

**ORTHOPAEDIC AND REHABILITATION DEVICES PANEL OF THE  
MEDICAL DEVICES ADVISORY COMMITTEE**

**510(k) K082079 – ReGen Collagen Scaffold (CS)**

**ReGen Biologics, Inc  
411 Hackensack Ave., 10<sup>th</sup> Floor  
Hackensack, N.J. 07601**

**Reason for the Panel Meeting:**

ReGen Biologics, Inc. has submitted a 510(k) submission for the ReGen Collagen Scaffold (CS) and is requesting clearance of the device for the following indication:

*The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the meniscus. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.*

*The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure or provide full mechanical strength of the repair.*

FDA has cleared surgical meshes for indications to reinforce soft tissue throughout the body but has not cleared a mesh for the specific indication in the meniscus. ReGen has referenced several legally marketed surgical meshes for indications in multiple anatomic sites throughout the body; including other orthopaedic indications.

Clearance of surgical meshes through the 510(k) substantial equivalence (SE) process has historically been dependent on a demonstration that the new device has the same intended use (i.e., to reinforce soft tissue or bone where weakness exists) and similar composition and technology to previously cleared meshes; these requirements are clearly described in the law and regulations. Substantial equivalence is typically demonstrated by a comparison of performance of the new mesh to other cleared meshes, which requires biocompatibility testing, bench testing, and sometimes animal studies. For some new indications, limited clinical data were required (less than 30 patients having short-term follow-up) to support the clearance.

FDA is requesting the assistance of this panel in evaluating the data submitted by ReGen, in the context of legally marketed predicate devices, to determine that the CS device for use in the meniscus is as safe and effective as other predicate devices for their intended use.

**CONFIDENTIAL**

**ORTHOPAEDIC AND REHABILITATION DEVICES PANEL OF THE  
MEDICAL DEVICES ADVISORY COMMITTEE**

**510(k) K082079 – ReGen Collagen Scaffold (CS)**

**TABLE OF CONTENTS**

Section 1	Executive Summary
Section 2	Description of Collagen Scaffold (CS) and Its Intended Use
2.1	Description of the Device
2.2	Indication Statement
2.3	Method of Use
2.4	Purpose of Surgical Meshes (Intended Use) and FDA's Basis for Marketing Clearance
Section 3	Where CS Fits in Meniscus Treatment Options
3.1	Meniscal Injuries
3.2	Treatment Options
3.2.1	Partial Meniscectomy
3.2.2	Meniscus Repair
3.2.3	Use of Surgical Mesh in the Meniscus – the ReGen CS
Section 4	Regulatory Considerations for Clearance of the CS Device
4.1	Regulatory History of Surgical Meshes
4.2	Data Relied Upon by FDA to Clear Predicate Surgical Meshes
4.3	Substantial equivalence Comparison of CS to Other Meshes
4.3.1	Materials
4.3.2	Technology
4.3.3	Intended Use
Section 5	Pre-Clinical Testing
5.1	Bench Testing
5.1.1	Suture Pull-Out Testing of CS Device
5.1.2	Suture Retention Strength of the CS vs. Predicate Devices
5.1.3	Tensile Testing of the CS
5.1.4	Tensile Testing of the CS vs. Predicate Devices
5.1.5	Reinforcement at the Time of Placement
5.2	Animal Testing
5.2.1	Canine Study to Assess Suitability of CS as a Scaffold for Tissue Growth
5.2.2	Canine Study to Evaluate Suture Pull-Out of CS Over Time
5.3	Biocompatibility
5.4	Biomechanical Requirements of Surgical Mesh in the Meniscus
5.4.1	Introduction
5.4.2	Mechanical Design Requirements of Absorbable Mesh Devices
5.4.3	CS Provides Reinforcement of the Meniscus

- 5.4.4 Tensile Stress is Key Force in the Meniscus
- 5.4.5 The CS Provides Reinforcement to the Meniscus
- 5.4.6 Tensile Forces in the Shoulder: Same or Greater than in the Meniscus
- 5.4.7 Conclusion – Biomechanical Requirements of the CS vs. Shoulder Mesh

**Section 6 Clinical Outcomes Data for CS Device**

- 6.1 Overview of Clinical Data for the CS
- 6.2 Feasibility Study
- 6.3 Case Studies from the IDE Data
  - 6.3.1 Relook Data – Tissue Growth
  - 6.3.2 Relook Data – Articular Surfaces
  - 6.3.3 Clinical Outcomes Measures
  - 6.3.4 JBJS Publication
  - 6.3.5 European Publications
  - 6.3.6 Conclusion – Clinical Benefit Seen with the CS

**Section 7 Safety Data for the ReGen CS Device**

- 7.1 Complications and Risks: Comparison of Use of CS Device and Predicate Surgical Meshes
- 7.2 Serious Adverse Events: Comparison of CS Device Patient Group and Partial Meniscectomy Patient Group in IDE Study
- 7.3 Histological Evaluation of Tissue from Patients Receiving the CS Device in the IDE Study
- 7.4 Evaluation for Immunological Effects
- 7.5 Marketing Experience Outside of U.S.
- 7.6 Conclusion: Safety of the CS Device

**LIST OF ATTACHMENTS**

- ATTACHMENT A Table of Cleared Surgical Meshes with New Indications and Data Relied Upon**
- ATTACHMENT B Comparison of Risks in Surgical Meshes**
- ATTACHMENT C Diagrams showing Surgical Placement of the CS in the Meniscus And the Restore in the Shoulder**
- ATTACHMENT D Histology Report – U.S. Multicenter Clinical Trial**
- ATTACHMENT E Draft Instructions for Use**

**Section 1. Executive Summary**

The CS device is a collagen-based surgical mesh having an intended use identical to predicate surgical meshes, which is to reinforce soft tissue where weakness exists [21 CFR §878.3300], and like other legally marketed resorbable surgical meshes, to provide a scaffold that is replaced by the patient's own tissue. Within the intended use of soft tissue reinforcement, the CS device has specific indications for use in the reinforcement and repair of chronic soft tissue injuries of the meniscus. This is not dissimilar to FDA cleared predicate surgical meshes which have specific indications for other anatomical locations throughout the body; including orthopedic applications, such as for use during repair of the rotator cuff (another articulating joint), repair of various tendon and ligaments, and for vertebral body defects.

The new indication for the CS device for use in the meniscus represents the same therapeutic effect (*i.e.*, to reinforce soft tissue) as the other new indications for surgical meshes that FDA has cleared. Consistent with the 510(k) regulations, a substantial equivalence determination for the CS device should be based on the device having the same intended use and technological characteristics as the predicate device(s), and an assessment as to whether new types of safety and effectiveness questions are raised as compared to use of legally marketed predicate surgical meshes. This assessment must be made in the context of the data required by FDA to assess other surgical meshes. Substantial equivalence has typically been demonstrated by a comparison of performance of the new mesh to other cleared meshes, which requires biocompatibility testing, bench testing, and sometimes animal studies. For some new indications, limited clinical data were required to support the clearance (see **Attachment A**).

The data presented in the 510(k) demonstrate the CS device performs its intended use of providing soft tissue reinforcement and a scaffold for tissue growth. The adequacy of the mechanical characteristics of the CS device are demonstrated through the results of clinical experience. The relook arthroscopies at 12 months performed in the combined chronic and acute patients receiving the CS device showed an average increase in tissue of [redacted] the average increase of tissue for the chronic arm in the CS group was [redacted] and the average increase for the acute arm was [redacted] Please see Figure 1 below.

**Figure 1. INCREASE IN TISSUE**

Population	Initial Surgery		Relook Surgery			P Value Change
	N	Meniscus Remaining	N	Total Tissue	Tissue Gain	
Chronic + Acute	160	[redacted]	140	[redacted]	[redacted]	[redacted]
Chronic CS	85	[redacted]	76	[redacted]	[redacted]	[redacted]
Acute CS	75	[redacted]	65	[redacted]	[redacted]	[redacted]

Histological evaluation at 12 months showed the development of meniscal-like tissue. These results showing an increase in the amount of viable tissue growth in the meniscus

support the effectiveness of the device. In addition, follow-up through five years showed no late failures of the device, providing further evidence of effectiveness based on the ability of the device to remain in place and to provide a durable scaffold for tissue remodeling and growth.

In addition to demonstrating effectiveness as a surgical mesh to reinforce soft tissue and provide a scaffold for tissue growth, clinical outcome measures showed patients exhibited statistically significant improvements in measures of pain, knee function, self-assessment, and Tegner Activity Level as compared to baseline levels at the time of surgery. Please refer to Figure 2 below. These indications of clinical improvement serve to complement the effectiveness of the CS as a surgical mesh.

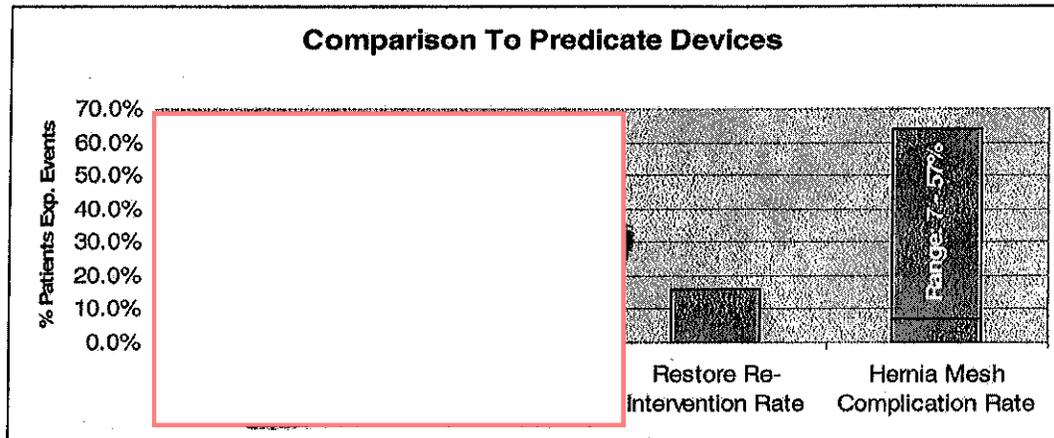
**Figure 2. Clinical Outcomes**

Parameter	Mean Score Pre-Injury	Mean Score Pre-operative	Mean Score at Longest Follow-up	Change in Mean Score	p-Value
<b>Pain</b>	...	[redacted] N=160	[redacted] N=150	[redacted] N=148	[redacted]
<b>Lysholm Knee Function</b>	...	[redacted] N=162	[redacted] N=150	[redacted] N=150	[redacted]
<b>Self-Assessment</b>	...	[redacted] (normal or nearly normal) [redacted] (abnormal or severely abnormal) N=162	[redacted] (normal or nearly normal) [redacted] (abnormal or severely abnormal) N=150	[redacted] [redacted] N=142	[redacted]
<b>Tegner Activity</b>	[redacted] N=162	[redacted] N=162	[redacted] N=150	[redacted] N=142	[redacted]

The safety of the CS device was also extensively evaluated through data collected from the IDE study with up to seven years of patient follow-up. The adverse events and complications that occurred in the clinical study were not unexpected and were consistent with the types and rates associated with predicate surgical meshes used in other anatomic locations. Please refer to Figure 3 below and ATTACHMENT B (list of well known risks for predicate surgical meshes) which compare the types and rates of complications occurring with use of the CS and predicate devices. It is important to note that the impact of failure of the CS device would be for the patient to be left with a partial meniscectomy, the current standard of care procedure. This device failure mode is similar to the failure

mode of predicate surgical meshes, in that the patients are left with a recurrence of the soft tissue defect.

**Figure 3. Complications and Serious Adverse Events**



Note: That SAEs for CS would include any events resulting from the relook arthroscopy and biopsy required by the clinical trial protocol

Survivor-ship analysis (reported in the JBJS publication) out to five years follow-up demonstrated that patients in the chronic arm of the IDE study receiving the CS device had approximately half as many unplanned reoperations on the involved knee as did the controls for disability or persistent pain and/or mechanical meniscus symptoms (9.5% for the CS patients and 22.7% for the control patients). With a reoperation as the end point, the survival rate was 89% for the CS patients and 74% for the controls, which was a significant difference ( $p = 0.04$ ).

Additional safety information is provided by: results from the relook and biopsy evaluations at 12 months post-placement, with no observations of damage to the joint or adjacent articular surfaces attributed to the use of the device; results of an immunology study, showing no evidence of clinically significant antibody formation; and results from marketing experience outside of the United States.

In conclusion, the indication for use of the CS in the treatment of meniscus injuries to reinforce soft tissue and provide a scaffold for replacement by the patient's own tissue presents no new types of safety and effectiveness questions as compared to predicates, as demonstrated by bench testing, animal studies, extensive clinical data and a review of adverse events associated with the use of the device. The device successfully carries out its intended use as evidenced by significant new tissue filling the meniscal defect and statistically significant improvements in pain, function, self-assessment and activity level from their pre-operative status. This extensive information is sufficient to allow a determination of substantial equivalence as a surgical mesh under 21 CFR 878.3300 to reinforce soft tissue, regulated by Class II controls, which will provide reasonable

assurance of safety and effectiveness, consistent with the review and regulations of predicate surgical meshes

## Section 2. Description of Collagen Scaffold (CS) and Its Intended Use

### 2.1 Description of the Device

#### Physical Properties

The ReGen Collagen Scaffold (CS) is a resorbable collagen-based surgical mesh. It serves to reinforce damaged or weakened tissue and provide a structural matrix for tissue remodeling. The CS is provided in a semi-lunar shape with a triangular cross section to be used in the meniscus. In all cases, the surgeon trims the device to the size necessary to reinforce the damaged or weakened meniscal tissue.

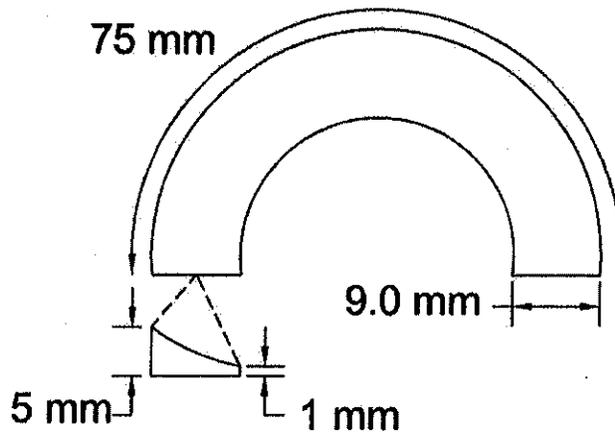


Figure 4. Representative drawing of the CS device

#### Material Composition

The CS device is a resorbable collagen matrix comprised primarily of bovine type I collagen derived from Achilles tendon, and small quantities of glycosaminoglycans. The bovine type I collagen is very similar in amino acid sequence to human type I collagen, and the degradation products of exogenous collagen follow the normal pathways of collagen metabolism.

The bovine-derived collagen is prepared from

While the animal is raised, veterinary inspections and vaccinations are administered to maintain the health of the herds per industry standards.

[REDACTED] USDA

Food Safety Inspection Service (FSIS) program personnel conduct pre-mortem inspections and post-mortem inspections of source animals in accordance with 9 CFR 309 and 9 CFR 310 respectively. [REDACTED]

## 2.2 Indication Statement

Please note that surgical mesh indications for use do not identify subpopulations, but rather focus on the contributions that the mesh offers surgeons and their patients, as it relates to the intended use to reinforce soft tissue. As a result, the data presented in the 510(k) submission and its attachments supports an indication for the use of this surgical mesh in both chronic and acute patients and the indication statement below reflects that belief. [REDACTED]

[REDACTED] the indication in the current submission was limited to chronic patients only because it was the company's understanding that such a change would enable a timely review without the need for outside expertise. As a panel has been convened to provide their expertise regarding the use of this device, and with the understanding of the FDA, it is requested that the panel consider the use of the CS for the following indication:

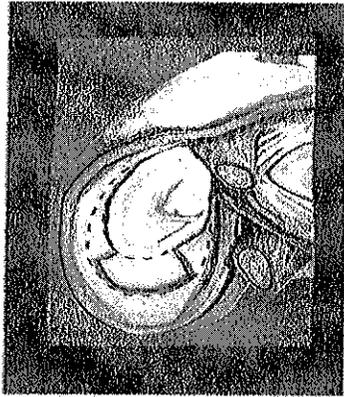
The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the meniscus. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure or provide full mechanical strength of the repair.

## 2.3 Method of Use

Following the partial meniscectomy that is carried out to remove damaged or torn meniscal tissue, the surgeon sutures the CS device to the remaining meniscal rim and horns. The CS initially provides reinforcement of the remaining meniscus allowing the surgeon to preserve more of the native meniscal horns than during a partial meniscectomy alone (see Figure 5 below). As the CS device is resorbed and replaced by the patients own tissue it is the newly formed tissue that fills the meniscal defect that reinforces the remaining meniscus.

CONFIDENTIAL



**Figure 5.**  
Damaged or loose tissue is removed, leaving the intact meniscus rim for support. The dotted line outlines additional tissue that would be removed if the CS were not going to be used to reinforce the defect.

#### **2.4 Purpose of Surgical Meshes (Intended Use) and FDA's Basis for Marketing Clearance**

Surgical meshes are Class II devices in the United States that are cleared for marketing by the presentation of data demonstrating that the new device is substantially equivalent to other legally marketed surgical meshes in intended use and technological characteristics. This means that the new device has been demonstrated to be at least as safe and effective as the existing device of the same type (in this case surgical mesh). For surgical meshes this determination has been made based generally on bench testing, some animal testing and in rare cases limited clinical data. The substantial equivalence of the CS, which has been determined to be a surgical mesh via numerous communications between ReGen and the FDA,<sup>1</sup> is based on the device having the same intended use and technological characteristics as numerous legally marketed class II surgical meshes that have been cleared by FDA. Use of Class II devices within the meniscus and in the articulation of the knee is not new to the FDA, as demonstrated by meniscus repair devices cleared by the Agency.

The intended use of the CS device is the same as that of each cleared surgical mesh identified in ReGen's 510(k) submission, *i.e.*, to reinforce soft tissue where weakness exists [21 CFR §878.3300], and in the case of resorbable meshes, to provide a scaffold that is replaced by the patient's own tissue. Within the general intended use to reinforce soft tissue, surgical meshes have numerous cleared specific indications for use in various soft tissue applications and anatomic sites. The CS is indicated for use in the soft tissue of the meniscus. Furthermore, the data and information submitted by ReGen establishes that the CS surgical mesh is as safe and effective for use in the meniscus as other surgical meshes are for their various cleared specific anatomical uses, and thus raises no new issues of safety or effectiveness questions relative to other cleared surgical meshes.

---

<sup>1</sup> ODE determined through the review of K053621 that the CS can be a Class II surgical mesh device that can be cleared with appropriate clinical data to demonstrate equivalent performance to predicate surgical meshes.

Numerous predicate surgical meshes have been cleared for marketing by the FDA with specific indications for use under the general intended use of soft tissue reinforcement. These cleared indications include, but are not limited to, the following:

- achilles tendon;
- anal fistulas;
- biceps tendon;
- bladder support;
- body wall defects;
- colon prolapse;
- enterocutaneous fistulas;
- facial defects;
- gastroenterological repair;
- lung resections;
- treatment of Peyronie's disease;
- plastic & reconstructive procedures, including use in the face, head, neck;
- pubourethral support/urethral slings for treating urinary incontinence.
- muscle flap reinforcement;
- patella tendon;
- pelvic floor reconstruction;
- quadriceps tendon;
- rectal fistulas;
- rotator cuff;
- sacrocolposuspension;
- soft tissue repair;
- suture line reinforcement;
- thoracic wall repair;
- vertebral body of the spine;

As is obvious from this list, FDA has determined substantial equivalence of meshes based on the intended use and technological characteristics of the device, not on their specific anatomical application. otherwise new anatomical applications could not be cleared. Moreover, FDA has typically found new anatomical applications substantially equivalent without requiring clinical data.

### ***Section 3. Where CS Fits in Meniscus Treatment Options***

#### **3.1 Meniscal Injuries**

The menisci are semilunar fibrocartilaginous structures interposed in the tibiofemoral articulation. The menisci act to distribute load during weight bearing to reduce the contact pressures experienced by the underlying articular cartilage. They also act as shock absorbers and secondary stabilizers, and they provide joint lubrication and nutrition for articular cartilage.<sup>1,8,9,16</sup>

Meniscus injuries are among the most common injuries seen and treated by orthopedic surgeons.<sup>1-4</sup> Historically, menisci were thought to be useless embryologic remnants which, when torn, were potent generators of arthritis.<sup>7-9</sup> Meniscus tears were thus treated with complete meniscectomy. Total meniscectomy was considered a benign procedure, and there were almost no attempts to preserve normal meniscus tissue at the time of meniscectomy.<sup>10</sup> However, the past half century has led to awareness of the multiple functions of the menisci, including load sharing, shock absorption, secondary stabilization, joint lubrication, and articular cartilage nutrition.<sup>1,3,4,8,9,11-13</sup> This understanding has led to efforts to preserve as much of the meniscus as possible, with repair

whenever possible and limited meniscus debridement (partial meniscectomy) if not.<sup>14,15</sup>

### 3.2 Treatment Options

Treatment of meniscus tears is based on symptoms, stability, tear type, and location. Not all tears are symptomatic; the prevalence of asymptomatic tears has been reported between 5% and 36%.<sup>4</sup> Nonetheless, treatment of meniscus injuries is a continuum of care starting with nonoperative therapy, and then meniscus repair, partial meniscectomy, reinforcement and regeneration of lost tissue (not available in the United States at present), and finally meniscus allograft. If all of these treatment options fail, then unicompartmental or total knee arthroplasty become the salvage procedures.

Degenerative tears and stable tears may initially be treated with physical therapy, and they may not ever require surgery.<sup>2,6</sup> Unstable, symptomatic tears require treatment that is based on location and tear patterns. Authors have stated that tears in the peripheral 3 mm are vascular (also referred to as the red-red zone), tears 5 mm from the meniscosynovial junction are avascular (white-white zone), and tears 3 to 5 mm have variable vascularity (red-white zone).<sup>16,20,34</sup> Tears located in the red-red zone may be amenable to suture repair if they are vertical tears. Tears located in the white-white zone lack vascularity and are best treated with partial meniscectomy. Horizontal, complex, radial, and oblique tears are not thought amenable to repair and are best treated with partial meniscectomy to remove all pathologic and unstable meniscus tissue. Tears in the red-white zone are somewhat controversial, but repair attempts should be considered to preserve as much meniscus tissue as possible.<sup>2,6,13,15</sup>

#### 3.2.1 Partial Meniscectomy

Partial meniscectomy involves resection of unstable torn meniscus tissue back to the level of stable tissue. Surgeons are cautioned to remove no more tissue than absolutely necessary. In the short term, such partial meniscectomy reliably alleviates symptoms, results in high patient satisfaction, and allows a return to activity. Nonetheless, there is documented evidence that supports the concern that any amount of meniscectomy, however minimal, is not wholly innocuous.<sup>21-25</sup>

Fairbank initially demonstrated that total meniscectomy resulted in the late development of degenerative radiographic changes.<sup>26</sup> Subsequent studies confirmed and correlated these radiographic changes with poor patient outcomes.<sup>21-25</sup> Since then, evidence has mounted and been documented that confirms that any amount of meniscectomy will, in the long term, lead to degenerative changes in the knee over time. These findings have been supported by biomechanical studies that show increased contact pressures with increased amount of meniscectomy and thus decreased amounts of remaining meniscus tissue.<sup>18,27-29</sup> The clear evidence is that increased contact pressures will overload

the articular cartilage and lead to the development of premature osteoarthritis.<sup>4</sup> These data confirm that knee degenerative arthritis, no matter how early in its course, is a progressive disease. Such progression might be slowed only by preserving a greater amount of meniscus or by regrowing or replacing the lost meniscus tissue.

### 3.2.2 Meniscus Repair

Preservation of meniscus tissue is the obvious goal; however, not all meniscus tears can be repaired.<sup>14,15,31-33</sup> Several characteristics of the meniscus tear and a variety of patient considerations must be factored to determine repair suitability and healing potential of a meniscus tear.<sup>14,15,31-33</sup> As noted above, much of the meniscus is relatively avascular, with only the peripheral portions receiving a blood supply. The concept of meniscus vascularity is critical to understanding meniscus repair because, on the basis of the vascular pattern and blood supply, tears in the vascular periphery of the meniscus have the ability to heal, whereas more central tears in the avascular zones do not exhibit the same healing potential. Nonetheless, because of the importance of the meniscus, tears in the red-white zone should be routinely considered for repair, especially in young and athletically active patients.<sup>14,15,31-33</sup>

Meniscus repair obviously is not a completely benign procedure.<sup>14</sup> Rather, there are many reported complications, but the true rate of adverse events (AE) may be significantly higher than stated in the literature.<sup>35-43</sup> Retrospective study data show that the rate of serious adverse events (SAEs) with meniscus repair is higher than that for meniscectomy alone due to the more extensive and technically demanding surgical technique necessary for meniscus repairs (though complication rates for both may be understated).<sup>35-43</sup> For example, at a large orthopaedic sports medicine clinic, [redacted] knees underwent meniscus suture repair by three different orthopaedic surgeons between 06 January 1992 and 30 March 2005. [redacted] had suture repair of both lateral and medial menisci; 294 had only medial meniscus suture; and [redacted] had only lateral meniscus suture. Repeat meniscus surgery was documented [redacted] knee [redacted].

Of the [redacted] patients who underwent repeat meniscus surgery:

- [redacted] had surgery within one year of suture repair;
- [redacted] had surgery between one year and two years following suture repair; and
- [redacted] had surgery greater than 2 years following suture repair.<sup>44,45</sup>

Other retrospective reviews found the incidence of complications associated with partial medial meniscectomy to be [redacted] 5% and for partial lateral meniscectomy 8.5%; however, for meniscus repair, an overall complication rate of 18% (19% for medial repairs and 13% for lateral repairs) was noted.<sup>35,46</sup>

### 3.2.3 Use of Surgical Mesh in the Meniscus – the ReGen CS

Following the partial meniscectomy that is carried out to remove damaged or torn meniscal tissue, the surgeon sutures the CS device to the remaining meniscal rim and horns. The CS initially provides reinforcement of the remaining meniscus allowing the surgeon to preserve more of the native meniscal horns than if performing a partial meniscectomy alone. As the CS device is resorbed and replaced by the patients own tissue it is the newly formed tissue that fills the meniscal defect that reinforces the remaining meniscus.

#### SECTION 3 REFERENCES

1. Rodkey WG, Bartz RL. The Meniscus: Basic biology and response to injury. *Sports Medicine and Arthroscopy Review*. 2004; 12:2-7.
2. Howell G. Clinical presentation of the knee. In: Bulstrode C, Buckwalter J, Carr A, et al, eds. *Oxford Textbook of Orthopaedics and Trauma*. New York, NY: Oxford University Press; 2002:1108-1113.
3. Cook JL. The current status of treatment for large meniscal defects. *Clin Orthop Relat Res*. 2005;(435):88-95.
4. Sohn DH, Moorman CT. Meniscal debridement. Current concepts. *J Knee Surg*. 2008;21:145-153.
5. Garrett WE Jr, Swiontkowski MF, Weinstein JN, et al. American Board of Orthopaedic Surgery practice of the orthopaedic surgeon: Part-2, certification examination case mix. *J Bone Joint Surg Am*. 2006;88:660-667.
6. Baker BE, Peckham AC, Puppato F, Sanborn JC. Review of meniscal injury and associated sports. *Am J Sports Med*. 1985;13:1-4.
7. Sutton JB: *Ligaments: Their Nature and Morphology*, ed 2. London, HK Lewis, 1897.
8. Arnoczky SP, Adams ME, DeHaven KE, Eyre DR, Mow VC: The meniscus, in Woo SL-Y, Buckwalter J (eds): *Injury and repair of the musculoskeletal soft tissues*, Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1988, pp 487-537.
9. Rodkey WG: Basic biology of the meniscus and response to injury, in Price CT, ed: *Instructional Course Lectures 2000*, Rosemont, IL, American Academy of Orthopaedic Surgeons, 2000, 49:189-193.
10. McMurray T. The semilunar cartilages. *Br J Surg*. 1942;29:407-414.
11. Buckwalter JA, Einhorn TA, Simon SR, eds. *Orthopaedic Basic Science*. 2nd ed. Iowa City, IA: American Academy of Orthopaedic Surgeons; 2000.
12. Fabricant P, Jokl P. Surgical outcomes after arthroscopic partial meniscectomy. *J Am Acad Orthop Surg*. 2007;15:647-653.
13. Greis PE, Bardana DD, Holmstrom MC, Burks RT. Meniscal injury: I. Basic science and evaluation. *J Am Acad Orthop Surg*. 2002;10:168-176.
14. Sgaglione N: Complications of meniscus surgery. *Sports Med Arthros Rev*. 2004;12:148-159.
15. Sgaglione N: Meniscus repair update: Current concepts and new techniques. *Orthopedics*. 2005;28:280-287.
16. Arnoczky SP: Gross and vascular anatomy of the meniscus and its role in meniscal healing, regeneration, and remodeling, in Mow VC, Arnoczky SP, Jackson DW (eds): *Knee Meniscus: Basic and Clinical Foundations*. New York, NY, Raven Press, 1992, pp 1-14.
17. Bullough P, Munuera L, Murphy J, Weinstein A. The strength of the menisci of the knee as it relates to their fine structure. *J Bone Joint Surg Br*. 1970;52:565-567.
18. Lee SJ, Aadalen KJ, Malaviya P, et al. Tibiofemoral contact mechanics after serial medial meniscectomies in the human cadaveric knee. *Am J Sports Med*. 2006;34:1334-1344.
19. Lanzer WL, Komenda G. Changes in articular cartilage after meniscectomy. *Clin Orthop Relat Res*. 1990;(252):41-48.

20. Arnoczky SP, Warren RF. Microvasculature of the human meniscus. *Am J Sports Med.* 1982;10:90-95.
21. Johnson RJ, Kettelkamp DB, Clark W, Leaverton P. Factors effecting late results after meniscectomy. *J Bone Joint Surg Am.* 1974;56:719-729.
22. Roos EM, Ostenberg A, Roos H, Ekdahl C, Lohmander LS. Long-term outcome of meniscectomy: Symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. *Osteoarthritis Cartilage.* 2001;9:316-324.
23. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: Prevalence of radiographic changes after twenty-one years, compared with matched controls. *Arthritis Rheum.* 1998;41:687-693.
24. Roos H, Lindberg H, Gardsell P, Lohmander LS, Wingstrand H. The prevalence of gonarthrosis and its relation to meniscectomy in former soccer players. *Am J Sports Med.* 1994;22:219-222.
25. Tapper EM, Hoover NW. Late results after meniscectomy. *J Bone Joint Surg Am.* 1969;51:517-526.
26. Fairbank TJ. Knee joint changes after meniscectomy. *J Bone Joint Surg Br.* 1948;30:664-70.
27. Baratz ME, Fu FH, Mengato R. Meniscal tears: The effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. *Am J Sports Med.* 1986;14:270-5.
28. Ihn JC, Kim SJ, Park IH. In vitro study of contact area and pressure distribution in the human knee after partial and total meniscectomy. *Int Orthop.* 1993;17:214-218.
29. Krause WR, Clemons MS, Pope MH, Johnson RJ, Wilder DG. Mechanical changes in the knee after meniscectomy. *J Bone Joint Surg Am.* 1976;58:599-604.
30. Schimmer RC, Brulhart KB, Duff C, Glinz W. Arthroscopic partial meniscectomy: A 12-year follow-up and two-step evaluation of the long-term course. *Arthroscopy.* 1998;14:136-142.
31. Klimkiewicz JJ, Shaffer B. Meniscal surgery 2002 update: Indications and techniques for resection, repair, regeneration and replacement. *Arthroscopy.* 2002;18 Suppl. 2:14-25.
32. Sgaglione NA, Steadman JR, Shaffer B, Miller MD, Fu FH. Current concepts in meniscus surgery: Resection to replacement. *Arthroscopy.* 2003;19 Suppl. 1:161-88.
33. Truman KA, Diduch DR. Meniscal repair. Indications and techniques. *J Knee Surg.* 2008;21:154-162.
34. DeHaven KE. Decision-making features in the treatment of meniscal lesions. *Clin Orthop Relat Res.* 1990;(252):49-54.
35. Austin KS, Sherman OH. Complications of arthroscopic meniscus repair. *Am J Sports Med.* 1993;21:864-869.
36. Small NC. Complications in arthroscopy: The knee and other joints. *Arthroscopy.* 1986;2:253-258.
37. Small NC. Complications in arthroscopic surgery performed by experienced arthroscopists. *Arthroscopy.* 1988;4:215-221.
38. Small NC. Complications in arthroscopic meniscus surgery. *Clin Sports Med.* 1990;9:609-617.
39. Barber FA. Meniscus repair: Results of arthroscopic technique. *Arthroscopy.* 1987;3:25-30.
40. Stone RG, Sprague NF III. Complication of arthroscopic meniscus repair. In: Sprague NF III (ed). *Complication In Arthroscopy.* Raven Press, New York, 1989.
41. Bernard M, Grothues-Spork M, Georgoulis A, Hertel P. Neural and vascular complications of arthroscopic meniscus surgery. *Knee Surg, Sports Traumatol Arthrosc.* 1994;2:14-18.
42. Rodeo SA, Forster RA, Weiland AJ. Neurological complications due to arthroscopy. *J Bone Joint Surg Am.* 1993;75:917-926.
43. Rodeo SA, Sobel M, Weiland AJ. Deep peroneal-nerve injury as a result of arthroscopic meniscectomy. *J Bone Joint Surg Am.* 1993;75:1221-1224.
44. Briggs KK, Rodkey WG, Steadman JR. Factors associated with repeat meniscus surgery in patients undergoing suture meniscus repair. Presented at the American Academy of Orthopaedic Surgeons, San Francisco, California, 05-09 March 2008.
45. Rodkey WG, Briggs KK, Steadman JR. Certain factors may influence repeat meniscus surgery in patients after suture meniscus repair. *Knee Surg Sports Traumatol Arthrosc.* 2008;16 (Suppl 1):S151.

46. Sherman O, Fox J, Snyder S, et. al. Arthroscopy – "No Problem Surgery". Analysis of complications in 2,640 cases. *J Bone Joint Surg Am.* 1986; 68: 256-265.
47. Milachowski KA, Weismeier K, Wirth CJ. Homologous meniscus transplantation. Experimental and clinical results. *International Orthopaedics.* 1989;13:1-11.

## **Section 4. Regulatory Considerations for Clearance of the CS Device**

### **4.1 Regulatory History of Surgical Meshes**

Initially soft tissue surgical mesh was constructed of non-absorbable polymeric materials. They were intended to be permanent implants and add significant strength to weakened soft tissues. Clinically these materials were effective; however, they presented certain limitations, one of which was excessive stiffness either initially or after they were encapsulated by tissue. This stiffness resulted in surgical complications such as adhesions, erosion, restricted mobility and recurrence of the defects. Permanent synthetic implants also potentially act as a nidus for infection.

Resorbable materials were introduced to address these limitations. These materials did not have the inherent strength of the non-absorbable materials and they were not intended, "...to replace normal body structure or provide the full mechanical strength to repair..." the defect, as described in the Indications for Use for the DePuy Restore Orthobiologic Soft Tissue Implant (K031969). This resorbable mesh device was instead intended to, "...reinforce(s) soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue."

The clearance of resorbable meshes represented a clear shift from a non-absorbable, permanent device whose inherent properties were intended to provide permanent reinforcement to soft tissue defects. The resorbable meshes were tissue scaffolds that had lower initial strengths but were designed to be replaced by the patient's own tissue during and after a period of restricted activity. It was the new tissue ultimately replacing the mesh that functioned to carry out the intended reinforcement.

As discussed above, FDA has cleared many new indications for use of surgical meshes functioning to repair or reinforce soft tissue in various ways. Some of the many ways to repair or reinforce soft tissue in widely variable clinical applications are shown in **Attachment A**. These include use:

- To maintain the relative position of bone graft material (such as autograft or allograft) within a vertebral body defect (*e.g.*, tumor) that does not impact the stability of the vertebral body and does not include the vertebral endplates (K014200);
- To reinforce soft tissues repaired by sutures or suture anchors, during tendon repair surgery including reinforcement of rotator cuff, patella, Achilles, biceps, quadriceps or other tendons (K042809);

- As a sling to support the urethra to treat urinary incontinence (K980483);
- For implantation to reinforce soft tissue where a rolled configuration is required, for repair of anal, rectal, and enterocutaneous fistulas (K050337);
- For use (as a mesh bag) where temporary wound or solid organ support is required (kidney, liver, spleen) (K051701);
- As a device intended to act as a resorbable scaffold that initially has sufficient strength to assist with soft tissue repair, but then resorbs and is replaced by the patient's own tissue (K001783);
- For temporary wound support wherever it is required (K024199); and
- For the repair of hernias and other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result (K033337);

These examples further demonstrate that the FDA has cleared surgical meshes for use in various anatomic locations and tissue types throughout the human body, representing multiple new indications. The new indication for use of the CS surgical mesh in the meniscus represents the same therapeutic intended use (*i.e.*, reinforcement of soft tissue) as the other new indications for surgical meshes that FDA has cleared, involving different anatomic locations and tissues. Each anatomic location presents its own unique design requirements. For example, hernia meshes require flexibility and different shape configurations to avoid irritation or erosion of the surrounding tissues with sufficient strength to prevent recurrence of the defect; fistula plugs are three-dimensional tapered cylinders designed to fill a defect and not migrate; lung patches serve as seals to prevent air leakage; and surgical mesh used in the spine must withstand cyclic compressive forces to maintain the position of bone graft material and resist generating potentially damaging wear particulates.

#### **4.2 Data Relied Upon by FDA to Clear Predicate Surgical Meshes**

Clearance of surgical meshes through the 510(k) substantial equivalence (SE) process has historically been dependent on a demonstration that the new device has the same intended use (*i.e.*, to reinforce soft tissue or bone where weakness exists) and similar composition and technology to previously cleared meshes; these requirements are clearly described in the Federal Food, Drug, and Cosmetic Act (the Act) and regulations. Substantial equivalence is typically demonstrated by a comparison of performance of the new mesh to other cleared meshes through biocompatibility testing, bench testing, and sometimes animal studies. For some new indications, limited clinical data were required (less than 30 patients having short-term follow-up) to support the clearance. Please refer to **ATTACHMENT A** and the following examples for the types of data that FDA has relied upon to clear surgical meshes with new indications:

1. K042809 – indication for use in tendon repair in patella, Achilles, biceps, quadriceps and other tendons; only bench testing supported these indications;
2. K001738 – indication for use in "...reinforcement of the soft tissues repaired by suture or suture anchors limited to the supraspinatus during rotator cuff repair surgery;" clinical data on only 5 patients followed for 3 months and letters of support from two surgeons were relied upon for the substantial equivalence determination;
3. K961440 – indications for use to reinforce, "...soft tissue of the lung thereby sealing or reducing air leaks that occur during pulmonary surgery". The substantial equivalence determination was based upon biocompatibility data and clinical results from 26 patients in an open-labeled study;
4. K014200 – indication for use, "...to maintain the relative position of bone graft material (such as autograft or allograft) within a vertebral body defect (e.g. tumor) that does not impact the stability of the vertebral body and does not include the vertebral endplates." The substantial equivalence was based on performance testing and no clinical data.

Meshes indicated for use for the first time in a new anatomic site or tissue, or with different technological characteristics were found substantially equivalent, not based on the specific location of use, but on the broad surgical mesh intended use, which is to reinforce the weakened tissue. Otherwise it would be impossible to compare use in hernia repair, to use in repairing an anal/rectal fistula, to use in treating urinary incontinence, to use in vertebral body repair.

Although it is well known that use of surgical mesh involves risks associated with the device itself and its surgical placement (*See ATTACHMENT B* listing these well known risks for predicate surgical meshes), in no case of which ReGen is aware did the FDA require large, well-controlled, long-term studies showing statistical or clinical superiority in outcome measures for surgical meshes with new indications (in most cases, no clinical data on use of the device were required). Nor has FDA previously required a demonstration that in reinforcing or repairing the weakened tissue the use of the surgical mesh resulted in superior clinical outcomes to the surgical procedure without the mesh. The clinical benefit is evident from the device performing its intended use of soft tissue reinforcement or repair. Instead, and consistent with the law and regulations, FDA relied primarily on performance data showing that a mesh can fulfill its intended use of reinforcing soft tissue where weakness exists, and for resorbable meshes, can provide a scaffold into which patient tissue replaces the mesh. As stated previously, this performance data typically consisted of biocompatibility testing, bench testing, occasionally animal studies, and in rare cases limited clinical data.

In the 510(k) submission under review, ReGen is presenting case history data from the IDE study on 160 patients with a mean follow-up of approximately 5 years. ReGen is not relying on the study itself as a whole to show relative safety

and effectiveness because the study was originally designed to support clinical outcome claims other than tissue reinforcement and tissue growth. Nonetheless, these patient outcomes viewed as case studies represent valid scientific evidence (as defined by FDA regulation) that the device performs as intended, *i.e.*, provides a scaffold for new tissue growth that reinforces the damaged meniscus. The data also support the conclusion that the CS mesh is as safe as other cleared meshes.

Importantly, a comparison of the CS device to partial meniscectomy is not relevant to the clearance of the CS as a surgical mesh for several reasons. First, and most critically, the clearance of a surgical mesh requires a comparison to another cleared surgical mesh and not a comparison to a surgical procedure that does not involve a mesh. Second, partial meniscectomy merely removes the damaged tissue and thus does not fulfill the intended use of a mesh which is to reinforce the weakened tissue; therefore, the benefit associated with any surgical mesh is missing with partial meniscectomy. Third, the law requires FDA to find that a new mesh is substantially equivalent to cleared meshes. However, in making that finding, the agency cannot legally require a demonstration of clinical equivalence, let alone superiority, to a surgical treatment that does not involve a device of the same type. Such a comparison does not bear on the substantial equivalence of the new mesh to legally marketed predicate meshes, and is irrelevant to the safety and effectiveness of the CS device for its intended use.

### **4.3 Substantial Equivalence Comparison of CS to Other Meshes**

#### **4.3.1 Materials**

The CS is composed primarily of bovine collagen, similar to the porcine-derived collagen of the DePuy Restore® Implant, the cross-linked collagen of the Kensey Nash BioBlanket™, and the porcine-derived collagen of the Cook Biotech SIS Fistula Plug and Plastic Surgery Matrices. Like the Cook Biotech products, the CS also contains small amounts of glycosaminoglycans (chondroitin sulfate and sodium hyaluronate) which are naturally occurring in the human body. Like the predicate devices, the CS is a biocompatible, sterile matrix that resorbs and is replaced by the patient's own tissue over time.

The CS product is manufactured and processed similarly to other cleared collagen-based surgical meshes, including procedures for minimizing exposure to transmissible diseases, such as bovine spongiform encephalopathy (BSE), and is supplied terminally sterilized.

#### **4.3.2 Technology**

Like the DePuy Restore product, the CS is a porous collagen matrix with a 3 dimensional micro-architecture that is available in configurations that are suitable for reinforcing or repairing the defect site. Both products are provided sterile, packaged in moisture resistant foil packaging and re-hydrated prior to use. Both

can be trimmed to size for the target area, and are sutured into place. Like the Kensey Nash BioBlanket, the CS is a porous cross-linked collagen material that is trimmed to the size needed and sutured into place.

Like the Cook Biotech SIS Fistula Plug, the CS is comprised of animal-derived collagen. The SIS Fistula Plug is supplied in a three dimensional configuration for the specific application of filling a soft tissue defect (fistula), similar to the three dimensional semi-lunar configuration in which the CS is available for meniscus use. Both products are rehydrated, trimmed as necessary to fill the defect, sutured into place, and remodeled by host tissue over time. Both the Cook product and the CS are manufactured in a pre-shaped configuration to fit the needs of the operating surgeon.

Another surgical mesh supplied in a three-dimensional configuration is the SIS Facial Implant. The SIS Facial Implant is provided pre-attached to a trocar for ease of use. This is similar to the pre-configured semi-lunar shape of the CS for ease of use in the meniscus.

Although not a surgical mesh but also a Class II device, the Bionx Implants Meniscus Arrow™, like the CS is comprised of material that is resorbed over time in the meniscus area. The Bionx product is comprised of a copolymer (poly-L/D-poly lactide) as compared to the collagen comprising the CS. Both devices provide temporary reinforcement of a defect in the meniscus while healing takes place and both devices are subjected to the same forces in the intra-articular space of the knee

The CS for use in the meniscus and the DePuy, TEI Bioscience, and Artimplant devices for use in the repair of rotator cuff injuries are used in the same way to address the issues of surgical repair and tissue remodeling. All of these devices are used in articulating joints. In all cases the damaged tissue is thinned, delaminated or completely torn resulting in a gap and the frayed or damaged tissue is debrided or removed to prevent further damage to the remaining tissue. In all of these applications, the mesh is sutured to the remaining healthy and viable native tissue (*i.e.*, the mesh reinforces the native tissue). In the case of the rotator cuff, the standard surgical repair of the tear is undertaken, which involves suturing to secure the attachment of the tendon. In the case of the meniscus, the standard surgical technique is followed for treatment of an irreparable meniscus tear, which is a partial meniscectomy. The final step in both treatments is to trim the surgical mesh to fit the defect and suture it in place to allow integration and replacement by host tissue with the goal of adding tissue volume to reinforce the damaged native tissue. Please refer to **ATTACHMENT C** for detailed diagrams showing this comparison.

### 4.3.3 Intended Use

The CS has the same intended use as all of the other FDA cleared surgical meshes which is to reinforce soft tissue or bone where weakness exists. Cleared surgical meshes perform this function in a number of ways. Some, like the Surgisis Mesh (K974540, K980431, K992159, K034039), the TissueMend device (K031188 and K051766) and the Restore implant (K031969, K001738 and K982330) reinforce the host tissue by being buttressed to the surface of tissue that is approximated, although in many instances total tissue approximation is not possible. Some reinforce by bridging a gap or filling a void like the IMMIX device (K024199 and K032673), again the Restore implant (K031969, K001738 and K982330), the SIS Fistula Plug (K050337), the SIS Plastic Surgery Matrix (K034039) and the SIS Facial Implant (K050246). In filling a soft tissue defect, such as SIS Plastic Surgery Matrix or SIS Facial Implant, the devices provide minimal, if any, true biomechanical reinforcement other than to increase the tissue volume.

Like the intended use of the DePuy Restore® Orthobiologic Soft Tissue Implant, the TEI Bioscience TissueMend, the Artimplant Sportmesh, and the Kensey Nash BioBlanket™, the CS is for general surgical procedures for reinforcement of soft tissue where weakness exists, and is not intended to replace normal body structure. All of these products are intended to provide a resorbable, or degradable, scaffold that is replaced by the patient's own tissue or is incorporated in the patient's own tissue. These predicate devices differ from the CS in that they are additionally indicated for use during rotator cuff surgery, as compared to the CS which is additionally indicated for use during meniscus surgery. The Kensey Nash product also has indications of specific use for defects of the thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, and for suture line reinforcement.

The CS device functions to reinforce soft tissue defects by both buttressing the remaining meniscus rim and horns, by bridging the gap between the meniscal rim and anterior and posterior horns and by filling the void left by the damaged meniscus tissue. All of this ultimately results in the CS providing a scaffold that is replaced by the patient's own tissue which serves to provide the long term reinforcement and repair of the meniscal defect.

Like the predicate resorbable surgical meshes, the CS is not intended to replace a normal body structure or provide the full mechanical strength to repair the meniscus. The CS is sutured to the intact native meniscus which must be present for device use, and does not replace that structure or its function. The intact native meniscus rim, with or without the CS, continues to provide the biomechanical function of the meniscus in the knee by virtue of its mechanical integrity and anterior and posterior attachments. Once sutured to the meniscal rim, the CS functions to reinforce the remaining meniscal rim and anterior and

posterior horns and to provide a scaffold for replacement by the patient's own tissue which takes over this function for the long term.

While there are no predicate surgical mesh devices that have been cleared for use in the meniscus, pre-amendment use of surgical mesh in the intra-articular space of the knee is reported by Parrish.<sup>2</sup> He reports on five cases in which Marlex surgical mesh was used intra-articularly in the knee prior to the enactment of the device amendments in May of 1976. These include use in the repair of defects in the medial and lateral femoral condyles as well as in the patella.

While not a surgical mesh predicate because it is in a different classification, the Bionx Implant device (K012334 and K955768), like the CS, is an absorbable device used for meniscus repair. The device is an absorbable polymeric material that is placed within the intra-articular space of the knee in the same manner as the CS device. FDA found the Bionx substantially equivalent to devices regulated in Class II under 21 CFR 888.3030, *single/multiple component metallic bone fixation appliances and accessories*. In other words, these meniscus repair devices were found substantially equivalent to metal bone plates and screws, which are more significantly different from the Bionx device than any surgical mesh, including the CS, is from its respective predicates. The Bionx clearance thus represents an important regulatory precedent that supports Class II regulation of the CS as a surgical mesh for use in the meniscus.

## **Section 5. Pre-Clinical Testing**

### **5.1 Bench Testing**

While bench testing provides some basic information regarding the comparative mechanical properties of a new surgical mesh to those of cleared meshes, it has limited value in assessing resorbable meshes or meshes for new indications. Because resorbable meshes have varying mechanical properties as they are resorbed and replaced by tissue, the most effective testing of these materials is in animal models and clinical evaluation, as appropriate.

#### **5.1.1 Suture Pull-Out Testing of CS Device**

FDA required testing was performed to characterize the suture retention strength of the CS. This testing measures the amount of force required to pull the suture through the CS. Testing consisted of hydrating the CS,

through the CS approximately 20 mm from the suture

<sup>2</sup> Parrish F, Murray J, Urquhart B. 1978. The Use of Polyethylene Mesh (Marlex®) as an Adjunct in Reconstructive Surgery of the Extremities. *Clinical Orthopaedics and Related Research*. 1978;137: 276-286

The average suture pull-out strength for the CS with a [redacted] height was [redacted]; with a standard deviation of [redacted]

### 5.1.2 Suture Retention Strength of the CS vs. Predicate Devices

Testing was conducted to characterize the suture retention strength of the CS mesh as compared to that of predicate absorbable meshes. This comparative testing is required by FDA for 510(k) surgical mesh submissions.

Test articles included three finished samples of each of the following meshes: CS (ReGen Biologics); Restore<sup>®</sup> Orthobiologic Implant (DePuy); TissueMend<sup>®</sup> Advanced Soft Tissue Repair Matrix (TEI Biosciences); and Surgisis<sup>®</sup> ES<sup>™</sup> Soft Tissue Graft, Surgisis<sup>®</sup> Gold<sup>™</sup> Hernia Repair Graft, and Surgisis<sup>®</sup> AFP<sup>™</sup> Anal Fistula Plug (Cook Biotech).

[redacted]

Results of the suture retention testing demonstrate that the suture retention strength of the CS is within the range of predicate surgical meshes, and similar to the Restore<sup>®</sup> and TissueMend<sup>®</sup> products which were cleared for use in the shoulder and subjected to greater forces than those expected to be seen in the meniscus.

### 5.1.3 Tensile Testing of the CS

To characterize the strength of the CS in the longitudinal and perpendicular planes of finished devices, tensile testing was performed to quantify the force required to rupture or break apart the CS. The test consisted of [redacted]

[redacted]

For the CS having a nominal [redacted] the average peak forces to failure in the longitudinal and perpendicular planes were [redacted] with a standard deviation of [redacted] in the longitudinal plane and [redacted] with a standard deviation of [redacted] the perpendicular plane.

### 5.1.4 Tensile Testing of the CS vs. Predicate Devices

Tensile testing was performed to quantify the force required to rupture or break apart the CS relative to comparable absorbable surgical mesh products, as part of the comparative testing required for surgical mesh submissions. Figure 6 summarizes the results of the tensile testing, in which the average peak load to failure is reported for each device tested, with corresponding standard deviation.

The results indicate that the CS has a failure strength in the same range as comparable surgical meshes indicated for use in hernia repair and tendon repair

**Figure 6. Summary of Tensile Testing**

Surgical Mesh	Average Peak Load to Failure, in Newtons	Standard Deviation
ReGen Collagen Scaffold		
Surgisis AFP Anal Fistula Plug		
Surgisis Soft Tissue Graft		
Surgisis ES Soft Tissue Graft		
DePuy Restore		
Surgisis Gold Hernia Repair Graft		
Tissue Mend		

**5.1.5 Reinforcement at the Time of Placement**

Testing was conducted to demonstrate that the CS, when sutured to the weakened or damaged meniscus, provides reinforcement at the time of placement. Freshly harvested, native bovine meniscus was used in the testing model due to its anatomic similarity to human meniscus in structure and composition.

[Redacted]

The failure mode consisted of suture pull-through or tearing of the CS. Results of testing three samples showed a mean reinforcement strength of [Redacted] attributable to placement of the CS.

Although the native intact meniscus rim is required to use the CS clinically and bears the biomechanical stress in the joint, results from this testing demonstrate that the CS provides reinforcement to the native meniscus at the time of placement, using a conservative, worst-case model. The reinforcement strength

o [redacted] measured for the CS exceeds the tensile stress of [redacted] calculated and reported for the average tensile stress on the native meniscus.<sup>3</sup>

## 5.2 Animal Testing

### 5.2.1 Canine Study to Assess Suitability of CS as a Scaffold for Tissue Growth

This study evaluated the ability of the CS to reinforce a defect within the meniscus of a dog and to assess its ability to provide a suitable scaffold for replacement by the animal's own tissue. Testing was conducted using finished devices.

The canine knee (stifle) joint is known to be highly sensitive to trauma and is prone to joint degeneration on injury. Dog knees have been used extensively as an animal model for joint disease. This model represents a worst case test environment for the CS, due to the lack of a non-weight bearing period during the early healing stage.

Bilateral knee arthrotomies were performed via a medial approach with bisection of the medial collateral ligament. Experimental knees received an 80% resection of the meniscal tissue and the remaining meniscal rim was reinforced by the CS which was sutured to host tissue. Skeletally mature mix breed dogs of both sexes, weighing an average of 25.5 Kg were used. Two animals were sacrificed at each post surgery time point: 3 weeks, 6 weeks, 12 months and 17 months and one animal at 13 months. Scoring of the gross appearance of the newly formed tissue was assessed as Excellent, Good, Fair or Poor/Failure in relation to photographic reference standards established for this study.

[redacted]

[redacted] No untoward effects attributed to the CS were noted and the CS supported the replacement of the matrix with the animals' own tissue. In the demanding environment of this animal study, where animals were immediately weight-bearing, the device remained adhered to the meniscal rim and provided an adequate template for new tissue formation.

<sup>3</sup> The chosen load was representative of an average weight male standing, which is a reasonable model in the context of use of the CS given the restrictions on movement and weight bearing defined by the post-operative rehabilitation protocol. Parsons IM, Apreleva M, Fu FH, Woo SL. The effect of rotator cuff tears on reaction forces at the glenohumeral joint. *J Orthop Res.* 2002 May;20(3) 439-446

<sup>4</sup> Krause WR, Pope MH, Johnson RJ, Wilder DG. Mechanical changes in the knee after meniscectomy. *Journal of Bone and Joint Surgery.* 1976;58(A):599-604.

Long term follow-up

Five animals were added to this study to assess the long term cellular response to the matrix material over a 12 to 17 month period. These dogs underwent the same procedure as described above. Gross observations were taken between 12 and 17 months, and [REDACTED]

Histology

The CS in the canine knee model demonstrated a predictable evolution of reparative granulation tissue evolving into fibrochondrocytic incorporation of the scaffold. After one year, the histopathologic changes were best described as benign gradual assimilation of the CS into the host meniscal tissue. The reporting pathologist stated that long term resorption of the CS and further integration with the host tissue are subtle at the light microscopic level, and possess similarities to longstanding bone graft incorporation into human bone tissue.

**5.2.2 Canine Study to Evaluate Suture Pull-Out of CS Over Time**

Suture pull-out testing was performed using specimens explanted at specified time intervals. At the same explant intervals, portions of these specimens were also evaluated histologically and correlated with MRIs obtained *in situ* prior to explantation. As with the canine studies described above, finished CS devices were used.

Suture pull-out testing was conducted using: (1) CS prior to insertion; (2) the excised portion of the dog meniscus; and (3) excised portions of the CS from the four subgroups of animals at 3, 6, 12, and 24 weeks. The CS and native menisci samples served as control groups. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Testing results show that the CS capably performed its intended use, with no untoward effects, degenerative changes, or joint motion interference

seen, by MRI or histological evaluation. These results indicate the strength of the CS is adequate throughout the remodeling process.

Five sequences of MRI were performed on 18 dog knees after placement of the CS. Six knees each were scanned at 3 weeks and 6 weeks and 3 knees each were scanned at 3 months and 6 months. After MRI scanning, the menisci were explanted and a portion of each meniscus specimen was sent for histological evaluation for correlation with the MRI findings.



In summary, the results of this study confirmed those reported for the suture pull-out study, that the strength of the CS is adequate throughout the remodeling process.

### **5.3 Biocompatibility**

Biocompatibility testing has been performed according to ISO testing standards and demonstrates that the material meets those standards.

### **5.4 Biomechanical Requirements of Surgical Mesh in the Meniscus**

#### **5.4.1 Introduction**

The ability of a resorbable mesh to function adequately to reinforce soft tissue and provide a scaffold for new tissue growth is dependent on its ability to remain adequately adhered to the host tissue and resist the forces exerted on it. Below, we discuss the suture retention strength as a primary factor in assessing this ability. In addition, this section describes the forces to which the CS is subjected, the initial reinforcement of the defect repaired by the CS, and how forces on a surgical mesh within the meniscus are no greater than those on a surgical mesh used in the shoulder, another articulating joint.

### 5.4.2 Mechanical Design Requirements of Absorbable Mesh Devices

All biomaterials, but especially naturally occurring biomaterials such as collagen and extracellular matrix, are subject to host remodeling that begins immediately following surgical implantation.

Tissue-derived surgical mesh materials such as the CS device require mechanical properties sufficient to secure the device *in situ* to withstand the local environmental conditions, mechanical stressors, and cells that perform remodeling functions. The mechanical properties of the device at the time of placement only need be sufficient to secure the device in place during the period of time in which integration of the device into the surrounding native tissue occurs. Furthermore, the mechanical properties of the "device" at any given point in time are comprised of the new remodeled host tissue that has been deposited. There is no reason for the device to possess mechanical properties identical to the native structure because it inevitably will change during the remodeling process, typically strengthening over time in parallel with the patient returning to pre-surgery activity levels.

During the remodeling process, the host simultaneously degrades the device while depositing new extracellular matrix along with variable numbers and types of cells. This new tissue remodels in response to local tissue stressors. The new host tissue organizes its collagen fibers, aligns these fibers, and deposits the type of extracellular matrix (*e.g.*, fibrocartilage) that is appropriate for the site. There is a constantly changing composite material at the site of remodeling surgical mesh, and this composite material will possess mechanical properties that are a function of the loads being applied. This "dynamic reciprocity" between infiltrating cells and the surrounding matrix has been long understood,<sup>5</sup> and is a desirable phenomenon that occurs with virtually all surgical meshes.

In order to adequately assess the ability of a resorbable material to function in a given biomechanical environment, it is necessary to assess the use of the device in an *in vivo* model that can account for the remodeling process. The ability of the CS to function adequately to resist the mechanical stresses of the knee joint was assessed through animal testing, a feasibility study with a mean follow-up of 5.8 years with relook arthroscopies at approximately 1 year and again at 5 years and case studies on 162 patients from a Multicenter Clinical trial with a mean follow-up of 4.9 years.

### 5.4.3 CS Provides Reinforcement of the Meniscus

One of the primary technological characteristics of surgical mesh is that it reinforces weakened soft tissue. Like the predicate absorbable meshes, the CS first acts to reinforce soft tissue and then it serves as a scaffold for tissue growth and remodeling which leads to additional reinforcement. Eventually, the resultant

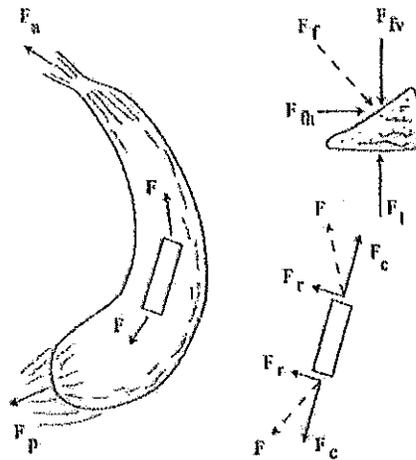
---

<sup>5</sup> Bissell MJ, Aggeler J. Dynamic reciprocity: how do extracellular matrix and hormones direct gene expression? *Prog Clin Biol Res.* 1987;249:251-262.

new tissue takes over the function of reinforcement. To understand how the CS reinforces weakened soft tissue in the meniscus, it is important to first understand how the meniscus functions and the primary forces to which it is subjected. The forces in the meniscus can then be compared to forces seen in other anatomical locations such as the shoulder, in which predicate surgical meshes are cleared. Accordingly, testing was conducted to demonstrate that the CS mesh provides quantifiable reinforcement.

#### 5.4.4 Tensile Stress is Key Force in the Meniscus

The meniscus is a semi-lunar shaped structure with firm attachments to the tibial plateau at its anterior and posterior horns. It is subjected to compressive, tensile and shear stresses (Figure 7).



**Figure 7. Forces in the Meniscus**

Articular joints have very low frictional coefficients, therefore shear stress (stress parallel to or between the articulating contact surfaces) is relatively negligible.<sup>6</sup> As the round femoral condyles and flat tibial surfaces are forced together, the meniscus is compressed and the resulting load is transmitted through it. Pressure on the superior surface of the meniscus has both vertical and horizontal components, due to its wedge-shaped cross section. The horizontal component of pressure on the meniscus acts outward from the center in a radial direction, and for the meniscus to remain in equilibrium, the radial component must be resisted. Circumferential or hoop tension in the meniscus arises as the radial force is resisted, creating a state of equilibrium in which the radial force is balanced against the hoop tension.<sup>7</sup> Although the meniscus of the knee functions under

<sup>6</sup> McBride ID, Reid JG. Biomechanical considerations of the menisci of the knee. *Can. J. Spt. Sci.* 1988;13(4): 175-187

<sup>7</sup> Setton LA, Guilak F, Hsu EW, Vail TP, Biomechanical factors in tissue engineered meniscal repair. *Clinical Orthopaedics and Related Research.* 1999;367S:S272

compression, it is well known that the circumferential hoop tensile stress that develops under load dominates function and failure of the meniscus<sup>8</sup>, and tensile stress is therefore the dominating force. Krause and colleagues conducted cadaveric studies<sup>9</sup> which measured circumferential displacement of the meniscus under load,<sup>10</sup> and they calculated the average tensile stress on the meniscus to be approximately 350 kPa.

#### **5.4.5 The CS Provides Reinforcement to the Meniscus**

Given that tensile stress is the dominating force, testing was conducted (and is presented in **Section 5.1.5**) that demonstrates that the CS, when sutured to the weakened or damaged meniscus, provides reinforcement at the time of placement. This reinforcement strength is within the range of tensile stress experienced by the native meniscus. Like other predicate meshes, the CS provides adequate reinforcement at its indicated anatomical location, and is not intended to replace or provide the full mechanical strength for repair.

#### **5.4.6 Tensile Forces in the Shoulder: Same or Greater than in the Meniscus**

Numerous similarities exist between the anatomical environments and tissues that comprise the meniscus and rotator cuff tendons. Both soft tissues function within articulating joints, experiencing forces described as tensile, compressive, and shear loading. In the shoulder, the rotator cuff tendons connect force-generating muscles to the head of the humerus, translating muscular tension to kinetic skeletal movements. The supraspinatus tendon glides between the humeral head and subacromial space, which constitutes an articulating joint, experiencing shear, compressive, and tensile forces. Like in the meniscus, the greatest force in the shoulder is that related to tension.

The intact joint reaction force in the shoulder has been reported to be, on average, 337 N.<sup>11</sup> Given this load, and the cross sectional area of the rotator cuff tendon, tensile forces in the 2800 kPa range would be expected in this tissue. As in the meniscus, compressive forces in the shoulder are less than tensile, and have been reported to be in the range of 1140 kPa.<sup>12</sup>

---

<sup>8</sup> Fithian DC, Kelly MA, Mow VC. Material properties and structure-function relationships in the menisci. *Clinical Orthopaedics and Related Research*. 1990;252:19-31

<sup>9</sup> Krause WR, Pope MH, Johnson RJ, Wilder DG. Mechanical changes in the knee after meniscectomy. *Journal of Bone and Joint Surgery*. 1976;58(A):599-604

<sup>10</sup> The chosen load was representative of an average weight male standing, which is a reasonable model in the context of use of the CS given the restrictions on movement and weight bearing defined by the post-operative rehabilitation protocol.

<sup>11</sup> Parsons IM, Apreleva M, Fu FH, Woo SL. The effect of rotator cuff tears on reaction forces at the glenohumeral joint. *J Orthop Res*. 2002 May;20(3) 439-446

<sup>12</sup> Machida A, Sugamoto K, Miyamoto T, et al. Adhesion of the subacromial bursa may cause subacromial impingement in patients with rotator cuff tears: pressure measurements in 18 patients. *Acta Orthop Scand*. 2004 Feb;75(1): 109-113

The calculated primary force of tension in the shoulder of 2800 kPa is nearly an order of magnitude greater than the primary force of tension reported for the meniscus of 350 kPa.<sup>13</sup> These studies indicate that the primary forces in both the shoulder and meniscus are those of tension, and that the tensile force transmission in the rotator cuff is comparable to, if not greater than, that in the meniscus. Correspondingly, a surgical mesh used in the shoulder would be subjected to forces comparable to or considerably higher than the forces applied to a surgical mesh in the meniscus.

For both the meniscus and the shoulder, the tensile stress translates to stress at the points of attachment between the mesh and tissue. Each device relies upon the intact native tissue to bear the biomechanical stress transmitted through the tissue to the joint. The CS requires an intact meniscal rim and horns which bear the biomechanical stress, as they do in a patient who has a partial meniscectomy. The resorbable scaffolds do not replace native tissue or provide the full mechanical strength for repair. The CS, Restore, and TissueMend devices all have comparable suture retention strengths, and are expected to remain firmly attached to the respective native tissues while experiencing comparable intra-articular stresses. Given the comparable physical properties of the CS to other meshes, use of the device in the meniscus does not present new types of safety or effectiveness questions as compared to its predicates, in particular the Restore device, because it is intended for use during rotator cuff repair.

#### **5.4.7 Conclusion – Biomechanical Requirements of the CS vs. Shoulder Mesh**

In summary, both the meniscus and supraspinatus function within articulating joints while performing load transmission roles. Both are also subjected to compressive, tensile and shear forces. In both indications the tensile forces are the major forces seen by the tissue and the tensile forces present in the shoulder are equal to or greater than those seen in the meniscus. The Restore Implant and ReGen CS both provide immediate reinforcement of the surgical repair and a resorbable template to facilitate tissue remodeling allowing the patient's own tissue to replace the scaffold. This new tissue provides the potential for long-term reinforcement of the damaged or weakened tissue. Similar surgical techniques are used to implant both devices and both devices are used to address similar types of tissue damage.

While the FDA has stated that the Restore device and other shoulder meshes are intended for suture line reinforcement, that is not consistent with the cleared labeling or intended use of these devices. The cleared indication use is for "reinforcement of the soft tissues" and the labeling states that the device is use for tissue that is thin, delaminated or frayed tissue and where coverage of the humeral head is incomplete.

---

<sup>13</sup> Refer to footnote 4

Bench and animal testing show that the CS has mechanical properties sufficient to secure the device *in situ* to withstand the local environmental conditions, mechanical stressors, and cells that perform remodeling functions. The clinical data demonstrate that the device has sufficient strength to function as a surgical mesh, and results of late relook arthroscopies show that the resulting tissue maintains its presence and viability even past 6 years.

## **Section 6. Clinical Outcomes Data for CS Device**

### **6.1 Overview of Clinical Data for the CS**

The Collagen Scaffold functions as a surgical mesh in that it reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own tissue. The CS functions in the meniscus to reinforce the remaining meniscus by initially bridging the meniscus defect between the meniscal rim and horns. It also provides a scaffold that is replaced by the patient's own tissue that fills the void as the scaffold resorbs.

Extensive clinical experience with the CS is available from the following studies:

1. Feasibility Study – single center published results on 8 patients with follow-up to 6 years;<sup>14, 15</sup>
2. Case studies on 162 CS patients from an IDE Multicenter Clinical Study (Multicenter Safety and Effectiveness Study of the Collagen Meniscus Implant) with average follow-up to 4.9 years (maximum 7 years); and
3. Clinical data published in *The Journal of Bone and Joint Surgery* (2008) comparing data in the chronic and acute arms of the IDE study, with survival analysis to 5 years; and
4. European publications on two case series (2 and 4 patients, respectively) with follow-up to 12 months.

The clinical data resulting from these studies confirm the conclusions from the bench testing and animal studies that the device is biocompatible, resorbable, and provides a scaffold for tissue growth.

### **6.2 Feasibility Study**

A clinical feasibility study of the CS device under IDE G920211 was conducted at a single investigational site in 8 patients between the ages of 18 and 60 years old. The objectives of the feasibility study were to confirm that the device was implantable arthroscopically, that there were no significant adverse reactions

---

<sup>14</sup> Rodkey, WG, Steadman, JR, Li ST. 1999. A clinical study of collagen meniscus implants to restore the injured meniscus. *Clin Orthopedics* 367: S281-S292

<sup>15</sup> Steadman JR, Rodkey W. 2005. Tissue-engineered collagen meniscus implants: 5 to 6 year feasibility study results. *Journal of Arthroscopic and Related Surgery* 21: 515-525.

associated with the use of the device, and that the device remained adequately attached to the host tissue to support host tissue growth.

Eight patients, coincidentally all of whom were male, were enrolled in the study. The average amount of meniscus loss was 62%. After surgery, subjects underwent a rehabilitation program that lasted 6 months. Clinical follow-up and blood collection were performed at 1, 6, and 12 weeks, and at 6 and 12 months. Six patients underwent a relook arthroscopy and biopsy at 6 months and two underwent these procedures at 12 months. The protocol was approved to extend the follow-up period to 6 years. MRIs were taken at 6 and 12 weeks, and at 6 and 12 months.

There were no significant complications attributed to the CS in any of the eight patients and no untoward effects on the joint as a result of the device or the tissue replacing it. One patient had an additional relook arthroscopy at 9 months to debride excessive scar tissue formation. All patients returned to activities of daily living by 3 months and were fully active by 6 months. By two years, all patients had improved Lysholm scores compared to their preoperative scores. Seven (7) patients had an improved Tegner score at 2 years. For patient self-assessment at 2 years, 5 patients rated their knees as improved compared with preoperatively.<sup>16</sup>

Immunology testing (ELISA assays) showed no significant increase in antibodies at any time point. Relook arthroscopy at 6 or 12 months follow-up revealed remodeled tissue in all patients. The average filling of the defect was estimated to be 77% at the time of the relook arthroscopy. Histologic analysis confirmed new fibrocartilage matrix formation. MRIs showed that the implant did not shrink and the decreasing signal intensity suggested that the new tissue was undergoing maturation.

All Feasibility Study patients returned for clinical, radiographic, magnetic resonance imaging, and arthroscopic examinations at an average of 5.8 years (range 5.5 to 6.3 years) after CS implantation.<sup>17</sup> Lysholm, Tegner, and patient satisfaction scores remained improved significantly compared to pre-operative values. From pre-operative to 5.8 years, pain scores were still improved, but had declined from the 1 and 2-year post-operative values. The meniscus-like tissue that developed in the scaffold presented no complications throughout the follow-up period of approximately 6 years. There were no signs of joint damage as a result of the treatment through the clinical, radiographic, MRI, and arthroscopic assessments. The amount of the defect filled remained similar to the initial relook at 6 to 12 months (69% vs 77%). The hypothesis was affirmed that these patients significantly improved, on average, at 2 years compared to preoperative status, and remain improved at 5.8 years.

---

<sup>16</sup> Refer to footnote 11

<sup>17</sup> Refer to footnote 12

### 6.3 Case Studies from the IDE Data

ReGen Biologics is conducting a long-term randomized, controlled clinical trial of the CS under IDE G920211. Enrollment is complete and follow-up information continues to be collected in order to obtain long-term data on clinical outcomes of the device through seven years. ReGen intends to complete this trial as a post-market study. In the 510(k) submission case history data were presented from the IDE study on 160 patients with a mean follow-up of approximately 5 years. ReGen is not relying on the entire dataset of the study itself because it was originally designed to support clinical outcome claims other than tissue reinforcement and tissue growth. For the purpose of demonstrating that the CS is as safe and effective as other cleared surgical meshes, these case studies represent valid scientific evidence that the device provides a scaffold for new tissue growth that reinforces the damaged meniscus and supports the conclusion that it is as safe as other cleared meshes.

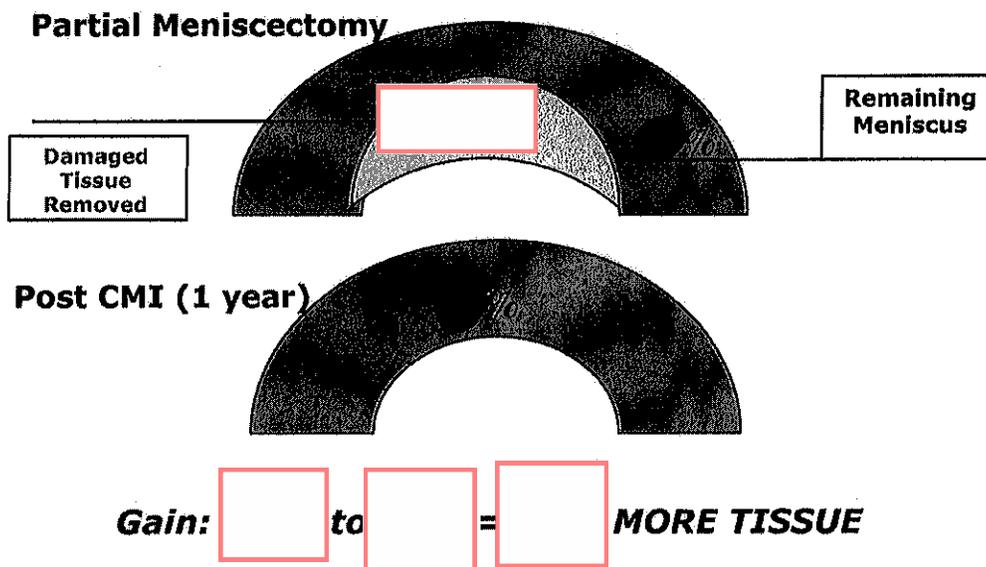
A summary of the results relevant to performance as a surgical mesh in the knee from the IDE clinical trial is provided below. The data on safety and re-look arthroscopy observations from this study confirm that the CS device: 1) is well-tolerated: 2) poses no unique risks as a surgical mesh in actual clinical use: 3) functions as predicted from bench testing, animal models and human feasibility studies as a scaffold for the growth of the patient's own tissue: 4) presents no unanticipated adverse events and further, the adverse events are consistent with those of cleared predicate devices: and 5) does not damage the joint.

#### 6.3.1 Relook Data – Tissue Growth

Baseline operative data indicate an average of [ ] of meniscus tissue was removed during the partial meniscectomy in the CS patients, leaving an average of [ ] of their original meniscus surface area coverage remaining prior to placement of the CS.

Of the 162 patients receiving the CS, 141 (87%) underwent second-look arthroscopy at approximately 12 months for the purpose of evaluating the status of the CS and the surrounding joint space. The remaining 21 patients (13%) were either lost to follow-up, underwent explant prior to 12 months, or refused to allow the additional surgery. At the one-year relook, the surgeon documented that the CS patients had, on average, a total meniscus tissue surface area coverage of [ ] indicating a gain in tissue quantity of [ ] relative to the [ ] original meniscus remaining at the time of CS placement).

**Figure 8. Tissue Replacing the Scaffold at 1 Year Post-op**



This gain of [ ] more tissue illustrates that the CS successfully performed the function of a surgical mesh by providing a scaffold for tissue to grow in the area of the damaged meniscus.

In addition, histological analysis at 12 months of the tissue maturing connective tissue, best described as a fibrous connective tissue differentiating toward a fibrochondrocytic (meniscal-like) tissue. There were no clinically relevant negative findings such as severe inflammation or a giant-cell response in any of the biopsy specimens examined. A complete report of the descriptive histology of evaluable specimens from all patients can be found in **Attachment D**.

### 6.3.2 Relook Data – Articular Surfaces

Surgeons were asked to evaluate the articular surfaces of the knee using the Outerbridge scale at the time of study surgery.<sup>18,19,20</sup> The Outerbridge score ranges from 0 to 4, with 4 representing the most extensive damage to the articular surfaces. Surgeons were asked to repeat this evaluation at the time of the protocol required relook arthroscopy on the CS patients. At the index surgery, the mean Outerbridge score was [ ] points for the patients in both groups who received

<sup>18</sup> Baratz ME, Fu FH, Mengato R: Meniscal tears: The effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. *Am J Sports Med* 1986; 14:270-275.

<sup>19</sup> Hede A, Larsen E, Sandberg H: Partial versus total meniscectomy. A prospective, randomised study with long-term follow-up. *J Bone Joint Surg* 1992; 74B:118-121.

<sup>20</sup> Andersson-Molina H, Karlsson H, Rockborn P: Arthroscopic partial and total meniscectomy: Long-term follow-up study with matched controls. *Arthroscopy* 2002; 18:183-189.

the CS device. Chronic patients in the CS group (patients having one to three prior meniscal surgeries) had a mean reported Outerbridge score of [redacted]

At the time of the one-year relook arthroscopy, the mean Outerbridge score had improved to [redacted] points for all patients who received the CS device. Patients in the chronic group had improved to [redacted] differences were not statistically significant). Articular cartilage changes following knee injury are progressive and the fact that there was no statistically significant difference in the mean Outerbridge scores demonstrate no damage to the joint occurred as a result of CS placement.

Using the Outerbridge scoring system, relook arthroscopies also confirmed that articular surfaces in [redacted] of CS patients improved and [redacted] remained the same, while [redacted] worsened. It is important to note that of the [redacted] of cases that worsened, only [redacted] worsened by [redacted] grades or more. Because the Outerbridge Scoring Scale is a subjective measure, a change of 1 grade as noted in [redacted] of these cases could be attributed to the subjective nature of the scale.<sup>21,22</sup> Following damage to the soft tissue of the knee, there is a known pathway of degenerative changes that occur, including degenerative arthritis.<sup>23 24 25</sup> Surgeons expect the articular surfaces of this patient population to worsen over time depending on the amount of meniscal loss, which is why surgeons attempt to conserve as much meniscus tissue as possible. The fact that the articular surfaces of [redacted] of CS patients improved in this study and [redacted] showed no worsening is favorable, and not generally expected, following meniscal loss.

More important than the Outerbridge scoring evaluation is the direct visual assessment during the relook procedures of the meniscus and adjacent articular surfaces. In these relook surgeries there were no observations of damage to the articular surfaces caused by the CS device. There was no evidence in the histological specimens from [redacted] patients that the CS or resulting tissue posed the potential for damage to the articular surfaces.

### 6.3.3 Clinical Outcomes Measures

In addition to the primary assessment of tissue reinforcement and growth to demonstrate the CS device is performing its intended function, clinical outcomes of pain, knee function and self-assessment were assessed to compare results in the

<sup>21</sup> Brismar BH, Wredmark T, Movin T, Leanderson J, Svensson O. Observer reliability in the arthroscopic classification of osteoarthritis of the knee. *J Bone Joint Surg Br* 2002 ;84B(1) :42-47

<sup>22</sup> Noyes FR, Stabler CL. A system for grading articular cartilage lesions at arthroscopy. *Am J Sports Med* 1989;17:505-513

<sup>23</sup> Baratz ME, Fu FH, Mengato R. Meniscal tears: The effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. *Am j Sports Med* 1986; 14:270-275

<sup>24</sup> Bolano LE, Grana WA. Isolated arthroscopic partial meniscectomy: Functional radiographic evaluation at five years. *Am J Sports Med* 1993; 21:432-437

<sup>25</sup> Andersson-Molina H, Karlsson H, Rockborn P. Arthroscopic partial and total meniscectomy: Long-term follow-up study with matched controls. *Arthroscopy* 2002; 18:183-189

CS patients at 12 months, 24 months, and beyond 24 months as compared to their pre-operative status to determine the amount of clinical improvement noted after treatment with the CS device. While clinical outcome claims are not the basis for the determination of substantial equivalence of the CS device as a surgical mesh, they support the safety of the device for its proposed intended use in the meniscus.

**Pain**

Subjects were asked to rate their pain level during the previous 48 hours on a visual analog scale (VAS) under three conditions: 1) during the highest level of activity; 2) during routine activities of daily living; and 3) at rest. The scale was the standard 100 mm VAS scale, where the left side (minimum 0 mm) corresponded with no pain and the right side (maximum 100 mm) corresponded with the worst possible pain. For analysis purposes a composite pain score was derived by combining the values from the three separate conditions noted above.

Figure 9 below presents the mean composite pain score for the chronic CS patients at the pre-operative time point, the mean composite score at longest follow-up, the difference between those score, and the p-value for this difference.

**Figure 9. Comparison of Pain at Pre-operative and Longest Follow-up – all CS Patients**

Group	Mean Pain Score Pre-operative	Mean Pain Score Longest Follow-up	Change in VAS Mean Pain	p-Value
All CS Patients N=162	[Redacted] N=160	[Redacted] N=150	[Redacted] N=148	[Redacted]

These data show that the CS patients experienced a clinical benefit of decreased pain in the operative knee at the longest follow-up time point. This reduction in pain is statistically significant at the  $p < 0.0001$  level.

**Knee Function (Lysholm Knee Score)**

Subjects were asked to rate knee function in specific categories using the Lysholm scale. This validated scoring system, based on subscale weights published by Tegner and Lysholm (1985), has eight domains (subscales) and an overall score calculated as the sum of the domains. Each domain contributes to the overall score; however, the weight of each domain ranges from maximal 5 to 25 points. The maximum overall score ranges from 0 – 100, with 0 representing the worst possible knee function, and 100 representing the best possible knee function.

Figure 10 below presents the mean Lysholm score for all CS patients at the pre-operative time point, the mean Lysholm score at longest follow-up, and the difference between those scores, and the p-value for this difference.

**Figure 10. Comparison of Lysholm Score at Pre-operative and Longest Follow-up**

Group	Mean Lysholm Score Pre-operative	Mean Lysholm Score Longest Follow-up	Change in Lysholm at longest follow-up	p-Value
All CS Patients N=162				< .0001

At their longest term follow-up, the CS patients experienced a clinical benefit of improved knee function as demonstrated by a statistically significant increase in function from their pre-operative status as measured by the Lysholm scale.

**Tegner Activity Level**

The Tegner activity scale has been the most widely used activity scoring system for patients with knee disorders and has been validated for use in patients with meniscus injuries.<sup>26,27,28,29</sup> It is a numerical scale ranging from 0 to 10. Each value indicates the ability to perform specific activities. An activity level of 10 corresponds to participation in competitive sports at the national or professional or other elite level; an activity level of 6 points corresponds to participation in recreational sports; and an activity level of 0 is assigned if a person is on sick leave or receiving a disability because of knee problems.

Tegner activity scores were obtained pre-injury (retrospectively, on the basis of patient recall), preoperatively, and postoperatively. This allows calculation of the percentage of the lost activity level that was regained as a result of the treatment intervention. This measurement is the Tegner index, and it normalizes the return to activity across a diverse patient population. For example, a Tegner index of 1.0 indicates that the patient regained 100% (all) of the activity level that had been lost as a result of the injury, whereas a Tegner index of 0.25 shows that the patient regained only 25% of lost activity.

<sup>26</sup> Paxton EW, Fithian DC, Stone ML, Silva P. The reliability and validity of kneespecific and general health instruments in assessing acute patellar dislocation outcomes. *Am J Sports Med.* 2003;31:487-92.

<sup>27</sup> Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;198:43-9.

<sup>28</sup> Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF. Development and evaluation of an activity rating scale for disorders of the knee. *Am J Sports Med.* 2001;29:213-8.

<sup>29</sup> Briggs, KK, Mininder SK, Rodkey, WG, Steadman, JR. Reliability, Validity, and Responsiveness of the Lysholm Knee Score and Tegner Activity Scales for Patients with Meniscal Injury of the Knee. *JBJS.* 2006; 88A:698-705

**Figure 11. Change in Tegner Activity Level (Pre-operative to Longest Follow-up)**

Group	Pre-Injury Tegner Activity Level	Pre-operative Tegner Activity Level	Longest Term Follow-up Tegner Activity Level	Longest Term Follow-up Tegner Index
All CS Patients N=162	[redacted] N=162	[redacted] N=162	[redacted] N=150	[redacted] N=142

At the longest term follow-up patients who received the CS regained [redacted] of their lost activity level. This gain from pre-operative levels is statistically significant with a p-value of < .0001. CS patients therefore saw a clinical benefit of increased activity as compared to their pre-operative activity level.<sup>30</sup>

### Patient Self-Assessment

Patients were asked to rate their knee function at the pre-operative visit, and at subsequent follow-up visits. The response choices were “normal”, “nearly normal”, “abnormal”, and “severely abnormal”. At the pre-operative time point [redacted] of patients rated their knee as normal or nearly normal, while [redacted] % of patients rated their knee as abnormal or severely abnormal.

At the longest term follow-up [redacted] % of patients felt their knee was normal or nearly normal, while the number of cases who felt their knee was abnormal or severely abnormal had decreased to [redacted]. This change in self-assessment was statistically significant with a p-value of < .0001.

### 6.3.4 JBJS Publication

Published results of the outcomes associated with the use of the CS in ReGen’s IDE study appear in the July 2008 edition of the *Journal of Bone and Joint Surgery*. A summary of the data and corresponding analyses reported in this peer

<sup>30</sup> In the JBJS article, the Tegner index was used, not the raw Tegner scores because the Tegner index normalizes return to activity across a patient population of the type we report here. However, in a recent publication<sup>3</sup> the standard error of the measurement was 0.4, and the minimum detectable change with a 95% confidence interval was 1.0 for meniscus lesions. Therefore, any changes in raw Tegner scores from preoperative to post intervention with a change equal to or greater than 1.0 can be considered detectable by the instrument and not due to error. Although “clinical significance” of the Tegner index has not been reported in the literature, the data from this study show that patients in the CS treatment group regained significantly more of their lost activity than did patients in the control group, and therefore returned closer to their pre-injury activity levels. This finding is statistically significant and has obvious clinical merit as the raw change score from pre-op is 1.4.

reviewed journal article were included in the 510(k) submission. Publication of this data in a prestigious scientific journal demonstrates the merit of this clinical experience to the medical community. Clinical results are presented for both the acute and chronic patients who received the CS as compared to the control groups undergoing partial meniscectomy only. (This differs from the combined data presented previously from the IDE study on all patients receiving the CS device.) The chronic patients who received the CS device regained significantly more of their lost activity than did the controls, and underwent significantly fewer non-protocol reoperations. No differences were detected between the CS group and control group in the acute arm of the study.

### **Overview (JBJS Publication)**

The Acute Study Arm includes a total of 157 patients (75 in the CS treatment group, and 82 in the control group). The Chronic Study Arm includes a total of 156 patients (87 in the CS group and 69 in the control group)<sup>31</sup>. Two patients in the chronic CS group were excluded from the data analysis because they had more than 3 prior surgeries to the involved meniscus leaving a total of 85 CS patients for analysis.

Both the CS implantation and control procedures were performed through the use of minimally invasive arthroscopic surgery. As described in the JBJS publication, the postoperative rehabilitation program was specific to each treatment group, with control patients prescribed standard physical therapy and CS patients receiving a brace and undergoing more prescribed rehabilitation protocol for up to six months.<sup>32</sup>

The mean duration of follow-up was 59 months (range, 16 to 92 months). Repeat arthroscopies at one year post-implantation on the CS patients demonstrated that the CS device resulted in a significant increase in total tissue within the meniscal defects for all CS patients. In addition, the chronic injury CS patients regained significantly more of their lost activity level and experienced significantly fewer

---

<sup>31</sup> Forty-nine cases enrolled in the study withdrew prior to, or at the time of surgery. The breakdown by group is: 15 in the CS group (10 chronic, 5 acute); and 34 in the control group (25 chronic, 9 acute). Reasons for withdrawals were not always noted by the study sites, but reasons that were noted include: did not want to be a control patient; insurance and/or financial issues; pain had resolved; would not consent to ACL repair; patient did not follow up with study surgeon.

More patients in the control group withdrew as compared to the CS group. This study was not blinded – patients were informed of the group to which they were randomized, due to the differences in the rehabilitation protocols on which they were informed as part of the consent process. Chronic patients randomized to the control group withdrew in greater numbers – surgeons indicated that these patients withdrew because they had already undergone previous meniscectomies, and withdrew after being randomized to receive that surgery again.

<sup>32</sup> While the rehabilitation protocols were different, these differences were not expected to have a profound effect on the two or five-year results reported. Although greater pain and more limited knee function was seen early (up to six months) in the CS group due to surgery associated with device placement and restriction of activity per protocol, no differences were evident beyond 6 months. Thus, it was concluded that the initial differences in rehabilitation had no effects on the long-term outcomes.

non-protocol required reoperations related to meniscus symptoms than the partial meniscectomy control group.

**Re-Look Arthroscopy Results (JBJS Article)**

At approximately the 12 month time point, 65 acute CS patients and 76 chronic CS patients underwent a second look arthroscopy to evaluate the CS and the surrounding articular surfaces. This procedure showed that the CS device resulted in a significant (p=0.001) increase in total tissue surface area. The increased tissue surface area included the area of the new tissue plus the existing meniscus rim. This information is summarized in Figure 12 below:

**Figure 12. TISSUE GROWTH ASSESSMENT**

Treatment	Initial Surgery		Relook Surgery	
	N	% Meniscus Remaining (SD)	N	% Total Tissue (SD)
Acute CS	75	51 (20)	65	73 (17)
Acute Control	82	59 (19)	0	59*
Chronic CS	85	37 (20)	76	73 (20)
Chronic Control	69	40 (22)	0	40*

\*No relooks conducted on control – assume no additional tissue growth based on literature

Please note that, at the time of initial surgery, in both chronic and acute groups the amount of meniscus remaining is less for the CS patients than the controls. The difference appears to relate to the fact that patients were excluded from the CS group if the defect was considered too small (less than 25% loss of the meniscus). Since partial meniscectomy was being performed on the controls patients regardless of the size of the defect, those patients were not always excluded in those cases. This is evident in the listings provided in the response to question on [redacted] where it is clear that more patients with small defects were included in the control groups. Furthermore, the greater meniscus loss in the CS group would be expected to present a worse case for the CS patients compared to the control group.

Because the intended use of the CS as a resorbable surgical mesh is to reinforce the remaining meniscus and provide a scaffold for replacement by the patient's own tissue, these data clearly demonstrate that the device fulfills that function. In addition, the use of the CS generally allows the surgeon to preserve more of the meniscal horns than would be possible when performing a partial meniscectomy alone, because without the reinforcement of the CS, leaving the meniscal horns could cause further meniscal damage. The CS provides the same clinical benefit

as any cleared predicate resorbable surgical mesh intended to reinforce and repair damaged soft tissue, by providing a scaffold for tissue growth.

Additionally at the 12 month relook the articular surfaces were inspected and Outerbridge scores were recorded. This information is summarized in Figure 13 below. A slight improvement in Outerbridge score was noted in the chronic CS group, but this improvement is not considered clinically significant. Since the control patients did not undergo second look arthroscopy, a similar comparison is not possible.

**Figure 13.**

<b>Treatment</b>	<b>Initial Surgery Mean Outerbridge Score</b>	<b>Relook Surgery Mean Outerbridge Score</b>
<b>Acute CS</b>	<b>1.3</b>	<b>1.3</b>
<b>Acute Control</b>	<b>1.2</b>	<b>Not evaluated</b>
<b>Chronic CS</b>	<b>1.5</b>	<b>1.3</b>
<b>Chronic Control</b>	<b>1.7</b>	<b>Not evaluated</b>

#### **Clinical Outcomes (JBJS Publication)**

All patients completed validated outcomes measures (VAS pain scale, Lysholm functional score, and Tegner activity scale) pre-operatively and at all follow-up time points.

All patients showed a statistically significant improvement in pain, function, and patient self-assessment when compared to their own pre-operative scores. No statistically significant differences were noted between the CS patients and the control patients in both the acute and chronic arms of the study for pain, Lysholm, or self-assessment. Chronic CS patients did regain significantly more ( $p = 0.002$ ) of their lost activity level as measured by the Tegner Index than did the chronic control cases. The chronic CS patients regained 42% of their lost activity level at approximately 5 years post-operative, as compared to the controls who regained only 29% of their pre-injury activity level. In the acute group, both CS and control cases regained an average of 41% of their lost activity level.

As noted by the authors of the JBJS article, the possibility of recall bias associated with the scoring of pre-injury activity levels to calculate the Tegner Index exists; however, if patients overestimated their pre-injury activity level, in most instances this overestimation would have resulted in an underestimation of the Tegner Index. Furthermore, within this study, both the control and the CS patients would have had equal probabilities of experiencing any recall bias as this data was prospectively collected under the IDE study protocol. Additional support for lack

of recall bias comes from the fact that the mean pre-injury Tegner Scores for both the CS and partial meniscectomy patients were essentially the same (6.5 for the CS patients and 6.6 for the partial meniscectomy patients) indicating that the patient's recall of their pre-injury Tegner scores were equivalent.

The authors of the JBJS publication believe that the benefits of being able to account for the pre-injury activity levels in the Tegner Index outweigh this potential weakness. It is very different for one patient to gain 3 points in activity level as a result of injury, when they have lost only 3 points and another to gain 3 points when they have lost 6. This sort of difference is accounted for with the Tegner Index. The fact that the paper was published with a discussion of this limitation indicates that the reviewers and editors of the *Journal of Bone and Joint Surgery* felt the use of the Tegner Index was a clinically acceptable method of reporting changes in activity level in this study.

### **Complications (JBJS Publication)**

Safety was assessed by an examination of serious or clinically relevant complications in the study knee that required some form of treatment. The severity of each event and whether it was related to the implant was determined by the surgeon-investigator at the time of the report of the event. A serious or clinically relevant complication was identified in twelve patients (7.5%) who had received the CS and eleven (7.3%) in the control group. Of the twelve documented serious complications in the CS patient group, seven were classified as probably or at least possibly related to the collagen meniscus implant.

The rates of serious complications were essentially equal for the CS patient group and control group. Although seven of the twelve complications in the CS group were classified as being probably or at least possibly related to the implant, it appears that placement of the collagen meniscus implant did not lead to any more serious complications than did partial meniscectomy, the current standard of care. We believe that this finding is noteworthy especially because the patients who received the CS were required to undergo a second surgical procedure with a biopsy of the meniscal tissue.

Safety of the device was also supported by the fact that during the relook surgeries there was no evidence of damage to the chondral surfaces due to the device or the new tissue resulting from the use of the device. No exuberant tissue growth was observed in any of the 141 patients who had relook arthroscopies. Histologically there were no clinically relevant findings such as severe inflammation or giant cell response in any of the biopsy specimens examined.

**CONFIDENTIAL**

### Reoperation and Survival Rates (JBJS Publication)

Reoperation and survival rates were determined through five years of follow-up for the chronic patients (82 in the CS group and 69 in the control group)<sup>33</sup> to assess the durability of the result of the surgical procedure using the Kaplan-Meier method. The Kaplan-Meier method estimates the probability of the proportion of patients with reoperations at a particular time. Because of the low number of patients with follow-up past five years, survival results were estimated at five years. Furthermore, five years was the average time for the clinical outcomes results reported in the article; hence, this fact was further reason to use five years as the cut-off for the survivorship analysis.

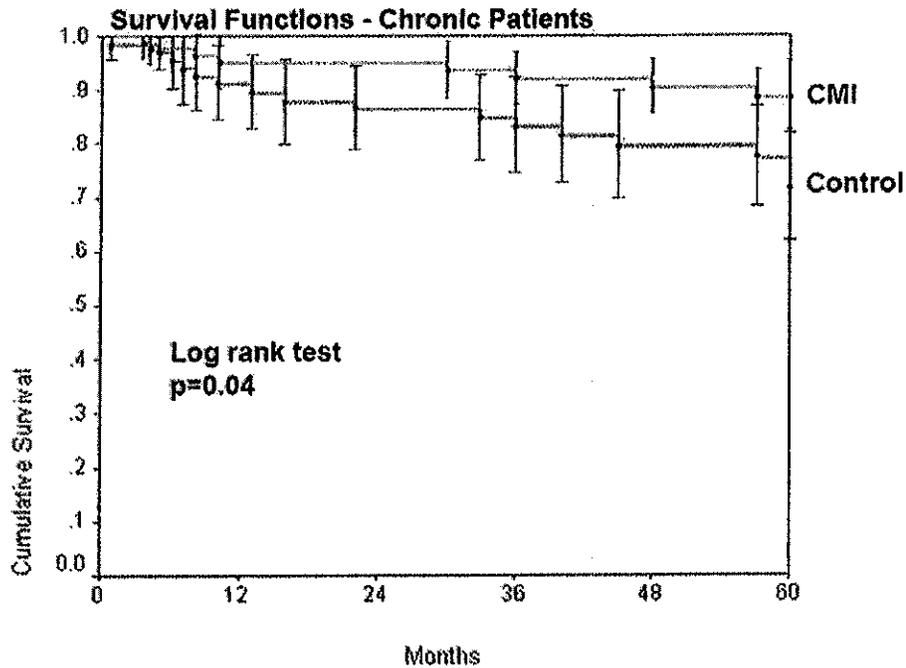
Because the study protocol required the CS patients to have an additional relook surgery and biopsy that was not required of the control group, it was necessary to develop, *a priori*, a scientifically valid analysis plan. As part of this plan, the authors developed a clinically relevant definition of a reoperation, which was defined as: "*an unplanned additional operation (outside of the protocol) on the study knee as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus.*" A reoperation was performed when it was the surgeon-investigator's professional judgment that such an intervention at that time was in the patient's best interest. Once a patient underwent a "reoperation" as defined above, that patient was eliminated from further consideration for survivorship.

In this study, chronic CS patients had about half as many unplanned reoperations on the involved knee as did the controls for disability or persistent pain and/or mechanical meniscus symptoms. The odds for the requirement of an additional such surgery within the survivorship analysis were 2.7 times greater for the controls than the chronic CS patients (95% confidence interval = 1.2 to 6.7;  $p = 0.04$ ). The reoperation rate was 9.5% for the CS patients and 22.7% for the control patients. At five years, with a reoperation as the end point, the survival rate was 89% for the CS patients and 74% for the controls, which was a significant difference ( $p = 0.04$ ). The Kaplan-Meier survivorship curve is presented in Figure 14.

---

<sup>33</sup> The patient population in the JBJS article excluded 5 of the 87 CS patients enrolled and treated under the protocol due to protocol violations (2 patients had more than 3 prior surgeries), deaths (2), and early skin infection that tracked to the implant site and resulted in explantation at 3 weeks post-placement (1 patient).

**Figure 14. Kaplan-Meier survivorship curve**



It is especially noteworthy that although the CS patients were required to have relook arthroscopy with biopsy at one year, the reported non-protocol reoperations for the CS patients were a result of clinically significant pathology; hence, we do not believe that the protocol-required repeat arthroscopies biased the overall survivorship and reoperation rates. These findings from the survivorship analysis based on reoperations suggest that in the chronic CS patient group the new meniscal-like tissue may slow the progression of degenerative joint changes that otherwise would lead to further surgical intervention.

#### **Conclusions (JBJS article)**

The CS supports significant new tissue ingrowth that appears to lead to statistically significant improvements over partial meniscectomy in regaining lost activity (Tegner Index) and in the reoperations related to meniscus symptoms. The new tissue is stable and appears safe and biomechanically competent. Consistent with the data presented, the CS has the utility to reinforce and repair soft tissue defects of the meniscus and provide a suitable scaffold that is replaced by the patients own tissue, thereby providing clinical benefit to patients with chronic meniscus injuries.

### 6.3.5 European Publications

Clinical experience with the CS used in the meniscus has also been published by Reguzzoni et al.<sup>34</sup> and Ronga et al.<sup>35</sup>

Ronga and colleagues reported on two patients who received the CS and underwent biopsy via a second look arthroscopy at 6 months after implantation. MRI was performed prior to the second look arthroscopy at 6 months, and also at 12 months. Light microscopy and SEM were used to evaluate the 6 month biopsy specimens as compared to pre-implant CS devices.

At the re-look arthroscopies, macroscopic examination demonstrated continuity of the CS with the native residual meniscus. The stability of the CS as well as tissue consistency similar to fibrocartilage was shown through probing the implant area. The biopsy specimens demonstrated invasion of the scaffold by connective tissue and blood vessels, indicating viable tissue, with the newly synthesized collagen fibrils clearly distinguishable from the pre-implant CS device. No phagocytomacrophagic cells or inflammatory reactions were observed within the implant. MRI findings confirmed CS biocompatibility, showed evidence of the evolution of the integration process between the CS and the host meniscal rim from 6 to 12 months, and evidenced changes over time that may reflect initial resorption of the device or further organization of new tissue within the scaffold.

Reguzzoni and co-authors published a case series in which the CS was arthroscopically implanted in four patients affected by traumatic irreparable tears of the posterior horn of the medial meniscus. All patients were evaluated before CS surgery and at the time of biopsy with the use of the Lysholm score and Tegner activity scale.

All patients returned to activities of daily living by 3 months and were fully active at 6 months. No adverse events occurred in this series of patients after CS implantation. The Lysholm score and Tegner activity scale increased in all operated knees during the 6 month follow-up period. At the re-look arthroscopy, meniscus-like tissue formation was noted and the CS was healed to the capsule and host meniscus rim. One implant showed a small area of fragmentation that did not require debridement. There were no signs of synovitis or damage to the joint or apposing cartilage surfaces at 6 months post-operatively. SEM examinations at six months revealed that the multi-lamellar structure typical of the CS scaffold is less evident due to tissue invasion into the pores of the scaffold. These pores were filled by connective tissue, where many cells, either spindle-

---

<sup>34</sup> Reguzzoni M, Manelli A, Ronga M, Raspanti M, Grassi F. 2005. Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 74B: 808-816.

<sup>35</sup> Ronga M, Bulgheroni P, Manelli A, Genovese E, Grassi F, Cherubino P. 2003. Short-term evaluation of collagen meniscus implants by MRI and morphological analysis. *Journal of Orthopaedics and Traumatology* 4:5-10.

shaped or round, were surrounded by newly formed extracellular matrix and blood vessels. No phagocytes were observed. The invasion of the scaffold by fibroblast-like cells and connective tissue matrix, as well as the absence of phagocytes and macrophages, confirmed the biocompatibility of the CS. The authors concluded that the morphological findings of this case series demonstrate that the CS provides a three-dimensional scaffold for colonization by precursor cells and vessels leading to the formation of a fully functional tissue.

Both of these case study series provide evidence of active tissue replacement in the matrix and gradual resorption of the device. There were no histological signs of inflammatory response. MRI findings indicate integration of the device with host tissue and initial resorption of the device may occur between 6 and 12 months post-operatively. No adverse events were reported in the six patients. No damage to the joint or opposing articular surfaces was noted in relook arthroscopies. The findings are supportive of those from the animal studies.

### **6.3.6 Conclusion – Clinical Benefit Seen with the CS**

In all of the studies presented, patients treated with the CS device improved significantly from baseline levels in terms of pain, knee function, and self-assessment. Direct visualization of the meniscus at the time of relook arthroscopy surgery revealed that the CS performed its function as a surgical mesh. In the multi-center study there was   increase in tissue. This new tissue did not damage the articular surfaces as there was essentially no change in the mean Outerbridge scores for the articular surfaces and the surgeons noted no damage through direct visualization at the one year relook surgery.

In chronic patients, there was significant improvement in the Tegner Index, which indicates that the chronic CS patients regained more of their pre-injury activity level than the controls. Additionally, as shown through the survivorship analysis, the chronic CS patients underwent significantly fewer unplanned subsequent meniscal surgeries when compared to the chronic controls.

The clinical data presented clearly demonstrate that the CS device functions as a surgical mesh, and is safe and effective for its intended use.

## ***Section 7. Safety Data for the ReGen CS Device***

**Attachment A** provides a perspective on the amount and type of safety data that FDA has relied upon for clearance of surgical meshes with new indications. In evaluating the safety data presented by ReGen, it is relevant to reference the standard that has been applied to clearance of other surgical meshes with new indications and weigh the data in this submission appropriately. Only in rare cases were clinical data included to support the substantial equivalence of a surgical

mesh, and in these cases, the number of patients evaluated was low (less than 30), follow up short (less than 3 months), and typically no control arm was included.

Extensive information regarding the safety of use of the CS device has been gathered through direct clinical experience. This information includes data from an IDE study of 162 patients receiving the CS device having follow-up to 4.9 years on average (range, two years to seven years). The safety information collected includes the recording and assessment of all adverse events and complications, findings from arthroscopic relooks with biopsies at 12 months post placement, and results from serum studies to assess any immunological effects.

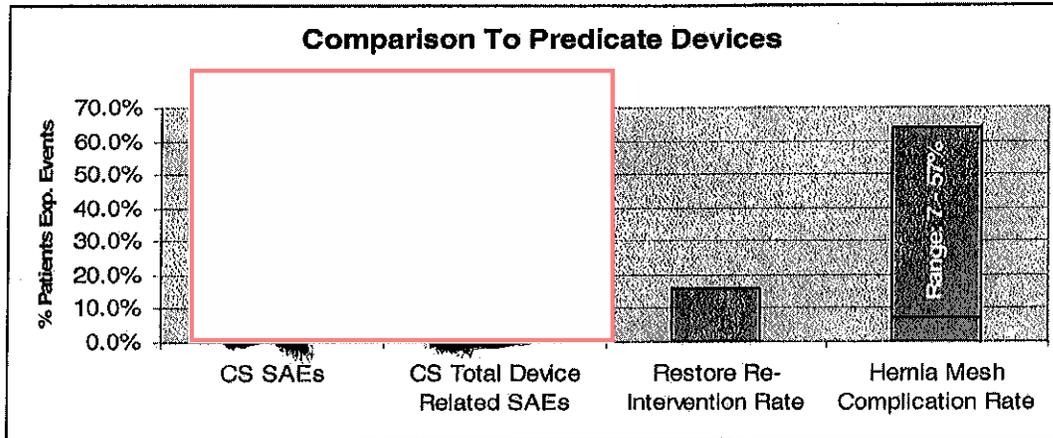
The following summary information provides evidence of the safety of the CS device for its proposed intended use. Specifically, this information includes: the risks/complications occurring with the CS device as compared to those reported for predicate surgical meshes; a comparison of serious adverse events reported in the IDE study between the group of patients receiving the CS device and the group undergoing only partial meniscectomy; histological findings from biopsy samples taken at 12 months post-placement; and findings from a study to evaluate the development of a humoral immune-mediated response to the CS device over a 12 month period.

Results from this extensive clinical experience demonstrate that no new types of questions are raised regarding safety of the CS device for its proposed intended use compared to legally marketed predicate devices.

#### **7.1 Complications and Risks: Comparison of Use of CS Device and Predicate Surgical Meshes**

The complications occurring with use of the CS device during clinical evaluations were compared with the risks and complications reported in the literature, Medical Device Reporting (MDR) database, and labeling for predicate surgical meshes. There were no reported adverse events that occurred during the IDE clinical study related to the CS device or CS device placement that were of a different type than those that have been reported for other surgical meshes. Please refer to **Attachment B** which lists the complications associated with placement of a surgical mesh in various anatomic locations (including general surgical risks), and to Figure 15 below which compares the types and rates of complications occurring with use of the CS and predicate devices. These complications include: infection, abscess, fever, wound drainage, incisional dehiscence, inflammation, swelling, redness, pain, hematoma, sterile effusion, seroma formation, general surgical risks such as neurological, cardiac or respiratory deficit, immunologic reaction, allergic reaction, adhesion, fistula formation, device tear, device migration, instability, restricted freedom of movement or stiffness, prolonged post-operative rehabilitation or patient non-compliance with rehabilitation, delayed or failed incorporation of the device, and recurrence of the soft tissue defect.

**Figure 15: Complications and Serious Adverse Events**



Importantly, recurrence of the tissue defect requiring reintervention is a risk that is associated with the placement of any surgical mesh. Recurrence attributable to the device is typically due to failure of the surgical mesh to reinforce the area of tissue defect through lack of incorporation into the surrounding tissue, through mechanical failure (tearing or fraying of device), or through device malposition or migration. In the IDE study [redacted] of the 162 patients receiving the CS device underwent explantation of the device due to delayed or failed incorporation of the device [redacted] or due to skin infection [redacted]. Explantation due to delayed or failed incorporation of the device occurred at six weeks [redacted], four months [redacted], six months [redacted] and nine months [redacted] post placement, and the explant due to infection occurred at three weeks post placement. In one of these five cases the patient violated the rehabilitation protocol; in a second, the patient fell within six weeks of placement; and in a third, the histology indicated that an infection was possible. The patient who violated the rehabilitation protocol received a second device and again violated the rehabilitation protocol. The second device was explanted due to failure to incorporate.

Like the types and rates of other complications associated with use of surgical mesh, the explant, recurrence and reintervention rates observed in the IDE study data are comparable to those reported for surgical meshes in other applications. During the 4.9 year mean follow-up (7 year maximum) of these patients, device failure requiring explantation occurred in [redacted]. In addition, there were [redacted] who had reinjuries of the treated meniscus requiring meniscectomy or meniscal transplantation (recurrence). This results in a total reintervention rate for the [redacted]. Brockman, et al<sup>36</sup> reported early recurrence rates requiring reintervention after laparoscopic hernia repair from 3.4% to 15.7%.

<sup>36</sup> Brockman JB, Patterson NW and Richardson WS. Burst strength of laparoscopic and open hernia repair. Surg. Endosc. 2004;18: 536-539

Malcarney, *et al.*<sup>37</sup> reported a reintervention rate of 16% in patients undergoing rotator cuff repair with the Restore device. Helton, *et al.*<sup>38</sup> reported a ventral hernia recurrence rate of 9% using the Surgisis product. LeBlanc, *et al.*<sup>39</sup> reported a recurrence rate of 6% for various types of surgical meshes in hernia repair. Heniford, *et al.*<sup>40</sup> reported a 4.7% recurrence rate for various types of surgical meshes used during laparoscopic repair of ventral hernias, and Lawson-Smith, *et al.*<sup>41</sup> reported a recurrence rate of 2.9% when using surgical mesh and fascia to repair incisional hernias.

It is apparent from the literature that the complications observed in the IDE study are not exclusive to the use of the CS device. These complications are similar in type and rate of occurrence to those reported for the cleared indications of predicate surgical meshes for various types of soft tissue repair. Therefore, no new types of safety and effectiveness questions are raised from use of the CS device as compared to use of the legally marketed predicate devices. Moreover, these complications have been appropriately identified in the labeling for the CS device (please refer to **Attachment E**).

## 7.2 Serious Adverse Events: Comparison of CS Device Patient Group and Partial Meniscectomy Patient Group in IDE Study

Safety performance of the CS device was assessed by thoroughly evaluating the adverse events occurring in the IDE study in all patients, and by comparing events occurring in the patient group receiving the CS device to the patient group undergoing partial meniscectomy only (serving as the control group). Results of this evaluation showed no statistically significant difference in the rate of serious adverse events (SAEs) between the CS patient group and the partial meniscectomy control group, even though the CS patients experienced an additional relook surgery and biopsy at approximately 12 months post-placement. In addition, none of the adverse events reported indicated that the CS device was responsible for damage to the joint or the adjacent articular surfaces.

Throughout the mean follow-up duration of 4.9 years (maximum 7 years), SAEs were recorded for [redacted] in the CS device group, an [redacted] [redacted] were recorded in the control group. This difference was not statistically

<sup>37</sup> Malcarney H, Bonar F, Murrell G. Early inflammatory reaction after rotator cuff repair with a porcine small intestine submucosal implant. *American Journal of Sports Medicine* 2005;33:907-911.

<sup>38</sup> Helton WS, Fisjeholla P, Berger R, Horgan S, Espat N, Abcarian H. Short-term outcomes with small intestinal submucosa for ventral abdominal hernia. *Archives of Surgery* 2005;140:549-562.

<sup>39</sup> LeBlanc KA. Complications associated with the plug and patch method of inguinal herniorrhaphy. *Hernia* 2001;5:135-138.

<sup>40</sup> Heniford BT, Park A, Ramshaw B, Voeller G. Laparoscopic repair of ventral hernias: Nine year's experience with 850 consecutive hernias. *Annals of Surgery* 2003;238:391-400.

<sup>41</sup> Lawson-Smith MJ, Galland RB. Combined fascia and mesh repair of incisional hernias. *Hernia* 2006; [epub].

significant [redacted] SAEs that could be considered fatal, life-threatening, or permanently disabling were reported for [redacted] in the study. [redacted] of these were deaths in the CS device patient group that were unrelated to the study. [redacted] were deep vein thromboses (DVT) most likely attributed to surgery. [redacted] each in the CS device and control groups. The remaining SAEs included pain, swelling, effusion, synovitis, stiffness, fever, infection, instability, and reduced mobility, as well as general medical problems that were unrelated to the knee surgery. All of these were anticipated adverse events and consistent with the types of adverse events noted for cleared indications for surgical mesh as described previously (**Attachment B**), and are described in the product labeling for the CS device (**Attachment E**).

In evaluating SAE rates on a per event basis, there were [redacted] SAEs recorded for 162 patients in the CS group (rate [redacted]), and [redacted] SAEs recorded for 151 patients in the control group (rate = [redacted]). This difference is not statistically significant. Of the [redacted] SAEs reported for the CS group, only [redacted] events were noted to have a relationship to the device. These [redacted] events involved [redacted], or [redacted] of the CS device group, and included [redacted] patients in whom the device was explanted (described above). In evaluating the SAE rates over time, there is no statistically significant difference in either the per-patient or per-event rates at any time point through the mean of 4.9 years of follow-up.

In evaluating the non-serious AEs reported in the study for both the CS device patient group and the control group, differences in rates were shown, however, these differences occurred within six months of the surgery, that is, during the healing and rehabilitation period associated with the CS device, and again at the 1 year timepoint when the CS patients underwent the protocol-required relook surgery and biopsy (the control group did not undergo a relook or biopsy procedure). By the two year time point and beyond, the rates of non-serious AEs occurring in the CS device group were equal to those occurring in the control group. Because the patients of the IDE study have been followed for a mean of 4.9 years and a maximum of 7 years, these data clearly establish the long-term safety of the device to an extent that the Agency has not seen in any predicate surgical meshes with new indications undergoing review for substantial equivalence via the premarket notification (510(k)) process. Clinical safety data on cleared surgical meshes with new indications were limited or non-existent.

In summary, patients in the CS device group and partial meniscectomy control group experienced no statistically significant difference in the rate of serious adverse events, neither cumulatively nor at any time point through the mean 4.9 year follow-up, providing evidence of long term safety. Furthermore, the SAE rate [redacted] through 4.9 years of follow-up for the CS patients is comparable to the complication rates for predicate surgical meshes used in hernia repair (7% - 57%) or rotator cuff repair (16%).<sup>1-6</sup> The transient difference in rates observed between patient groups for non-serious AEs during the initial two years of the study is expected due the protocol-required differences in the treatment and

control groups (surgical placement of the CS device and one year relook and biopsy procedures).

Overall, the type and extent of adverse events noted for patients receiving the CS device were similar to those for the control patients. The events were not unexpected, were consistent with those associated with the cleared indications for use of predicate surgical mesh devices, and have been incorporated in the CS device product labeling (**Attachment E**). Of course, this represents a worst case comparison, as the partial meniscectomy group had no device placement and no relook surgery or biopsy at 1 year post operatively. Other surgical meshes with new indications have not undertaken a comparison of adverse events or complications associated with treatment with and without the use of the device. Thus, the Regen CS 510(k) provides FDA with greater assurance of safety relative to predicate meshes than any predicate mesh demonstrated when cleared for a new anatomical location/indication.

### 7.3 **Histological Evaluation of Tissue from Patients Receiving the CS Device in the IDE Study**

Patients receiving the CS device in the IDE study were required to undergo a relook procedure and biopsy of tissue in the area where the CS device was placed at 12 months post-placement. Biopsy samples were obtained for [ ] of the [ ] patients undergoing re-look arthroscopy in the CS device group. Biopsies were unavailable for ten patients due to patient refusal or because the surgeon was unable to obtain an adequate biopsy specimen for evaluation. Needle biopsies were performed under direct visual observation using a 14 to 15 gauge soft tissue biopsy needle, yielding a specimen for examination of approximately 1.3mm in diameter and varying lengths.

Of [ ] cases, all underwent histological evaluation; however, only [ ] were confirmed to contain residual CS and were therefore evaluated to determine the direct cellular response to CS placement (*i.e.*, in the other specimens, either the CS device was totally replaced by host tissue in the specimen or the biopsy could not be confirmed to be taken from the defect area where the CS device was placed). Histologic examination of all [ ] evaluable biopsies demonstrated infiltration of the pores within the CS with maturing connective tissue, best described as a fibrous connective tissue differentiating toward a fibrochondrocytic (meniscal-like) tissue. Most evaluable cases demonstrated some degree of CS assimilation into a newly developing fibrochondrocytic matrix. This assimilation was varied in type. Most often the CS became embedded in a benign fashion and was resorbed or assimilated without obvious surface cellular resorption. In some cases resorbing cells were noted on the surface of the CS.

When an interface between the CS and host meniscus rim could be identified in the biopsy specimen, incorporation of the new tissue generated by the implant into the host tissue was consistently present and characterized by an angiogenic

tract connecting the implant matrix into the host tissue. An incidental, rare finding was inflammation of the synovium in the biopsy specimen, but none of these cases were associated with any clinical findings of synovitis at the time of relook arthroscopy. There were no clinically relevant negative findings such as severe inflammation or a giant-cell response in any of the biopsy specimens examined. A complete report of the descriptive histology of evaluable specimens from all patients in the IDE study can be found in **Attachment D**.

In summary, the second look arthroscopy and biopsy evaluations demonstrate that the CS provides a scaffold for meniscus-like matrix production by the host. There appeared to be no damage to the joint or adjacent articular surfaces attributed to the use of the device. Like predicate absorbable surgical meshes, tissue integrates into the device as the device is assimilated and resorbed. The lack of any clinically significant inflammatory reaction, and the presence of new tissue, demonstrates that the CS is biocompatible in this location, and performs the function for which it was intended.

#### **7.4 Evaluation for Immunological Effects**

Safety of the CS device was also evaluated through a study conducted to assess the development of humoral antibodies against the CS device. Sera were obtained from patients in both the CS device group and the partial meniscectomy control group for up to 12 months post-surgery. The protocol excluded subjects previously exposed to CS or collagen. Sera were collected at the investigational sites, frozen and shipped directly to an independent laboratory where they were assayed in an ELISA modified for human immunoglobulin detection using CS as the antigen. The laboratory was blinded to the treatment group at the time of assay.

The results demonstrated no significant differences between the control and CS treated groups that could not be accounted for by normal assay variability. There was no evidence of significant antibody formation to the CS at any timepoint up to the 12 month endpoint. Analysis of results from individual subjects demonstrated few with elevated antibody levels in this assay. Of the individuals having reactive sera, some were in the control group and some in the CS treatment group. In addition, the clinical course of subjects with the highest levels of antibody reactivity against the CS using ELISA was normal, with the individuals showing no evidence of a significant inflammatory response or impaired healing. In summary, there were no relevant elevations of antibodies against CS in treated subjects and no evidence of clinically significant humoral immune-mediated response immunity to the implant, indicating no safety concerns regarding development of an immune response to the CS device.

## 7.5 Marketing Experience Outside of U.S.

The CMI, a product with similar shape and technology, but different indications and instructions for use from the CS, is currently approved and marketed in the EU (Austria, Belgium, Germany, Italy, Spain and Switzerland). In 2007 product distribution to Poland and South Africa began. As of September 2007 [redacted] devices have been sold to ReGen's international distributor.

There have been [redacted] reported complaints involving a total of [redacted]. One involved a single device that had a tear that was noted prior to surgery and the device was therefore discarded and not used. The second involved radial tears that appeared on the inner margin of three devices at the time of placement; all devices were placed by the same physician. The tears were judged due to trauma during introduction through the cannula, and the physician was informed of proper placement techniques. No untoward effects occurred as a result of the tears noted (devices remained in place). The third involved a post operative infection which did not appear to be related to the device. The device was explanted, the patient treated with antibiotics and the patient recovered without further complications. The fourth involved a patient that developed pain and swelling in the operative knee at the four month post-operative time period. The patient underwent explant of the CMI. Histologic evaluation of the tissue samples indicates that patient had an infection. The fifth involved a patient that developed pain and swelling at approximately five months post-implantation. The patient underwent an explant at this time period.

There have been no published reports or complaints related to changes in articular surfaces due to the use of the device. The complaints reported for the product are the same types of complaints that are reported for other types of surgical mesh as those listed in **Attachment B**.

## 7.6 Conclusion: Safety of the CS Device

Results from extensive clinical experience with up to seven years of follow-up information demonstrate the safety of the CS device for its proposed intended use. The adverse events and complications that occurred in the clinical study were not unexpected and were consistent with those associated with predicate surgical meshes used in other anatomic locations. Suitability and safety of use is also supported by the results from the relook procedures and biopsies which showed the device provided a scaffold for meniscus-like matrix production by the host, with no apparent damage to the joint or adjacent articular surfaces attributed to the use of the device. Evidence of safety of use of the CS device is further supported through results of the immunology study, showing no evidence of clinically significant antibody formation and through the marketing experience outside of the United States.

CONFIDENTIAL

Reasonable assurance is therefore provided that the CS device is as safe as legally marketed surgical mesh predicates and raises no new types of safety or effectiveness questions when compared to those predicates with the same intended use, which is to reinforce soft tissue and provide a scaffold for replacement by the patient's own tissue.

CONFIDENTIAL

## **Attachment A**

### **Table of Cleared Surgical Meshes with New Indications And Data Relied Upon**

**CONFIDENTIAL**

**Pedicate Resorbable Surgical Meshes (21CFR878.3300) with New Indication(s)**

510(K)	INDICATIONS	COMMENTS
K923657 Bio-Vascular Supple Peri-Guard	For repair of hernias and other intra-abdominal soft tissue defect or deficiency	No 510k summary; Purged 510k
K940205 Bio-Vascular Peri-Strips	For surgical stapling of lung tissue, gastric stapling, rectal and vaginal prolapse, urethral sling, reconstruction of the pelvic floor, and hernia or defects of the diaphragm, thoracic and abdominal wall	No 510k summary; Purged 510k
K942911 Glycar Tissue Repair Patch	For repair of hernias and other intra-abdominal soft tissue defect or deficiency	No 510k summary; Purged 510k; Bio-Vascular Peri-Guard device used as predicate
K954665 Glycar Staple Strips	For surgical stapling of lung tissue, gastric stapling, rectal and vaginal prolapse, urethral sling, reconstruction of the pelvic floor, and hernia or defects of the diaphragm, thoracic and abdominal wall	No 510k summary; Purged 510k; Bio-Vascular Peri-Strips device used as predicate
K961440 Fusion Medical RapidSeal Patch	Reinforces soft tissue of the lung thereby sealing or reducing air leaks that occur during pulmonary surgery	Evaluation in 26 patient open-labeled study with endpoint of leak closure. Results showed out of 52 leaks, 96% were successfully closed.
K963226 Boston Scientific Surgical Fabrics (aka Protegen Sling)	Intended to reinforce soft tissue where weakness exists for the urological, gynecological and gastroenterological anatomy inclusive but not limited to the following procedures: pubourethral support, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, and sacro-colposuspension.	Tested and compared to the predicate devices (synthetic meshes and Peri-Guard mesh) Note: Device was removed from the market in 1999 due to high incidence of erosion
K964857 Fusion Medical RapidSeal Patch	Provides a temporary matrix during the natural tissue repair process, resulting in the additional benefit of hemostatic tamponade	Clinical evaluation in 48 patients during "pre-commercial phase." Results were no patch-related complications, and patch was capable of successfully reducing or sealing air leaks intraoperatively. Note: no clinical data to support benefit of tamponade, only animal data.
K980483 Mentor Suspend Sling	Intended to reinforce soft tissue where weakness exists in the urological anatomy inclusive of the following procedures: pubourethral support and bladder support, urethral and vaginal prolapse repair, reconstruction of the pelvic floor, and sacro-colposuspension. Intended for the treatment of female urinary incontinence resulting from urethral hypermobility or intrinsic sphincter deficiency.	Comprised of segmented polyether urea urethane elastomer with an anti-bacterial coating. Tested for biocompatibility and suture pull strength. Cited predicates were the GoreTex Tissue Reinforcement Patch and the Protegen Sling.

510(k)	INDICATIONS	COMMENTS
K983162 Bio-Vascular Peri-Guard and Peri-Strips	<p>For repair of pericardial structures and for use as a prosthesis for the surgical repair of soft tissue deficiencies which include: defects of the abdominal and thoracic wall, gastric banding, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, and hernias (including diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, scrotal, and umbilical hernias).</p> <p>For use as a prosthesis for the surgical repair of soft tissue deficiencies using surgical staplers. To reinforce staple lines during lung resections including pneumonectomy, pneumoreduction, pneumectomy, lobectomies, segmentectomies (segmental resections), wedge resection, bullectomies, blebectomies, bronchial resections, and other lung incisions and excisions of lung and bronchus.</p>	<p>No performance data cited other than cross-linked treatment with 1M NaOH</p>
K001738 DePuy Restore	<p>For use in general surgical procedures for reinforcement of soft tissue where weakness exists. The device is intended to act as a resorbable scaffold that initially has sufficient strength to assist with a soft tissue repair, but then resorbs and is replaced by the patient's own tissue. In addition, the implant is intended for use in the specific application of reinforcement of the soft tissues which repaired by suture or suture anchors limited to the supraspinatus during rotator cuff repair surgery.</p>	<p>Feasibility study 5 patients followed for 3 months, with several surgeon letters of support (from purged 510k)</p>
K014200 Spineology OptiMesh	<p>OptiMesh is intended to maintain the relative position of bone graft material (such as autograft or allograft) within a vertebral body defect (e.g. tumor) that does not impact the stability of the vertebral body and does not include the vertebral endplates.</p> <p>The safety and effectiveness of this device used for fusion of the interbody space has not been established.</p>	<p>510(k) Summary cites performance data was provided – appears that no clinical data was provided for this indication</p>
K021160 Carbon Medical Technologies Dermatrix	<p>Intended for use in the treatment of hernias where the connective tissue has ruptured or for implantation to reinforce soft tissues where weakness exists in the urological, gynecological and gastroenterological anatomy. This includes but is not limited to the following procedures: pubourethral support including urethral slings, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, tissue repair, and sacro-colposuspension.</p>	<p>510k Summary cites bench testing and "numerous clinical experiences"</p>
K024199 OsteoBiologics IMMIX Thin Film	<p>For use wherever temporary wound support is required, to reinforce soft tissue where weakness exists, or for the repair of hernia or other fascial defects that require the addition of a reinforcing, or bridging material to obtain the desired surgical result. This includes, but is not limited to the following procedures: vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor and sacral colposuspension.</p>	<p>Bench tested cited to "support its suitability for use in a clinical situation"</p>

510(k)	INDICATIONS	COMMENTS
K031969 DePuy Restore	For use in general surgical procedures for reinforcement of soft tissue where weakness exists. In addition, the implant is intended for use in the specific application of reinforcement of the soft tissues, which are repaired by suture or suture anchors, during rotator cuff repair surgery. The Restore Implant is not intended to replace normal body structure or provide the full mechanical strength to repair the rotator cuff. Sutures to repair the tear and sutures or bone anchors to reattach the tissue to the bone provide mechanical strength for the rotator cuff repair. The Restore Implant reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue.	Clinical data "replaced by the patient's own tissue"
K030782 Gore Seamguard Staple Line Reinforcement	For surgical procedures in which soft tissue transection or resection with staple line reinforcement is needed. Can be used for reinforcement of staple lines during lung resection and for reinforcement of gastric staple lines during bariatric surgical procedures of gastric bypass and gastric banding.	Device "integrity testing" performed
K03337 Ethicon UltraPro Mesh	For the repair of hernias and other abdominal fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.	510k summary states: "comparison to other commercialized surgical meshes indicates equivalency in clinical performance." "Additionally, animal testing demonstrated that UltraPro would achieve good tissue ingrowth."
K040364 Porex Surgical Medpore Surgical Implant	For non-weight bearing applications of craniofacial reconstruction/cosmetic surgery and repair of craniofacial trauma	No testing cited
K042809 Organogenesis CuffPatch	For reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery including reinforcement of rotator cuff, patella, Achilles, biceps, quadriceps or other tendons. Not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff rotator cuff, patella, Achilles, biceps, quadriceps or other tendons. Sutures, used to repair the tear, and sutures or bone anchors, used to attach the tissue to the bone, provide biomechanical strength for the tendon repair. CuffPatch surgical mesh reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue.	510k summary states bench testing indicates suitability for its intended clinical applications
K043259 Kensey Nash BioBlanket	For use in general surgical procedures for the reinforcement and repair of soft tissue where weakness exists including, but not limited to defects of the thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, hernias, suture line reinforcement and reconstructive procedures. The device is also intended for reinforcement of the soft tissue which are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff repair surgery.	510k summary cites biocompatibility, integrity, in vitro and in vivo performance testing

CONFIDENTIAL

510(k)	INDICATIONS	COMMENTS
K043388 Pegasus Biologics OrthoAdapt Surgical Mesh	For implantation to reinforce soft tissue including but not limited to: defects of the abdominal and thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, hernias, suture-line reinforcement, and reconstructive procedures. The device is also intended for the reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patella, Achilles, biceps, quadriceps, or other tendons. OrthoAdapt is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patella, Achilles, biceps, quadriceps or other tendons. Suture, used to repair the tear, and sutures or bone anchors, used to attach the tissue to the bone, provide biomechanical strength for the tendon repair.	No 510k summary – statement only
K050337 Cook Biotech SIS Fistula Plug	For implantation to reinforce soft tissue where a rolled configuration is required, for repair of anal, rectal, and enterocutaneous fistulas.	Clinical experience in ~25 patients with approximately 3 months follow-up to show fistula closure.
K050445 AMS Collagen Dermal Matrix	For use in the treatment of hernias where the connective tissue has ruptured or for implantation to reinforce soft tissues where weakness exists in the urological, gynecological and gastroenterological anatomy. This includes but is not limited to the following procedures: pubourethral support including urethral slings, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, tissue repair, sacral colposuspension and reinforcement in the repair of Peyronie's disease. By providing pubourethral support, the AMS collagen dermal matrix may be used for the treatment of urinary incontinence resulting from urethral hypermobility or intrinsic sphincter deficiency.	510k summary cites bench testing
K051701 Ethicon Vicryl Mesh Bag	For use wherever temporary wound or solid organ support is required (kidney, liver, spleen)	No testing cited in 510k summary; Vicryl mesh used as predicate
K061892 Cryolife ProPatch Soft Tissue Repair Matrix	For implantation to reinforce soft tissues where weakness exists, including but not limited to: defects of the abdominal and thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, hernias, suture-line reinforcement, and reconstructive procedures. The device is also intended for the reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patella, Achilles, biceps, quadriceps, or other tendons. Device is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps or other tendons. Suture, used to repair the tear, and sutures or bone anchors, used to attach the tissue to the bone, provide biomechanical strength for the tendon repair. The device reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue.	510k cites bench testing performed

CONFIDENTIAL

**Attachment B**

**Comparison of Risks in Surgical Meshes**

CONFIDENTIAL

COMPARISON OF COMPLICATIONS WITH PREDICATES

Complications and Potential Risks	Collagen Scaffold (ReGen)	Restore (DePuy)	Fistula Plug (Cook Biotech)	Surgisis /Stratasis (Cook Biotech)	CuffPatch (Organogenesis)	TissueMend (TEI)	ZCR Patch, Enduragen, Permacol, Pelvicol (TSL)	Peri-Guard (Synovis)
Infection		X*†	X*	X†			X†	
Abscess		X†	X*	X†			X†	
Wound drainage / incisional dehiscence/ Op site blister		X†			X†	X†	X†	X†
Inflammation / Swelling / Redness / Pain / Fever / Granuloma tissue/ Cyst/ Synovitis		X*†	X*	X†	X†	X†	X†	
Sterile Effusion		X*†			X†			
Seroma/Hematoma Formation			X*				X†	
Induration			X*				X†	
Allergic reaction		X*	X*					
Immunologic reaction		X*†						
Adhesion / Agglutination		X*					X†	
Fistula Formation			X*	X†			X†	
Device Stretch / Fracture / Tear/ Instability		X*					X†	X†
Device Migration / Extrusion			X*		X†		X†	X†
Delayed or failed incorporation / inadequate healing / Recurrence of Defect		X*†	X*	X†	X†	X†	X†	X†
Tissue necrosis							X†	
Restricted Freedom of Movement / Stiffness		X*†						
Prolonged Post-op Rehab		X*						
Patient non-compliance with rehab		X*						

CONFIDENTIAL



**Attachment C**

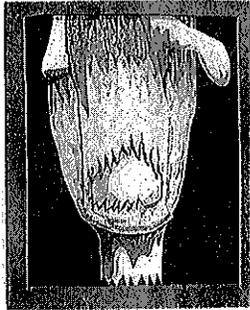
**Diagrams showing Surgical Placement of the CS in the Meniscus  
And the Restore in the Shoulder**

=

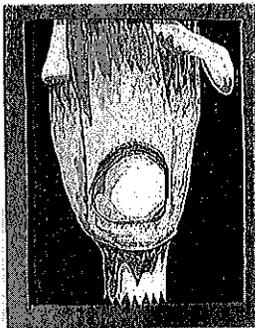
CONFIDENTIAL

# SURGICAL TECHNIQUE FOR SURGICAL MESH

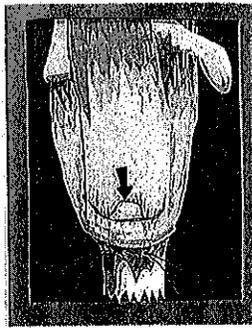
## IN THE SHOULDER



A rotator cuff tear results in thinned, delaminated or deficient rotator cuff tendon.



Damaged or loose tissue is removed and the rotator cuff is supported by suturing, if necessary.

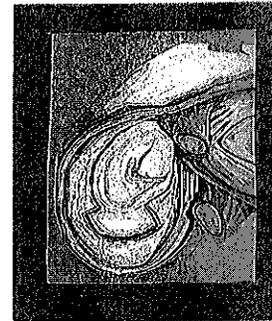


The surgical mesh (Restore) is trimmed to fill the void and it is sutured to the rotator cuff. It acts as a scaffold to increase tissue volume.

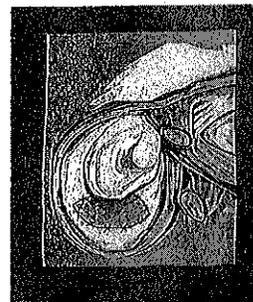
## IN THE MENISCUS



A meniscus tear results in thinned or deficient meniscus.



Damaged or loose tissue is removed, leaving the intact meniscus rim for support. The dotted line outlines additional tissue that would be removed if the CS were not going to be used to reinforce the defect.



The surgical mesh (CS) is trimmed to fill the void and it is sutured to the meniscus rim. It acts as a scaffold to increase tissue volume.

## **Attachment D**

Histology Report - U.S. Multicenter Clinical Trial

**CONFIDENTIAL**

**Histologic Evaluation of Biopsy Samples from Patients  
Enrolled in the U.S. Multicenter Clinical Trial  
Of the Collagen Meniscus Implant  
IDE #G920211**

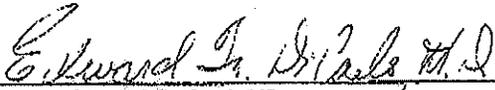
Conducted by  
Vincent J. Vigorita, M.D.  
Professor of Pathology and Orthopaedic Surgery  
SUNY Health Science Center at Downstate  
And  
Edward F. DiCarlo, M.D.  
Director -- Laboratory for Histopathology  
Hospital for Special Surgery



Vincent J. Vigorita, M.D.

12/22/06

Date



Edward F. DiCarlo, M.D.

12/22/06

Date

CONFIDENTIAL

## Introduction

Meniscal injuries are common and if not corrected a potential source of osteoarthritis of the knee. The loss of the protective effects of the meniscus result in articular cartilage damage and impaired knee function. The collagen meniscus implant (CMI) is a porous type I bovine collagen scaffold developed by ReGen Biologics which is surgically sutured to the medial meniscus rim. The CMI provides support to the meniscus after removal of damaged tissue and a scaffold for replacement by the patient's own tissue.

A randomized, controlled, multicenter clinical trial (IDE #G920211) was conducted to evaluate the use of the CMI in patients age 18 to 60 years of both sexes with meniscus deficiencies resulting from irreparable tears of the medial meniscus. The study was divided into two arms, one arm was for patients who had no previous treatment to the involved meniscus and the other was for patients with from one to three previous treatments to the involved meniscus. For purposes of this histologic analysis, all patients who received the CMI are evaluated as a single treatment group.

## Materials and Methods

A total of 313 patients were enrolled and treated under the clinical protocol. Of these patients, 162 patients received the CMI and 151 patients received the control procedure, a partial meniscectomy. The protocol required all patients who received the CMI to return one year post surgery for a relook arthroscopy and biopsy to assess the condition of the implant and the tissue that replaced it. [redacted] of the 162 CMI patients had biopsy samples taken at the time of relook surgery or at the time of explantation. Needle biopsies directed at the interface region of the CMI and native meniscus were performed at the time of relook arthroscopy under direct visual observation, using a [redacted]. These yielded a specimen for examination of approximately 1.5mm in diameter and varying lengths. Due to the nature of soft tissue biopsy, the size and location of the exact area sampled varied. During the arthroscopic biopsy procedure it was, therefore, not possible to confirm the exact depth at which the biopsy specimen was taken within the meniscus. Herein we report the histologic findings from these [redacted].

## Results

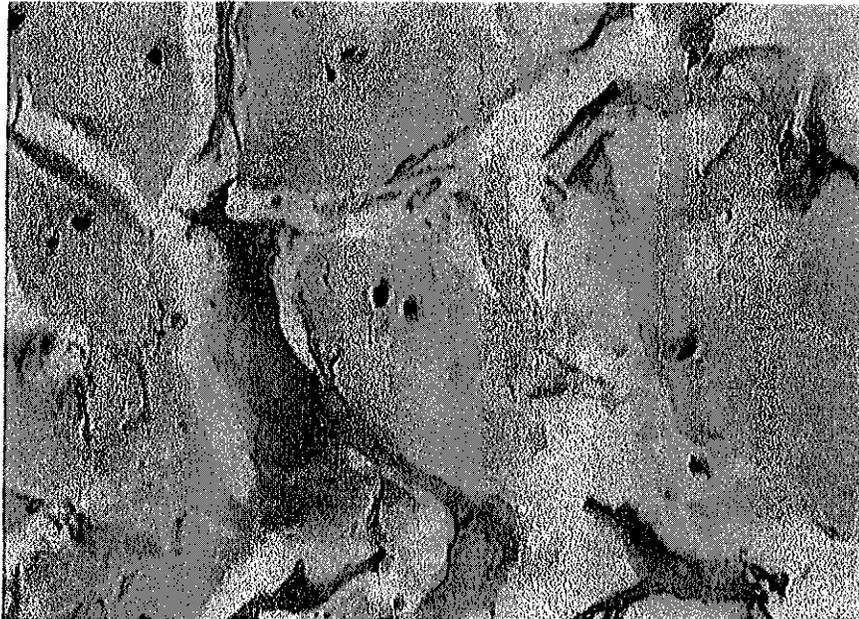
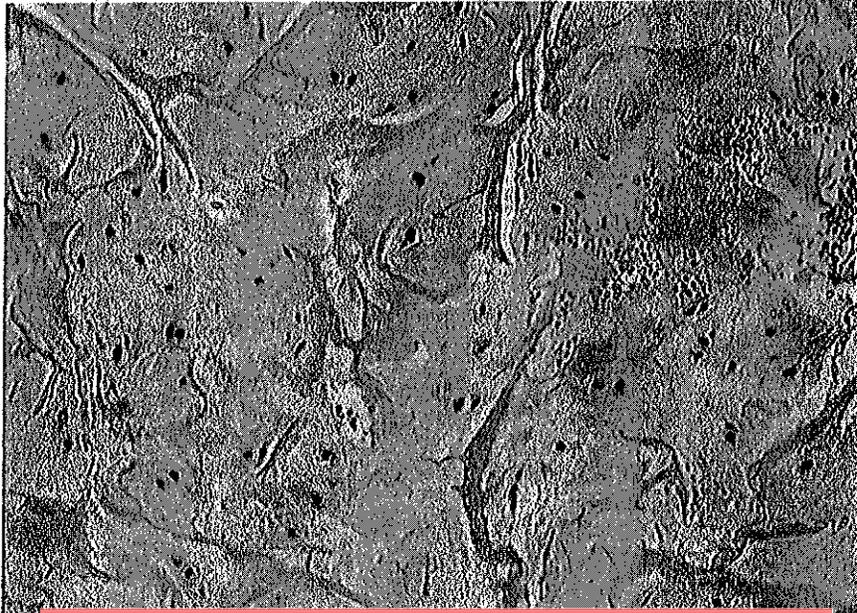


**Conclusion**

In summary, the CMI appears to provide a scaffold for a predictable benign process of meniscal-like fibrochondrocytic matrix production by the host, and the CMI is integrated into this tissue as it is assimilated and resorbed. Healing incorporation into host tissues is demonstrable in this study. Except for a rarely observed inflammatory synovitis and implant inflammation, CMIs were not associated with a significant adverse reaction out to 12 months post placement of the device.

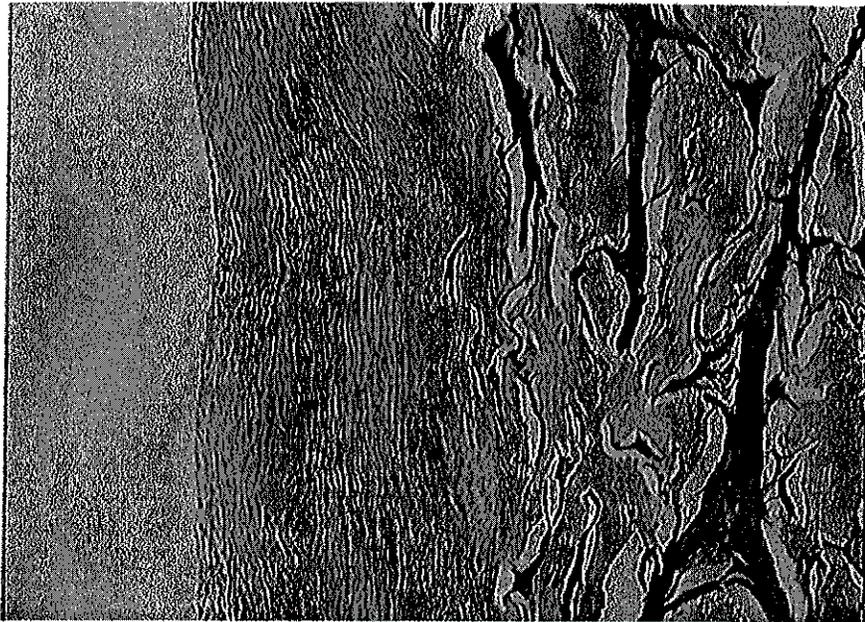
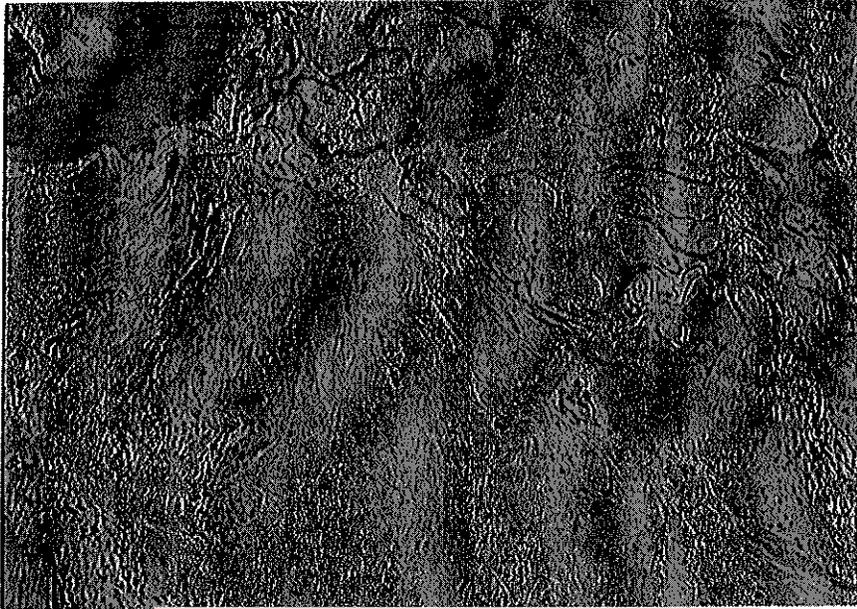
CONFIDENTIAL

Figures



CONFIDENTIAL

Figures



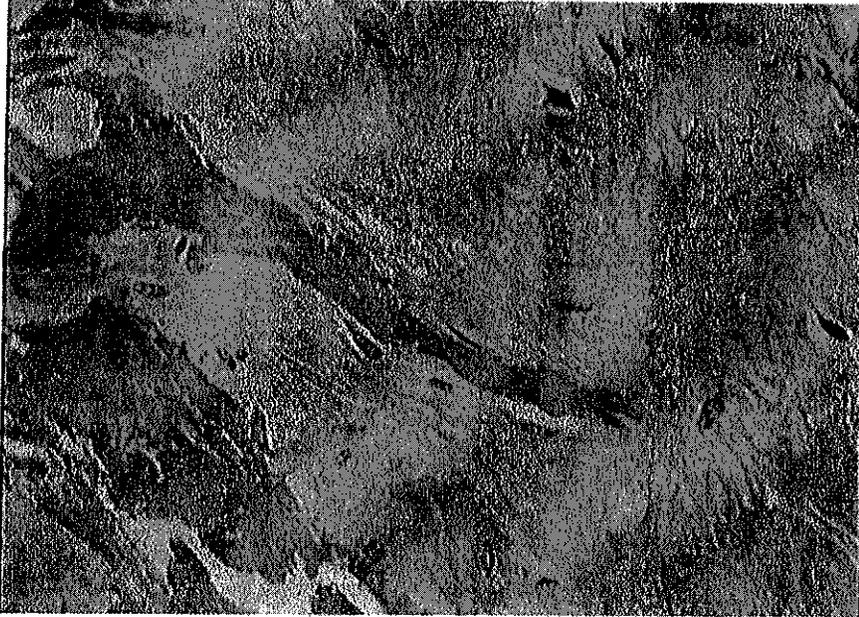
CONFIDENTIAL

Figures



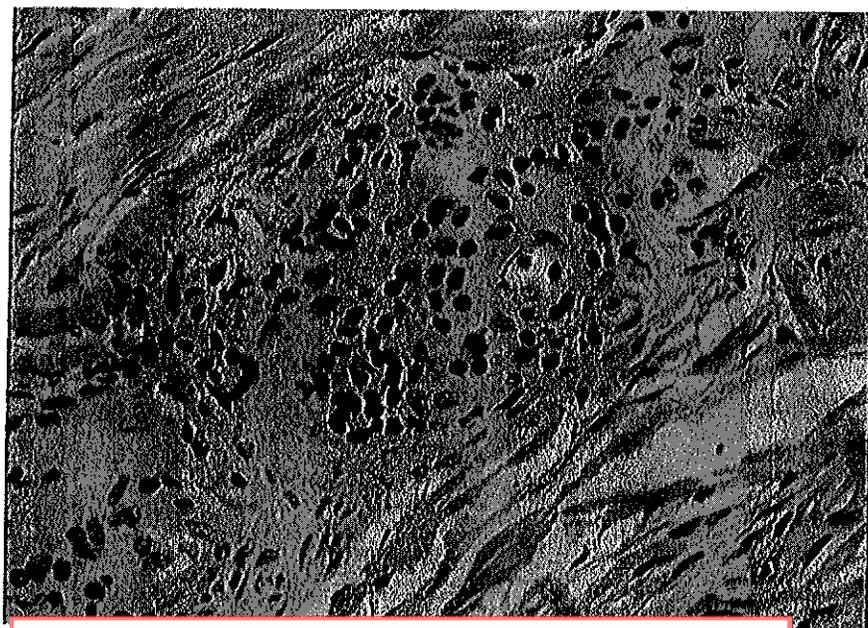
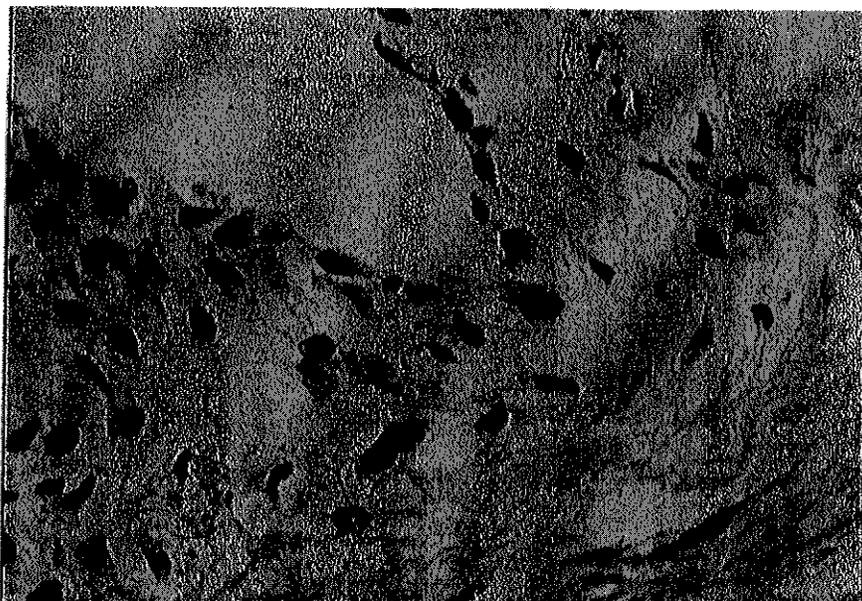
CONFIDENTIAL

Figures



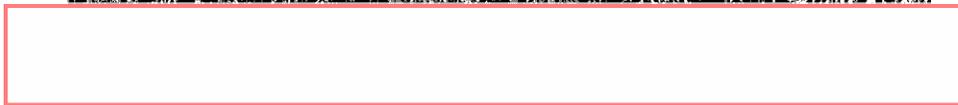
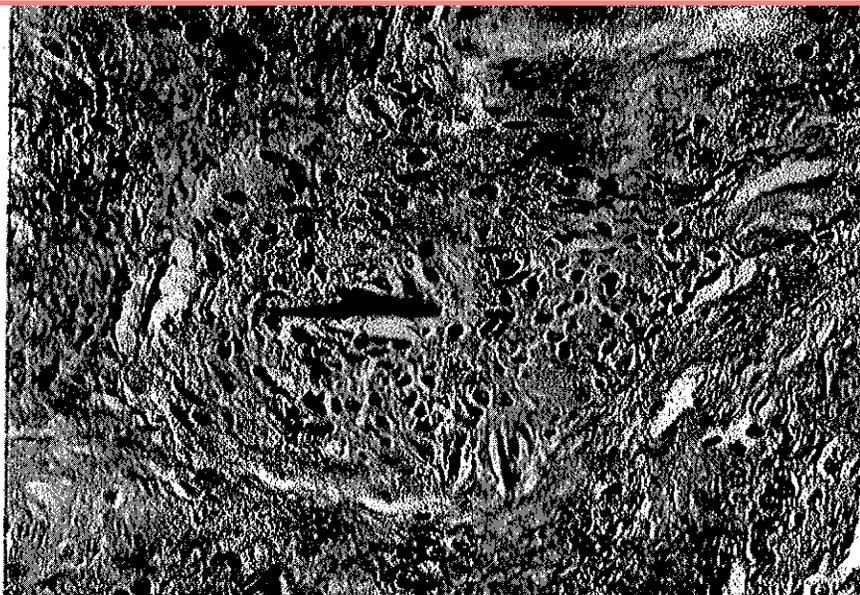
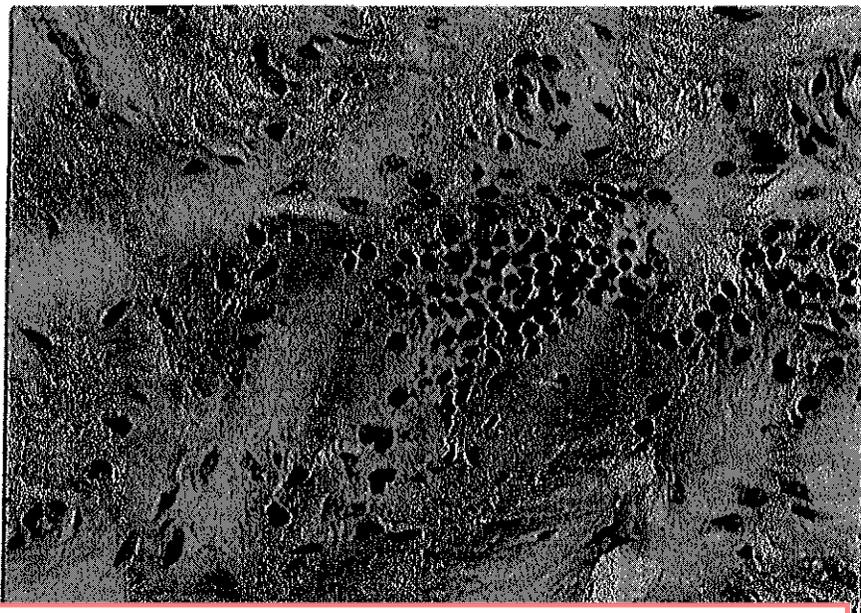
CONFIDENTIAL

Figures



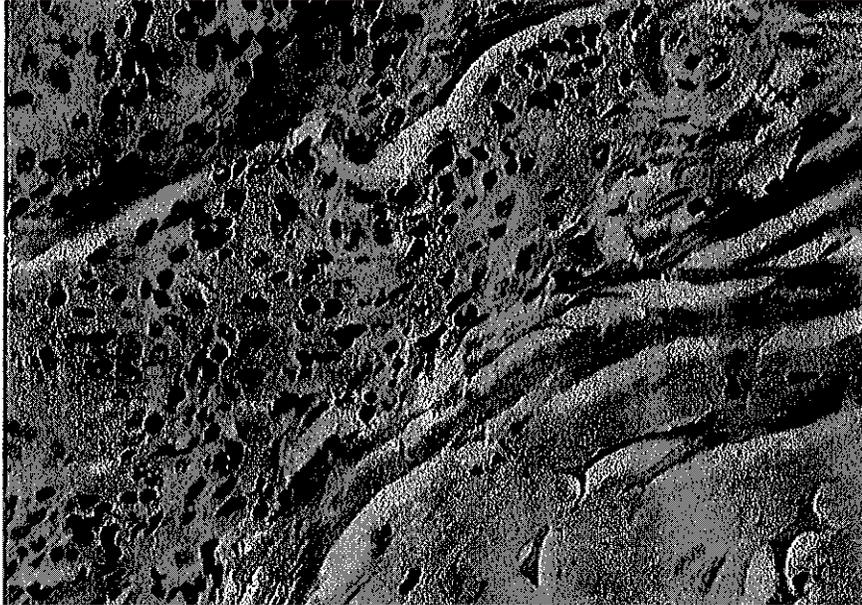
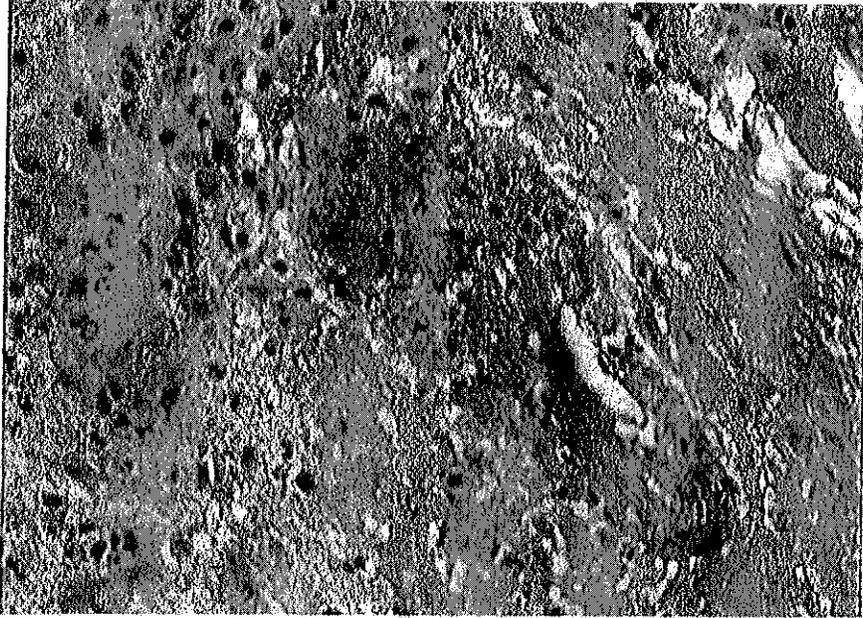
CONFIDENTIAL

Figures



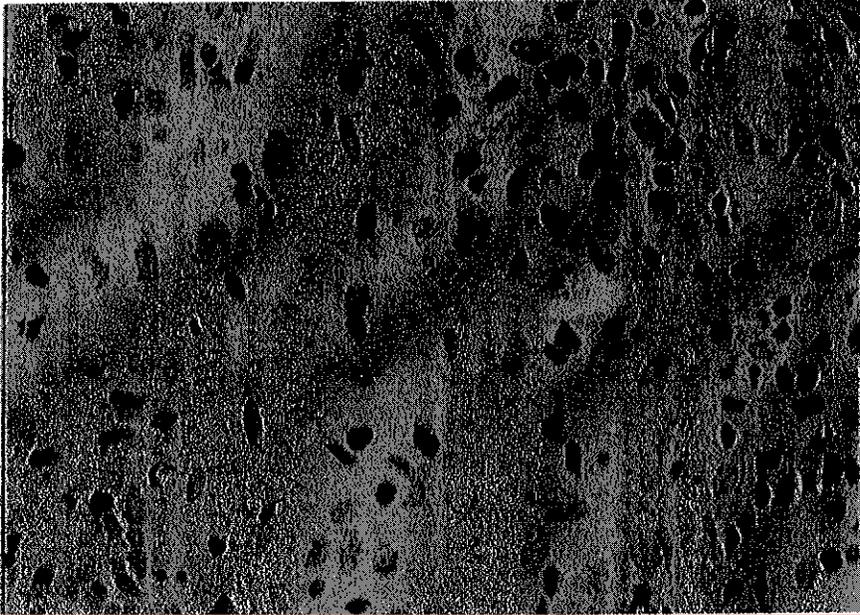
CONFIDENTIAL

Figures



CONFIDENTIAL

Figures



CONFIDENTIAL

**Appendix E**  
**Draft Instructions for Use**

CONFIDENTIAL

## Draft Instructions for Use for the (CS™)

### Device Description

The Collagen Scaffold (CS) is comprised primarily of bovine type I collagen (nominally 99%) derived from Achilles tendon, and small quantities of glycosaminoglycans (GAGs: chondroitin sulfate and sodium hyaluronate). The device serves as a resorbable scaffold that is replaced by the patient's own tissue.

### Intended Use

The CS is supplied sterile and is intended for single use.

**Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.**

### Contraindications

- Use in patients allergic to bovine or bovine derived products or who have a history of multiple severe allergies, allergies to animal derived products, or an overly sensitized immune system
- Patients with systemic or local infection
- Evidence of osteonecrosis in the targeted area
- Patients with medical history of severe degenerative osteoarthritis
- **Patients without an intact meniscal rim and anterior and posterior horns**

### Warnings

- If device is contaminated, unsterile, damaged, torn or has been improperly handled or altered without authorization, do not implant under any circumstance. **Do not resterilize.**

### Precautions

CONFIDENTIAL

- Rehydrate device prior to placement
- Place device in maximal contact with healthy tissue to encourage cell ingrowth and tissue remodeling
- Following surgery, physical activity should be limited to the rehabilitation protocol.
- No studies have been conducted to evaluate the effects of device remodeling when used in patients having received systemic administration of corticosteroids, antineoplastics, immunostimulating, or immunosuppressive agents within 30 days of surgery.
- No studies have been conducted to evaluate use in pregnant or lactating mothers.
- No studies have been conducted to evaluate use in patients with relapsing polychondritis, rheumatoid arthritis, or inflammatory arthritis.

### **Potential Complications**

Complications that may occur with use of surgical mesh materials include: infection, adhesion, sterile effusion, fistula formation, seroma formation, inflammation, instability, pain, and recurrence of defect. Complications associated with the surgical procedure and anesthesia may include hematoma, and neurological, cardiac or respiratory deficit. Device-related complications that may occur include: stretching or tearing of the device, restricted freedom of movement, prolonged post-operative rehabilitation, delayed or failed incorporation of the device, allergic reaction, and immunologic reaction.

### **Storage and Handling**

- Careful handling is required to avoid damage to the device
- The CS must be stored in the original packaging, unopened.
- The package containing the CS must be stored at temperatures between 2°C and 25°C (36°F to 77°F).

### **Sterilization**

The CS is gamma irradiated. **Do not resterilize.**

### **Suggested Instructions for Use**

**Note: Use aseptic techniques during handling of the CS device**

1. Aseptically remove the CS device from its sterile packaging and place in sterile field.
2. Rehydrate the CS device in a sterile dish using sterile irrigation solution
3. Surgically prepare the targeted graft site using standard techniques.
4. Remove any unstable or degenerative tissue, and carefully prepare a bleeding bed, as needed. For best results, the CS should be placed in an area with good tissue contact.

5. Trim the fully hydrated CS device to the desired size and shape for the targeted area.
6. Suture the CS in place using non-resorbable suture with a recommended suture spacing of 4-5 mm. **Use extreme care to avoid damaging any surrounding neurovascular structures.**
7. Complete the standard surgical procedure
8. Discard any unused portions of the CS device

### Pictograms



"Follow the Instructions for Use"



"Not to be re-used"



"To be used by... (Year, Month)"



"Sterile" and "Sterilization by irradiation"



"Temperature limitation"

### Trade marks

ReGen® is a registered trademark of ReGen Biologics, Redwood City, CA 94063, USA and Franklin Lakes, NJ 07417, USA.

Manufactured by: ReGen Biologics, Redwood City, CA 94063, USA