable and is replaced by bone. Results of in vivo simulation have not been shown to quantitatively predict clinical performance. Data on file at Smith & Nephew in Report No. 15001194.*

Table 1. Summary of pre-clinical studies evaluating REGENESORB biocomposite material, including two longer and two shorter term implantation studies conducted for a total of 82 animals implanted, with no adverse events observed related to the REGENESORB-based implants.

Description	Design	N	Key Results
Long-term absorption 9x10 mm solid REGENESORB interference screw	• Sheep • Direct-in-bone • Time points: 6, 12, 18, 24 months	24	• REGENESORB replaced by bone within 24 months • No adverse events
Long-term absorption 2.3 mm REGENESORB instability anchor	• Sheep • Direct-in-bone • Time points: 12, 18 months	12	• REGENESORB faster absorbing than PLLA/HA • No adverse events
Tendon re-attachment 2.3 mm REGENESORB instability anchor	• Sheep • Patellar tendon • Time points: 6, 12 weeks	26	• Comparable repair strength at 12 weeks to PLLA/HA anchors • No adverse events
ACL reconstruction Solid REGENESORB interference screw	• Sheep • ACL • Time points: 6, 12 weeks	20	• Comparable repair strength at 12 weeks to PLLA/HA screws • No adverse events

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