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

## Hilton Hotel, 620 Perry Parkway
## Gaithersburg, MD
## November 14, 2008: 8:00-5:00pm

## 510(k) K082079- ReGen Collagen Scaffold (CS)

### Applicant Name and Address:

ReGen Biologics, Inc.
411 Hackensack Ave., 10th floor
Hackensack, NJ 07601

### Reason for the Panel Meeting:

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

> For use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. 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.

FDA has not previously cleared a surgical mesh device for this specific indication. In its 510(k) submission, ReGen referenced several legally marketed surgical meshes used in orthopedics, thoracic, and general surgery as predicate devices (these are described in your panel pack on pp.4-6).

In order to establish that a device with a new indication is substantially equivalent to a legally marketed predicate device, the 510(k) submission must include appropriate supporting data showing that the manufacturer has considered the consequences and effects the new use might have on the safety and effectiveness of the device. The 510(k) submission also must explain why the new indication of the device should be considered to be substantially equivalent, in terms of relative safety and effectiveness, to the predicate devices when they are used as labeled. With respect to this 510(k), then, FDA must determine whether use of the CS device for the indication described is substantially equivalent to the predicate devices, when used in accord with their labeled indications. FDA is requesting the assistance of this panel in evaluating the data submitted by ReGen in making this determination.

The specific questions FDA would like you to address are included in Tab A of this Panel Pack.

We note that ReGen has included in its executive summary material regarding an additional indication, for use in the reinforcement and repair of acute soft tissue injuries. That indication is not included in the premarket notification 510(k) submission currently pending with FDA.

# Executive Summary

## Introduction

This is FDA's Executive Summary for the ReGen Biologics, Inc. ReGen Collagen Scaffold (CS) proposed for marketing clearance (510(k), K082079). Your time and effort in review of this summary are greatly appreciated.

The FDA Executive Summary contains an identification of the applicant and manufacturer, indications for use, and contraindications, and includes FDA's summary review of the device description, preclinical, and clinical information.

The Panel Pack contains the following sections:

## Indications for Use

ReGen Biologics Inc. has proposed the following Indications for Use:

> The ReGen Collagen Scaffold (CS) is indicated for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. 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.

## Contraindications

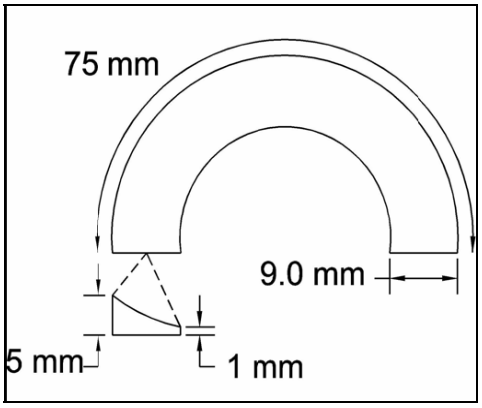
- Use in patients allergic to bovine or bovine derived products or who have a history of multiple severe allergies, allergies to animal derived products, or an overly sensitized immune system
- Patients with systemic or local infection
- Evidence of osteonecrosis in the targeted area
- Patients with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

Note: The complete Draft Instructions for Use is included in the Panel Pack in Tab B.

## Device Description

(From 510(k), pp.14-15; and, Attachment A pp.14-18, Appendix E and F)

The ReGen CS is a resorbable collagen matrix composed primarily of bovine Type I collagen (~99%) derived from Achilles tendon, and small quantities of glycosaminoglycans, i.e., chondroitin sulfate (~0.04% w/w) and sodium hyaluronate (~0.08% w/w). Ninety percent (90%) of the pores fall within the 50 – 400µm range. The device is provided in one configuration: a semi-lunar shape with a triangular cross-section which is intended for use in the meniscus. The surgeon assesses the defect and trims the device to the size necessary for repair of the damaged or weakened soft tissue. The semi-lunar configuration is designed to be sutured in place through a minimally invasive arthroscopic procedure to reinforce a defect in the human meniscus.




The shape of the subject ReGen CS device is unlike other predicate surgical meshes as it is shaped in a manner similar to the human meniscus (i.e., semi-circular with a near-triangular cross-section).

Please note: You will find references to a "flat sheet configuration" of the ReGen 510(k) K082079. However, the sponsor has advised us not to consider the flat sheet configuration. Therefore, please disregard references to flat sheet configuration within the premarket notification 510(k) submission.

# Predicate Device Information

**Review of Indications for Use and Intended Use of Predicate Surgical Meshes:**
We evaluate the proposed indications for use and intended use for a surgical mesh device and compare that information to legally marketed predicate devices. If the proposed indication for use is different from the indications for use of legally marketed predicate devices, we will evaluate the similarity of the "new" indication for use to the indications for use of the predicates. As part of this evaluation, we consider how the device is to be used, and whether information related to the predicate device provides information relevant to the new indication for use. Sometimes the information applicable to the predicate is not sufficient to permit us to determine whether the device, with the new indication, is as safe and as effective as the predicate. In those cases, additional data will be needed. [In some cases, biocompatibility, sterility, bench, and/or animal testing data may be adequate to demonstrate substantial equivalence. In others, clinical data related to the new indication for use will be necessary.]

Note that sponsor must also demonstrate in its 510(k) that the product has the same technological characteristics as the predicate, or that the new technological characteristics of its device do not raise new questions of safety and effectiveness. However, we are focusing our presentation on issues related to the indications for use of the ReGen CS device.

**510(k) "Substantial Equivalence Decision-Making Process": (a.k.a. "510(k) Flowchart")**
The 510(k) Flowchart is a decision making process CDRH uses to determine whether or not a device is substantially equivalent to a legally marketed device. A copy of the 510(k) Flowchart has been provided in Tab C of this Panel Pack.

Surgical Mesh devices are defined according to 21 CFR 878.3300:

- Title 21 – Food and Drugs; Part 878 – General and Plastic Surgery Devices
  - Section 878.3300 Surgical Mesh:
    - (a) Identification. Surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair, and acetabular and cement restrictor mesh used during orthopedic surgery.
    - (b) Classification. Class II.

**Comparison to Predicate Devices**
(From 510(k), pp.4-5)
The sponsor identified many surgical mesh devices as potential predicate devices. Table 1 on the following page identifies many of the cited predicate devices and their corresponding cleared indications statements.

**An Orthopedic Example:**
The sponsor has identified several surgical mesh devices for rotator cuff reinforcement as predicate devices in Table 1 below. Because this is an orthopedic use of a surgical mesh device, FDA has provided, as an example of one of these devices, the labeled Indications for Use and pictures from the surgical technique for the DePuy Orthopaedics, Inc. Restore Orthobiologic Soft Tissue Implant in Tab D (Parts 1 and 2) of the Panel Pack.

**Table 1: Predicate Device(s) – Cleared Indications for Use**

| Device | Cleared Indications for Use |
|---|---|

| | |
|---|---|
| Restore Orthobiologic Soft Tissue Implant, DePuy Orthopaedics, Inc. *(See Tab D (Parts 1 and 2) for Indications and Pictures of Surgical Technique)* | **K982330**<br>For use in general surgical procedures for reinforcement of soft tissue where weakness exists.<br>**K001738**<br>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 limited to the supraspinatus during rotator cuff repair surgery.<br>**K031969**<br>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 suture 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. |
| SIS Fistula Plug, Cook Biotech, Inc. | **K050337**<br>SIS Fistula Plug is for implantation to reinforce soft tissue where a rolled configuration is required, for repair of anal, rectal and enterocutaneous fistulas. |
| TissueMend, OrthoMend, TEI Biosciences, Inc. | **K031188**<br>OrthoMend is intended for surgical implantation to reinforce soft tissue where weakness exists and for the repair of damaged or ruptured soft tissue membranes. In addition, the device is intended to reinforce soft tissues that are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff surgery.<br>**K051766**<br>The OrthoMend Soft Tissue Repair Matrix is intended for reinforcement of soft tissues repaired by suture anchors, during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. OrthoMend Soft Tissue Repair Matrix 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. 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. OrthoMend Soft Tissue Repair Matrix reinforces soft tissue and provides a remodelable scaffold that is replaced by the patients own soft tissues. |
| SurgiSIS Mesh, Cook Biotech, Inc. | **K974540**<br>The SIS Hernia Repair Device is intended to be implanted to reinforce soft tissue where weakness exists. Indications for use include the repair of a hernia or body wall defect.<br>**K980431**<br>The SurgiSIS is intended for implantation to reinforce soft tissue.<br>**K992159**<br>The SurgiSIS Sling is intended for implantation to reinforce soft tissues where weakness exists in the urological, gynecological, and gastroenterological anatomic including 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, tissue repair, and sacrocolposuspension. By providing pubourethal support, the SurgiSIS Sling may be used for the treatment of urinary incontinence resulting from urethral hypermobility or intrinsic sphincter deficiency. |
| BioBlanket Surgical Mesh, Kensey Nash, Corp. | **K041923**<br>BioBlanket Surgical Mesh is indicated for use in general surgical procedures for reinforcement of soft tissue where weakness and for the repair of ruptured or damaged soft tissues.<br>**K043259**<br>BioBlanket Surgical Mesh is indicated 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 tissues which are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff repair surgery.<br>**K041923**<br>BioBlanket Surgical Mesh is indicated for use in general surgical procedures for the reinforcement and repair of soft tissue where weakness exists and for the repair of ruptured or damaged soft tissues. |

**Table 1: Predicate Device(s) – Cleared Indications for Use (continued)**

| Device | Cleared Indications for Use |
|---|---|
| ZCR Patch, Permacol, Tissue Science Laboratories | **K992556**<br>Permacol is intended for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. It is specifically indicated for the repair of abdominal, inguinal, diaphragmatic, femoral, scrotal, umbilical and incisional hernias; colon, rectal, urethral and vaginal prolapse; muscle flap reinforcement; reconstruction of the pelvic floor and procedures such as sacrocolposuspension and urethral sling.<br>**K013625**<br>Permacol is intended for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. It is specifically indicated for plastic and reconstructive surgery of the face and head.<br>**K021056**<br>Indicated for use in the reinforcement of the soft tissues which are repaired by suture or suture anchors limited to the supraspinatus during rotator cuff repair surgery.<br>**K043366**<br>Permacol is intended for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. It is specifically indicated for the repair of abdominal wall defects and hernias, including but not limited to parastomal hernias.<br>**K050355**<br>Permacol Surgical Implants are intended for use to support/reinforce soft tissue in surgical procedures. Permacol Surgical Implant T-pieces are shaped for use in rectal intussusception repair and Permacol Surgical Implant Rectocele-pieces are shaped for use in rectocele repair. |
| IMMIX Film, OsteoBiologics, Inc. | **K024199, K032673**<br>The IMMIX Thin Film is to be used 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. |
| SIS Plastic Surgery Matrix, Cook Biotech, Inc. | **K034039**<br>The SIS Plastic Surgery Matrix is for implantation to reinforce soft tissue where weakness exists in patients requiring soft tissue repair or reinforcement in plastic and reconstructive surgery. |
| Sportmesh, Artimplant | **K052830**<br>Sportmesh is intended for use in general surgical procedures for reinforcement of soft tissue where weakness exists. Sportmesh is also intended for reinforcement of soft tissues that are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff repair surgery. Sportsmesh is not intended to replace normal body structure or provide the full mechanical strength to support the rotator cuff. Sutures to repair the tear, and sutures or bone anchors used to attach the tissue to the bone, provide mechanical strength for the tendon repair. Sportmesh reinforces soft tissue and provides a degradable scaffold that is incorporated in the patient's own tissue. |
| Optimesh, Spineology, Inc. | **K014200**<br>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. |
| Fusion Medical Technologies, Inc. | **K961440**<br>The Patch reinforces the soft tissue of the lung thereby sealing or reducing air leaks that occur during pulmonary surgery. |

**Comparison of Indications**

The ReGen CS device represents a "new" indication for surgical mesh devices (i.e., "reinforcement and repair of chronic soft tissue injuries of the meniscus"). As outlined in Table 1 above, current predicate surgical mesh devices are indicated for patients to reinforce soft tissue where weakness exists, including the following:

- hernia;
- rotator cuff;
- anal, rectal and enterocutaneous fistulas;
- urethral and vaginal prolapse repair;
- colon and rectal prolapse repair;
- reconstruction of the pelvic floor;

- bladder support;
- soft tissue of the lung, etc.

FDA is not aware of any legally-marketed surgical mesh devices intended for the "reinforcement and repair of chronic soft tissue injuries of the meniscus."

Currently, there are legally marketed devices indicated for treating repairable meniscal tears. These devices include standard suture, meniscal tacks, darts, and arrow devices Patients with meniscal tears that cannot be repaired with the above devices typically receive partial meniscectomy. Neither of these options includes use of a surgical mesh. In the 510(k) submission (p.6), the sponsor stated that absorbable and non-absorbable sutures, darts, and arrows are "not cited as predicates for this device" and the "intended use of these devices differs from the ReGen CS." Sutures, tacks, darts, and arrows are for meniscal tears that are able to be repaired, meaning that the tissue is available and in an acceptable location to suture or tack back together using one of these fixation devices. The subject device is identified in the 510(k) submission as a surgical mesh for reinforcing and repairing chronic soft tissue injuries of the meniscus. We are not aware of any other surgical mesh devices used to treat the identified meniscal defects. Therefore, based on the stated indications for use, we believe the ReGen CS is a surgical mesh for a "new" indication.

The classification for surgical mesh includes "acetabular mesh used during orthopedic surgery." It should be clarified that these predicate acetabular meshes are not intended for placement in the articulating surface either as a covering (as described above) or as a replacement material for soft tissues. Typically, these metal or polymer meshes are placed to reinforce an acetabular bony defect that may or may not be in the joint space. If the bony defect is not in the joint space, the metallic or polymeric meshes serve to reinforce weakened bony tissue, autograft or allograft. If the bony defect is in the joint space, then, on top of the metallic or polymeric mesh and remaining bone, an acetabular component (part of a total hip replacement) is placed over the top of the mesh, typically with bone cement. Articulation then takes place between the femoral and acetabular components of the total hip replacement and not the acetabular mesh. So, none of the acetabular mesh predicates are for placement to function as a covering (as described above) or replacement material in a weight-bearing, soft tissue articulating surface.

The ReGen CS device is a surgical mesh into which fibrous tissue may grow. The CS device is indicated for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. 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 native tissue and provides a resorbable scaffold that facilitates tissue in-growth. The meniscus is subjected to different types of weight-bearing forces as it is loaded in compression, rolling, sliding, and radially (hoop stress) by the femoral condyles during activities of daily living. No other predicate devices cleared as surgical meshes have been used as weight-bearing articulating surfaces in the joint space.

The sponsor has indicated that surgical meshes cleared for rotator cuff repair are for use in a joint, and therefore, have a similar use as compared to the subject device. However, the tissue that corresponds to the meniscus in the shoulder is the glenoid labrum or glenoid ligament, not the rotator cuff. The rotator cuff is an anatomical term given to the group of muscles and their tendons that act to stabilize the shoulder joint. These muscles arise from the scapula and connect to the head of the humerus forming a cuff at the shoulder joint. Hence, the rotator cuff stabilizes and supports the shoulder joint; however it is not intra-articular and it is not considered weight-bearing. In addition, the surgical meshes which have been cleared for rotator cuff repair are to be used as a covering over a sutured repair and were not intended to provide additional mechanical strength to the repair over that provided by sutures or staples. Therefore, any comparison of the loading profile in the meniscus as compared to the rotator cuff may not be relevant as the surgical mesh used to repair the rotator cuff was not cleared to be used or designed for use to dissipate or transfer such loads. This is in direct contrast to the ReGen CS device where the treatment of meniscal defects is based on its proposed use in the weight-bearing intra-articular joint space of the knee.

# Pre-Clinical Information

The sponsor provided pre-clinical testing information on the following topics for the ReGen CS device:

- Suture Retention Strength
- Tensile Strength
- Biomechanics of the Meniscus and Forces in the Shoulder
- Animal Testing
- Biocompatibility
- Virus Inactivation
- Sterilization
- Packaging and Shelf Life

**Suture Retention Strength (Bench Testing)**
(From 510(k), p.20; Attachment A p.24-25; Attachment B, Appendix L)

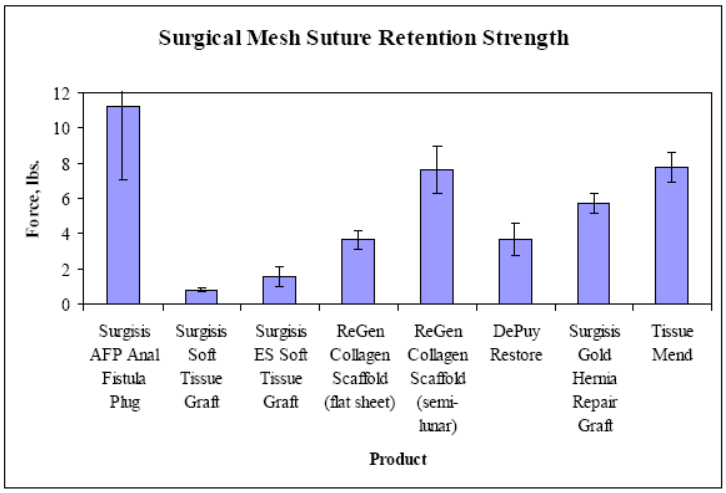
Test articles for suture retention strength included three finished samples of each of the following devices:

- ReGen CS (ReGen Biologics);
- Restore® Orthobiologic Implant (DePuy);
- TissueMend® Advanced Soft Tissue Repair Matrix (TEI Biosciences);
- SurgiSIS® (Cook Biotech);
- SurgiSIS® ES™ Soft Tissue Graft (Cook Biotech),
- SurgiSIS® Gold™ Hernia Repair Graft (Cook Biotech), and
- SurgiSIS® AFP™ Anal Fistula Plug (Cook Biotech).

Non-resorbable 2-0 polyester suture was threaded through each sample using a 2 mm bite depth from the sample edge and tied to form a loop. The loop of the suture was placed over the hook on the force gauge, and the sample was placed securely in a test fixture and pulled at a constant rate in the test stand until failure (indicated by the suture being pulled through the mesh); with the peak pull-through force recorded.

The results are summarized in the graph provided in Table 2 below (excerpt from pg 20 of the 510(k), Table 3). The average pull-out strength of the semi-lunar configuration of the ReGen CS (7.5 mm width and 4 mm height) was 7.65lbs (+/- 1.32).

Table 2: Summary of Suture Retention Strength Testing




Note that we are not currently considering the ReGen CS flat sheet device referenced in this table. Table 2 above shows that the results of the suture retention strength are similar to those of predicate surgical mesh devices for soft tissue reinforcement. However, none of these devices is indicated for meniscal defect repair or to replace damaged soft tissue in a weight-bearing, articulating joint. Consequently, you should consider whether the mechanical strength testing data provided for other predicate surgical mesh devices for hernia, rotator cuff repair, etc. are relevant to the ability of the CS device, proposed for "meniscal defect repair and reinforcement," to adequately withstand the mechanical forces required for meniscal repair.

Because none of these other surgical mesh predicates is intended to be used to replace or repair damaged soft tissue in a weight-bearing, articulating joint, additional non-clinical testing was performed to support the intended use of the ReGen CS. Specifically, FDA requested a comparison of the tensile strength and suture pull-out strength of human meniscus compared to the tensile strength and suture pull-out strength of the ReGen CS device to demonstrate that the device has adequate mechanical properties that approximate those of the removed meniscus and can withstand the functional demands placed upon it over a multi-year period of time prior to complete resorption. (Provided in Appendix C p.26-27 of the 510(k)).

The sponsor provided data on the suture pull-out strength for native canine meniscal tissue as a comparison. This information is summarized in the "Animal Testing" section below.

The sponsor also pointed to the results of the clinical testing to support their assertion that the device has adequate strength. Please see a summary of the one-year re-look arthroscopy and explantation information for more information regarding the device mechanical strength for the proposed indications for use in the "Clinical Information" section which follows.

Please note that the sponsor stated that the "CS is not intended to function as a prosthetic meniscus and therefore is not designed to have the mechanical strength of the native human tissue… The mechanical properties of the device are only relevant at the time of initial implantation because over time the mechanical properties of the construct change as tissue fills the scaffold, the scaffold resorbs and the tissue remodels…. During the first 6-months following implantation, the patient's activity level is restricted to reduce the stress on the mesh-reinforced meniscus, and to allow tissue in-growth and maturation to take place." (From 510(k), p.20)

**Tensile Strength (Bench Testing)**
(From 510(k), p.20; Attachment A p.26; Attachment B, Appendix M)

To characterize the strength of the ReGen CS (semi-lunar configurations) relative to the predicate absorbable surgical mesh products, tensile testing was performed to quantify the force required to rupture or break apart the surgical meshes.

The test consisted of clamping opposite ends of the surgical meshes in fixtures attached to a mechanical tester which moved the fixture at a fixed rate until the surgical meshes ruptured, recording the peak load to failure. The semi-lunar configuration of the ReGen CS was tested.

Table 3, 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. For the ReGen CS semi-lunar device, the average tensile strength was reported to be 6.23lb (27.7N). This value is similar to the results for suture pull-out testing (i.e., 7.65lb).

Table 3: Summary of Tensile Testing

| Surgical Mesh | Average Peak Load to Failure, in Newtons | Standard Deviation |
|---|---|---|
| Surgisis AFP Anal Fistula Plug | 124.0 | 55.6 |
| Surgisis Soft Tissue Graft | 8.5 | 2.8 |
| Surgisis ES Soft Tissue Graft | 20.4 | 2.8 |
| ReGen Collagen Scaffold (semi-lunar)* | 27.7 | 5.5 |
| ReGen Collagen Scaffold (flat sheet)* | 21.9 | 13.2 |
| DePuy Restore | 54.2 | 5.0 |
| Surgisis Gold Hernia Repair Graft | 80.1 | 12.9 |
| Tissue Mend | 116.4 | 41.2 |

Note that we are not currently considering the ReGen CS flat sheet device referenced in this table.

**Biomechanics of the Meniscus and Comparison to Forces in the Shoulder**
(From 510(k), p.21-22; Attachment A p.27-31; Attachment B, Appendix N and O)
The sponsor provided a biomechanical analysis of the forces in the meniscus to support its assertion that the ReGen CS will remain adequately adhered to the host tissue and resist the forces exerted on it and that the forces on a mesh in the meniscus are no greater than those on a mesh in the shoulder.

Within the submission, the sponsor stated that the shear forces on the meniscus are negligible and that the compressive forces have a horizontal and vertical component. The horizontal component of the compressive forces result in hoop tensile stresses which dominate function and failure and were reported to be, on average, approximately 350kPa (51psi). The sponsor measured the suture pull-through or tearing strength of 560kPa (81psi) using a cadaveric bovine meniscus model. Based on this analysis, the sponsor concluded that the ReGen CS provides adequate reinforcement to the native meniscus at the time of placement.

In addition, through a biomechanical analysis, the sponsor calculated the tensile forces on the rotator cuff tendon to be 2800kPa based on a joint reaction force for an intact tendon of 337N. The sponsor concludes that 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.

The sponsor stated that the ReGen CS for use in the meniscus and the predicate DePuy Restore device for rotator cuff injuries are used in the same way to address the issues of surgical repair and tissue remodeling.

Assuming a triangular cross-section for the ReGen CS device and an estimate of 2.5mm$^2$ (0.0039in$^2$) for the ReGen CS in cross-section, it appears the sponsor is stating that the tensile (hoop) stresses on native meniscus are on the order of 0.2lb (0.88 N) and that the ReGen CS can withstand a load of 0.32lb (1.41N). As summarized in the "Animal Testing" section, this load is much lower than the suture pull-out strength for native canine meniscal tissue as a comparison.

In addition, the information outlined above and provided by the sponsor comparing the forces in the meniscus and the shoulder (rotator cuff) is not consistent with the indications and intended use of the predicate DePuy Restore device for rotator cuff injuries (K031969, K001738) cleared for marketing. The DePuy Restore predicate was not cleared for use in repairing rotator cuff injuries but rather to reinforce soft tissues during rotator cuff repair surgery. Sutures are used to repair the rotator cuff tear and sutures or bone anchors are used to reattach the tissue to the bone to provide the mechanical strength of the rotator cuff repair. Then, based on the surgical technique, the DePuy Restore mesh is placed over the suture line to reinforce the already repaired rotator cuff. This information, regarding the indications and intended use, was taken directly from K001738, DePuy Restore Orthobiologic Soft Tissue Implant. (See Tab D (Parts 1 and 2) for predicate device indications and pictures of the surgical technique). Therefore, a comparison of forces in the meniscus and rotator cuff should be assessed with some caution in this context because the predicate was not cleared to mechanically support the loads in the shoulder.

**Animal Testing**
(From 510(k), p.22; Attachment A p.31-32; Attachment B, Appendix P)
FDA has no questions regarding the animal testing except we include for reference the information on the native canine meniscus suture pull-out for comparison to the ReGen CS suture pull-out. This information has been included because it may be relevant to your evaluation of the mechanical properties of the ReGen CS device as related to its ability to remain sutured in place and to serve as a scaffold for tissue ingrowth in the knee.

**Canine Study to Evaluate Strength of ReGen CS over Time – Suture Pull-out:**
A canine study was conducted to evaluate the strength of the ReGen CS over time. The specific purpose of this study was to determine the suture pull-out strength over time. Suture pull-out strength after insertion was evaluated by examining samples explanted at specific time points.

Suture pull-out testing was conducted using the following test specimens: (1) ReGen CS prior to insertion, (2) the excised portion of the dog meniscus, and (3) excised portions of the ReGen CS from an additional 4 groups of animals at 3, 6, 12 and 24 weeks. The ReGen CS (prior to insertion) and native menisci samples served as control groups. Tests were performed with 3-0 Ethibond suture placed 2 mm from the peripheral edge of the sample. The sample was pulled at a rate of 2.54 cm/min until failure (pull-out from the specimen).

**Results** – Average suture pull-out strength was measured to be:
- 4.9lb +/- 0.8 prior to insertion of ReGen CS (2.23kg +/- 0.37) (n=4);
- 4.8lb +/- 0.5 at 3 weeks (2.2 kg +/- 0.22) (n=5);
- 6.6lb +/- 1.2 at 6 weeks (3.0 kg +/- 0.56) (n=6);
- 4.3lb +/- 0.99 at 12 weeks (1.94 kg +/- 0.45) (n=4); and
- 7.4lb +/- 3.1 at 24 weeks (3.38 kg +/- 1.42) (n=5).
- The pullout strength of the native dog meniscus was reported to be 25.7lb +/- 4.0 (n=6) as a comparison (11.70 kg +/- 1.8).

(Note: The pull-out strength for the native canine meniscal tissue was a normalized value that was calculated after using fishing line because the full thickness native meniscus well exceeded the strength of the 3-0 Ethibond suture. Therefore, a higher strength alternative suture-like material (fishing line) was used).

Clinical Data for ReGen CS device for Consideration of ReGen CS Mechanical Properties
The sponsor also pointed to the results of the clinical testing to support their assertion that the device has adequate strength. Please see a summary of the one-year re-look arthroscopy and explantation information

for more information regarding the device mechanical strength for the proposed indications for use in the "Clinical Information" section which follows. Based on the histological evaluation report (Attachment B, Appendix T of the 510(k)), the ReGen CS was resorbed in 40% (55/136 biopsies had no CS remnants) of the cases at one year. This suggests that complete resorption will be a multi-year process, implying that for some patients, some portion of the CS "scaffold" device will be subjected to meniscal forces for more than one year. Based on the animal testing data provided, the ReGen CS has 3.5-6 times lower suture pull-out strength when compared to native canine meniscus suture pull-out strength.

**Biocompatibility**
(From 510(k), pp.18-19 and Appendix G; Attachment A p.22-23; Attachment B, Appendix K; and Attachment C, Appendix I and J)
The sponsor has satisfactorily demonstrated the biocompatibility of the device according to ISO testing.

**Virus Inactivation**
(From 510(k), p.17; and Attachment A p.20-21, Appendix J)
The sponsor has satisfactorily demonstrated virus inactivation.

**Sterilization**
(From 510(k), p.17; and Attachment A p.20)
The sponsor has provided adequate sterilization information.

**Packaging and Shelf-Life**
(From 510(k), p.16; and Attachment A p.19, Appendix G)
The sponsor has provided adequate packaging and shelf-life information.

**Summary of Pre-Clinical Testing Section:**
Regarding the animal and pre-clinical testing evaluation, the sponsor did not provide a comparison of the tensile strength or suture pull-out strength of the native human meniscus to the tensile strength or suture pull-out strength of the ReGen CS device. This information may have provided a direct comparison of the mechanical properties of the subject device to the human meniscus tissue it is intended to replace.

Based upon data provided in the canine study (Appendix P of the 510(k)), the suture pull-out strength of the ReGen CS device is significantly less than native canine meniscal tissue (i.e., 4.2-7.5lb for the ReGen CS device as compared to 25.7lb for the native canine meniscal tissue). In addition, based on the histological evaluation report from the Clinical Data for the CS device in Attachment B, Appendix T of the 510(k), the ReGen CS was resorbed in only 40% of the cases at one year, (55/136). This suggests that demonstration of complete resorption will be a multi-year process, implying that this "scaffold" device must perform a multi-year function.

On pp.24-26, the sponsor demonstrated that the tensile strength and suture pull-out strength of the ReGen CS device compared well to other surgical mesh devices. However, none of these devices are indicated for meniscal defect. Therefore, while bench studies are important to this evaluation, especially related to the safety of this material, it appears that bench testing alone cannot fully predict clinical performance for this indication.

# Clinical Information

**Indications/Intended Use**
In 510(k) K082079, the sponsor has proposed the following Indications/Intended Use:

> The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. 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.

**Data Sources:**
(From 510(k), p.23, Appendix A (Tab E in Panel Pack))

To support the proposed indications/intended use, the sponsor provided clinical data for the ReGen Collagen Scaffold (CS) from the following sources:

1. Feasibility Study – Single Center Published Results on Eight Patients

2. Published Results from Europe:
   a. Case Study on Four Patients
   b. Case Study on Two Patients

3. Journal Bone and Joint Surgery (JBJS) Article which acknowledges that it is based upon an approved FDA Investigational Device Exemption (IDE) Multicenter Clinical Study (G920211) with two arms, one each for patients with acute and chronic meniscus injuries and each with a partial meniscectomy control.

   Four analyses of the clinical data from the IDE study are presented in the 510(k) submission, as follows:
   a. Analysis of data from patients in the ReGen CS group of the chronic study arm
   b. Published results comparing patients in the ReGen CS group and partial meniscectomy control group for both the acute and chronic study arms:
      - Rodkey, WG et al., "Comparison of the Collagen Meniscus Implant with Partial Meniscectomy. A Prospective Randomized Trial," *J. Bone Joint Surg Am.* 2008; 90: 1413-1426. **(Note: This article is referred to throughout the Panel Pack as the "JBJS article**").
   c. Analysis of the adverse event data from the chronic arm of the IDE study
   d. Analysis of data pooled from both the chronic and acute arms

**Important Notes for the Panel:**
- **The ReGen CS subject device is sometimes referred to as CMI by the sponsor within the clinical data sets. CMI and CS refer to the same device.**
- **In K082079, the sponsor is seeking clearance for the indication corresponding only to the chronic group. Therefore, in the presentation of the results below, the focus will be primarily on the patients in the chronic study arm.**

## 1. Feasibility Study – Single Center Published Results on Eight Patients

(From 510(k), pp.50-51; Attachment A p.34-35Attachment B, Appendix Q; Attachment D, Appendix F)

A clinical feasibility study conducted under an FDA approved IDE, G920211, was conducted at a single investigational site in 8 patients. The objectives of the feasibility study were "...to evaluate the ability to effectively and efficiently implant the Collagen Meniscus Implant, evaluate whether the knee recovers from the surgery without clinically significant adverse effect from the implant, evaluate whether at three months the implant has stabilized in place." The results were published in the following literature:

- Rodkey, WG, Steadman, JR, Li ST. 1999. "A clinical study of collagen meniscus implants to restore the injured meniscus. *Clinical Orthopedics and Related Research* 367: S281-S292.
- 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.

## 2. Published Clinical Experience Reports from Europe

(From 510(k), pp.51-53; Attachment A p.35-37; Attachment B, Appendix R; Attachment D, Appendix G)

Clinical experience with the ReGen CS used in the meniscus has been published by Reguzzoni et al. (n=4 patients) and Ronga et al. (n=2 patients). These reports are based on European clinical experience with the semi-lunar configuration of the CS device for use in the meniscus [referred to as the Collagen Meniscus Implant (CMI)].

- Marcella Reguzzoni, Alessandro Manelli, Mario Ronga, Mario Raspanti, Federico A. Grassi, "Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation", Journal of Biomedical Materials Research Part B: Applied Biomaterials, Volume 74B, Issue 2, Pages 808 – 816.
- M. Ronga, P. Bulgheroni, A. Manelli, E. Genovese, F. Grassi, P. Cherubino, "Short-term evaluation of collagen meniscus implants by MRI and morphological analysis," Journal of Orthopaedics and Traumatology, Volume 4, Number 1, 5-10 April 2003.

## 3. Clinical Data reported in the Journal Bone and Joint Surgery (JBJS) Article, the FDA approved IDE Multicenter Clinical Study of ReGen CS, and the 510(k) K082079 submission

**Study Overview**

(From 510(k), p.24)

Journal Bone and Joint Surgery (JBJS) Article is based upon an approved FDA IDE study, G920211. ReGen Biologics conducted a randomized, controlled clinical trial of the Collagen Meniscus Implant (CMI) under the FDA approved IDE study, G920211. The phase I and phase II feasibility studies for this IDE were approved on July 8, 1993 and August 18, 1995, respectively. The multi-center clinical trial for this IDE was approved on August 30, 1996. Patient enrollment was completed in April 2003 and follow-up information continues to be collected to obtain data on clinical outcomes of the device.

The IDE study compared clinical outcomes of (1) subjects requiring arthroscopic partial meniscectomy (the control group representing the standard of care), with (2) patients treated with partial meniscectomy followed by ReGen CS placement as an add-on therapy (the treatment group). Please note that although the IDE study provides scientific data relevant to the CS device, we will ultimately be determining whether the CS device is substantially equivalent to the predicate devices. We will not be comparing the safety and effectiveness of the CS device to surgical intervention. Instead, we will be determining whether use of the CS device for its proposed indication affects the safety and effectiveness of the device when used as labeled.

The study consisted of two arms, designated as follows:

- Acute (protocol 9601: patients with no history of previous meniscus treatment); and
- Chronic meniscal injury (protocol 9602: patients with a history of one to three previous meniscus treatments). Please note that the 510(k) submission is requesting clearance for the chronic patient group (1-3 prior meniscus treatments).

The only difference between the two protocols was the number of prior meniscus surgeries the patients had upon entering the study. Post-operatively, subjects had follow-up visits at 1-7 days, 6 weeks, 3 and 6 months, and annually thereafter (see protocol for data to be collected at each follow-up time-point). A summary of the protocol and results relevant to performance as a surgical mesh in the knee from the clinical trial are provided below.

Complete protocols for the acute and chronic arms of the IDE study are provided in Tab G (G1 and G2) of this FDA Panel Pack. Included are the most recent IDE protocols – Version 5 dated November 15, 2006.

**Study Objective**
The protocols state that the primary objective of the (IDE) Multicenter Clinical Study is to assess the safety and clinical benefit of the CS.

- For the "acute arm" Protocol 9601: The CS will be evaluated in patients who have not been treated for the involved meniscus prior to enrolling in the study.
- For the "chronic arm" Protocol 9602: The CS will be evaluated in patients who have received prior treatment for the involved meniscus prior to enrolling in the study.

Please note that the 510(k) submission is requesting clearance for the chronic patient group (1-3 prior meniscus treatments).

According to the IDE protocol, safety was to be assessed by an assessment of serum markers and adverse events. Effectiveness was to be assessed in terms of both radiographic/biopsy and functional parameters, such as pain, swelling, knee function, and patient self-assessment. Descriptions of each parameter measured to evaluate the primary and secondary objectives of the CS follow. Criteria for success and failure for each measured parameter are described below in Tables A1 and A2 (p.18 of this Executive Summary).

An individual patient's success outcome was to be determined as follows:

| | |
|---|---|
| Primary Clinical endpoints: | Visual Analog Scale (VAS) pain score, Lysholm pain and function knee score, and Patient's Self- Assessment. A clinically significant improvement in any two of these three endpoints would be considered a success. |
| Surrogate endpoints: | Implant status as assessed using arthroscopy, histopathology, and radiographs. Improvement in any two of these three endpoints would be considered a success. |

**Patient Population**
The full-scale clinical trial was designed to enroll between 144 and 154 patients between the ages of 18 and 60 years, male and/or female in good health, requiring treatment for damage to the medial meniscus in the knee.

All patients enrolled in the IDE study were to be suffering from an irreparable injury to the medial meniscus. They were to be randomized to either the treatment or control arms of the study. All patients were to undergo full thickness debridement of the involved meniscus back into the vascular zone while assuring that the meniscal rim remained intact. The actual size of the defect was to be measured at surgery and recorded. In summary, according to the prospectively defined criteria, all lesions treated (control or CS implanted) were intended to be full thickness, extend into the vascular zone, and have an intact meniscal rim (i.e. no variability in thickness of the lesion, no "white-white" zone lesions, and no unstable segmental defects in which there was not an intact meniscal rim).

**Sample Size Considerations**
The sample sizes for this study were determined using formulae and methods for comparing two independent population means (knee function) according to Cohen (1988), and using formulae and methods for estimating a population proportion (tissue ingrowth) according to Fleiss (1981).

A total of 128 evaluable patients (64 evaluable patients receiving the ReGen CS with their partial meniscectomy and 64 evaluable patients with partial meniscectomy alone) were calculated as being necessary to be able to detect at least a difference of 20 percentage points and the percent of patients classified as a treatment success according to their Lysholm knee score, assuming that 70% of the control patients were classified as a treatment success, when comparing two independent population proportions at

a p=0.05 level of significance (in a two-sided test) with 80% power. With an expected 10% drop-out rate, 72 patients in each treatment group, for a total of 144 patients, were to have been enrolled in this study.

With the VAS pain scores, a conservative estimate of the standard deviation would be +/- 20 mm in the change from baseline values. A total of 128 evaluable patients (64 evaluable patients receiving the CS with their partial meniscectomy and 64 evaluable patients with partial meniscectomy alone) were calculated as being necessary to be able to detect at least a difference of 10 points in the average change from baseline VAS pain score between the two groups at a p=0.05 level of significance with 80% power. With an expected 10% drop-out rate, 72 patients in each treatment group, for a total of 144 patients, were to have been enrolled in this study.

Lastly, the sponsor indicated that, with 64 evaluable patients receiving the implant, they would be able to estimate the true percentage of patients showing tissue ingrowth to within 12.25 % with a true population proportion around 50%, or to within 11.25 % with a true population proportion around 70%.

**Inclusion Criteria**
(From 510(k), Attachment C, p.13)

- ***a. Protocol 9601 only:*** Patient has received no prior treatment to the involved meniscus.
- ***a. Protocol 9602 only:*** Patient has received 1, 2, or 3 prior treatments to the involved meniscus.
- b. 18 to 60 years with good health.
- c. Diagnosis of injury to the knee resulting in an MRI or arthroscopically confirmed medial meniscus cartilage tear deemed to be primarily irreparable and requiring a partial meniscectomy.
- d. Diagnosis of degenerative joint disease of grade 0, I, II, or III in the lateral, medial, or patellofemoral compartment(s).
- e. If a concomitant anterior cruciate ligament injury exists, the ACL must be stabilized within 12 weeks of implanting the CS.
- f. It has been at least three months since receiving any chondral regeneration procedures.
- g. Available for participation in the study during the course of the investigation (24 month follow-up).
- h. Agree to follow-up evaluations including "second-look" arthroscopy and biopsy,
- i. No scientific evidence of progression in healing, that is, no signs of spontaneous repair or regeneration of the meniscus,
- j. Willing to be randomized to either the control or CS group, and willing to follow the respective rehabilitation program,
- k. Willing to sign the informed consent.

**Exclusion Criteria**
(From 510(k), Attachment C, p.13-14)

- a. Diagnosis of a concomitant injury of the contralateral or involved limb which the investigator believes may interfere with study participation (i.e. confound efficacy assessments or healing of the involved knee).
- b. Diagnosis of a concomitant lateral meniscal injury in involved knee which requires suture repair or excision of > 15% of the lateral meniscus.
- c. Diagnosis of a concomitant PCL deficiency in involved knee.
- d. Diagnosis of grade IV degenerative joint disease in the lateral, medial, or patellofemoral compartment(s).
- e. Previous treatment with collagen or injectable collagen.
- f. Documented allergy to collagen of animal origin.
- g. Infections, systemic or local.
- h. A history of anaphylactoid reaction.
- i. Pregnant.
- j. A history of drug or substance abuse.
- k. Severe trauma other than as defined in this protocol.
- I. Clinically significant (as defined by the investigator) renal, hepatic, cardiac, endocrine, hematologic, autoimmune or any systemic disease which may make implementation/interpretation of the protocol or results difficult,

m. Systemic administration within 30 days prior to the study of any type of corticosteroid, antineoplastics, immunostimulating or immunosuppressive agents,
n. History of inflammatory arthritis,
o. Participation in another clinical trial using an investigational new drug or device within 30 days of entrance into this study,
p. Pending litigation regarding the knee injury,
q. Evidence of osteonecrosis in the involved knee,
r. History of peripheral neuropathy, active on-going neoplastic disease, or immunosuppression.

**Surgical Technique**

The following information is drawn from the IDE Study, G920211/S82, dated January 18, 2007. The complete surgical technique manual provided by the sponsor as part of the IDE has been provided in Tab H of this Panel Pack.

After thorough arthroscopic inspection of the knee joint, the damaged portion of the meniscus is evaluated. If meniscal repair cannot be accomplished, and the remaining "meniscal defect criteria" (described below) are fulfilled, then the patient would qualify to receive the Collagen Meniscus Implant (CMI).

Meniscus Defect Criteria
- Irreparable injury (same rationale used for partial meniscectomy control group)
- Traumatic or degenerative origin
- Both attachment sites for the anterior and posterior horns must still be intact
- Site preparation must result in a full thickness defect
- Defect site must extend into the red/red zone or the red/white zone
- Exclude unstable segmental defects in which the meniscal rim is not intact

After proper assessment of the meniscal lesion, standard arthroscopic instrumentation and techniques used for partial meniscectomy are used to prepare the defect site. Special attention is given to the preparation of the remaining meniscal rim and especially to both the posterior and anterior components. Ideally, the defect site should be prepared such that the remaining meniscal rim is of uniform width, debridement extends into the vascular zone, and that both the posterior and anterior components are appropriately tapered for good tissue approximation with the CS.

Once the defect site is properly prepared, the CS measuring instrument is inserted through an arthroscopic portal to accurately assess the arc length of the defect site of the rim. The arc length of the defect and the height of the remaining meniscal rim are determined and used to appropriately size the CS.
Once the CS is cut to the appropriate length, and both free ends are tapered such that they will approximate the host meniscal defect, the CS is hydrated in sterile saline and placed into the delivery system.

The CS is inserted into the joint through the arthroscopic portal. Once the CS has been delivered to the targeted site, and it is determined to be an adequate fit, it is sutured in place, taking special precautions to avoid damage to the neurovascular structures. An appropriate non-absorbable suture is used to secure the CS for subsequent tissue incorporation.

From the “Baseline Operative Data” presented in the Results Section, during the operative procedure, the CS patients had an average of 63% of meniscus tissue removed during the partial meniscectomy in the chronic group leaving 37% of their original meniscus volume remaining. For the control patients, an average of 60% of meniscus tissue was removed during the partial meniscectomy in the chronic group leaving 40% of their original meniscus volume remaining. Therefore, more native meniscus was removed in the CS device group, on average, as compared to the partial meniscectomy control group. Although the average amount of native meniscus remaining was 37%, 43% (37/87) of the tears in the treatment group had 20% or less of the native meniscus remaining, implying that there was 10% of the meniscus anteriorly and 10% posteriorly. Hence, in more than 40% of the cases, 80% or more of the native meniscus was removed from patients in the ReGen CS group.

**Rehabilitation Protocol**

The sponsor stated that "while we believe this is the best prospective concurrent control available, we recognize that there are differences in post-operative rehabilitation procedures between the control and the ReGen CS patients. The control patients require less formal rehabilitation and return to full normal function much sooner than the CS patients. The rehabilitation for the ReGen CS patients is specifically designed to allow the implant to stabilize in place, supporting tissue ingrowth by providing a protective, nonweight bearing environment with passive motion for a period of 1 week followed by 5 weeks of partial weight bearing with passive motion to a slow progression to full activities by 6 months. In contrast, the rehabilitation program for the control patients is a guideline for return to full activities by 2-3 weeks post-operatively since there is no period of "meniscal healing" required."

There is a noted difference in the rehabilitation necessary for the ReGen CS implant (up to 6 months) in comparison to the control, i.e., partial meniscectomy (~2-3 weeks).

**Study Endpoints**

For additional details on the prospectively-defined study endpoints for the IDE, which is what the JBJS paper is based upon, the actual protocols have been provided in Tab G (G1 and G2) of the Panel Pack.

Criteria for success and failure for each measured parameter are described below in Tables A1 and A2.

***Table A.1 Monitoring of Implant Safety***

Objective: Recovery of the patient without significant adverse reactions to the implant.

| Endpoint/Measure | Success | Failure |
|---|---|---|
| Blood Analysis (ELISA) | Less than or equal to 2 standard deviations from the mean immune response to the implant. | Greater than 2 standard deviations from the mean immune response to the implant. |
| Adverse Events | No significant adverse events documented as attributable to the implant. | Significant adverse events documented as attributable to the implant. |

***Table A.2 Monitoring of Implant Effectiveness***

Objective: Demonstrate clinical benefit to the patient.

| Endpoint/Measure | Success | Failure | Time point of Success/Failure Determination |
|---|---|---|---|
| Arthroscopic Appearance | Implant/new tissue complex remains firmly attached to host rim and at least 60% of original defect remains filled. | Implant/new tissue complex does not remain firmly attached to host rim and / or less than 60% of original defect remains filled. | 12 mo. |
| Histopathology | Indication of cellular ingrowth into the implant and indication of new extracellular matrix deposition. | Absence of cellular ingrowth into the implant and / or no new extracellular matrix deposition. | 12 mo. |
| Pain | VAS pain scale improved by at least 20% compared to pre-op. | VAS pain scale did not improve by at least 20% compared to pre-op. | 24 mo. |
| Swelling | Increase in knee circumference at the mid-patella less than or equal to 6 cm. compared to pre-op. | Increase in knee circumference at the mid-patella greater than 6 cm. compared to pre-op. | 24 mo. |
| Lysholm Knee Scoring Scale | For patients with pre-op score < 80, increase in score of at least 20% compared to the pre-op score. For patients with pre-op score ≥ 80, a final score of ≥ 95. | For patients with pre-op score < 80, increase in score of less than 20% compared to the pre-op score. For patients with pre-op score ≥ 80, a final score of < 95. | 24 mo. |
| Patient's own Evaluation/Overall Assessment | Improvement of at least one grade from pre-op. If pre-op grade was "normal" or "nearly normal", then no decrement. | Lack of improvement of at least one grade from pre-op. If pre-op grade was "normal" or "nearly normal", then decrement to lower grade. | 24 mo. |

In addition to data collection for evaluation of the above-noted study endpoints, information was also being recorded for the following endpoints outlined in Table 4 below. The sponsor included success/failure criterion for each endpoint.

Refer to Tab G (G1 and G2) of the Panel Pack for additional details.

Table 4: Additional prospectively defined endpoints for the IDE study (G920211)

| Additional Endpoints: | Success | Failure |
|---|---|---|
| Synovial Fluid | No evidence of significant inflammatory response with less than or equal to 2,000 white blood cells per ml. | Evidence of significant inflammatory response with greater than 2,000 white blood cells per ml. |
| Redness | Redness categorized as slight or none. | Redness categorized as moderate or severe. |
| Skin/Superficial Wound Healing | None to mild exudate is present in 6 weeks or less. | Moderate to severe exudate is present requiring on-going wound care for greater than 6 weeks. |
| Range of Motion | Show improvement if their pre-op score for the injured knee was worse than the non-involved knee, or return to their preop score if the injured knee at pre-op was the same or better than the non-involved knee. | No improvement if their pre-op score for the injured knee was worse than the non-involved knee, or did not return to their pre-op score if the injured knee at pre-op was the same or better than the non-involved knee. |
| Thigh Girth Measurement | Show improvement if their pre-op score for the injured knee was worse than the non-involved knee, or return to their preop score if the injured knee at pre-op was the same or better than the non-involved knee. | No improvement if their pre-op score for the injured knee was worse than the non-involved knee, or did not return to their pre-op score if the injured knee at pre-op was the same or better than the non-involved knee. |
| Functional Evaluation | The patient improves by at least one grade level if the pre-op score was a 4, 5, or a 6 (Severe limitation to Not allowed). If the pre-op score was a 1, 2, or 3 (Limitation is none to moderate), the score must not worsen. | The patient regresses or remains at the same grade level if the pre-op score was a 4, 5, or a 6 (Severe limitation to Not allowed). If the pre-op score was a 1, 2, or 3 (Limitation is none to moderate), the score worsens. |
| Tegner Activity Level | The patient's score is at least one grade level higher than the pre-op activity level, unless this would require them to exceed their pre-injury level. | The patient's score is the same as or worse than the pre-op activity level, unless their pre-op score was the same or higher than their pre-injury score. |
| Radiographic Evaluation | No *significant increase in osteophytes or other degenerative joint changes compared with the | *Significant increase in osteophytes or other degenerative joint changes compared with the same views of pre-op |

| | | |
|---|---|---|
| | same views of pre-op baseline radiographs. | baseline radiographs. |
| | ** A significant increase is defined as at least one grade deterioration (i.e., mild to moderate) in osteophyte formation and worsening in at least two of the three Fairbanks criteria (ridge formation, flattening of the femoral condyle and joint space narrowing).* | |
| Gross Appearance of Regeneration | Evidence of regeneration based upon description in protocol. | No evidence of regeneration based upon the above descriptio |
| Implant Appearance | Implant appears mostly smooth, with no significant irregularities. Surface does not have a cobblestone appearance with pitting; inner rim does not have a jagged "sawtooth" appearance. | Implant does not appear mostly smooth, and there are signifi irregularities. Surface has cobblestone appearance with pittin rim has jagged "sawtooth" appearance. |
| Implant - Host Stability | Implant appears stable on probing. Probing does not reveal tears or other integrity interruptions, nor demonstrate a lack of adherence to the host meniscal rim. | Implant does not appear stable on probing. Probing reveals te other integrity interruptions, or demonstrates a lack of adhere the host meniscal rim. |
| Presence of Loose Bodies or Fraying | No significant loose bodies or fraying which cause mechanical dysfunction of the joint (such as constant and persistent catching or locking). | Significant loose bodies or fraying which cause mechanical dysfunction of the joint (such as constant and persistent catch locking). |
| Implant-host Junction | Grades will be assigned based on the degree of "healing" between the implant and host tissue and recorded: 0 = Clear separation between host tissue and implant. No interdigitation; gaps in tissue not an artifact of sampling; 1 = Slight integration; 2 = Moderate integration; 3 = Fully healed; and 4 = Interface not observed (N/A)<br>• SUCCESS: A grade of "2" or "3".<br>• FAILURE: A grade of "0" or "1". | |
| Presence of Inflammatory Response | Evidence of an inflammatory response that is graded as none or mild. | Evidence of a significant inflammatory response that is grade moderate or severe. |

**Patient Accounting**

The figure below illustrates the accounting of patients enrolled within the IDE study. The "patient tree" was provided in the JBJS Article included within the 510(k), Appendix A (Tab E in Panel Pack):

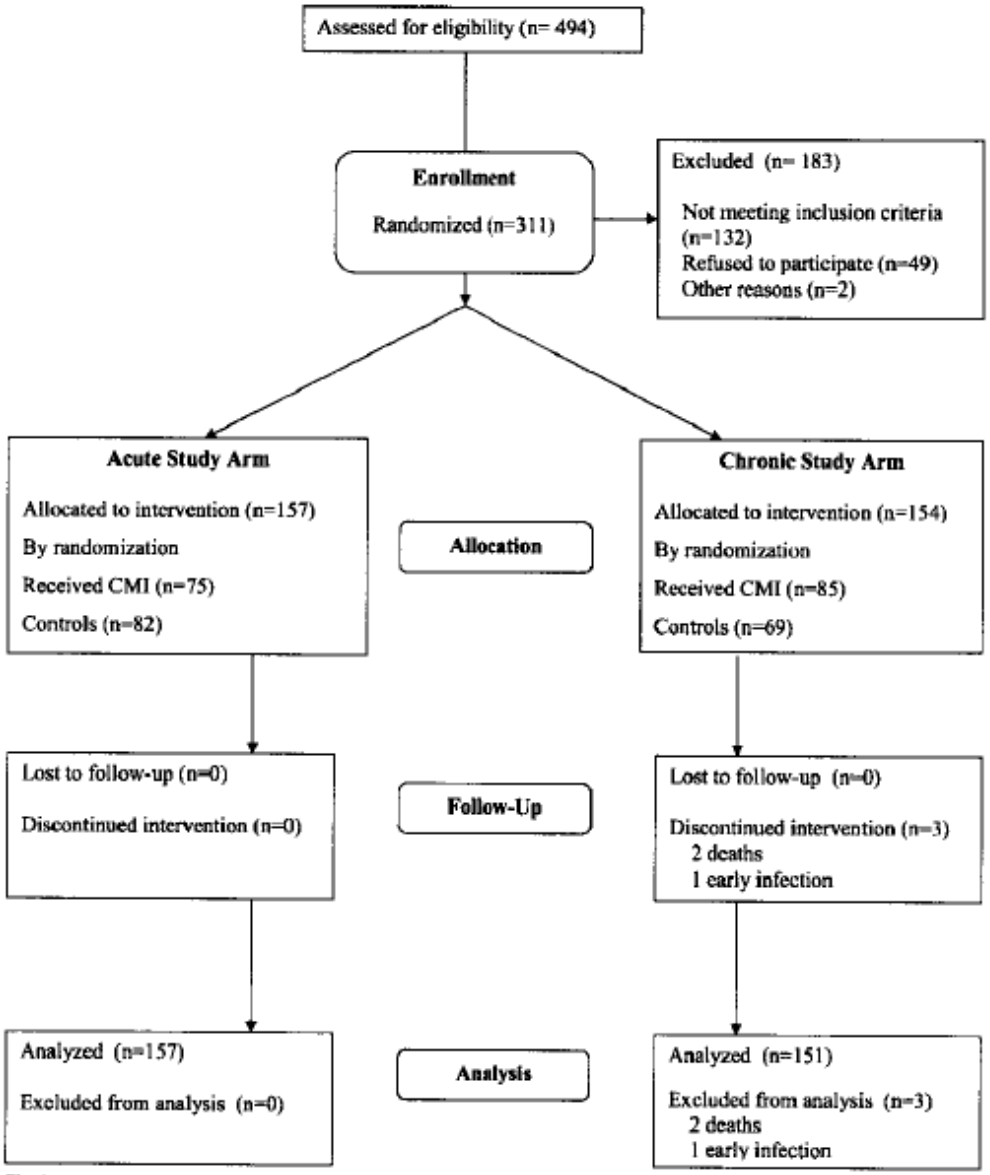



Fig. 1

Diagram illustrating the flow of participants through the trial. CMI = collagen meniscus implant.

**Patient Demographics**
Table 5 captures the demographic data was provided in the JBJS Article included within the 510(k), Appendix A (Tab E in Panel Pack).

Table 5: Demographic Data

TABLE I Demographic Data*

| | Acute Group (N = 157) | | Chronic Group (N = 154) | |
|---|---|---|---|---|
| | Collagen Meniscus Implant | Control | Collagen Meniscus Implant | Control |
| Patients enrolled and evaluated *(no.)* | 75 | 82 | 85 | 69 |
| Concurrent ant. cruciate lig. reconstruction *(no.)* | 22 | 16 | 25 | 22 |
| Follow-up time *(mo)* | | | | |
| Range | 23-89 | 16-85 | 23-90 | 23-92 |
| Mean | 64 | 60 | 60 | 57 |
| Mean age *(yr)* | 40 | 40 | 38 | 39 |
| Sex distribution *(no.)* | | | | |
| Male | 65 | 67 | 61 | 50 |
| Female | 10 | 15 | 24 | 19 |

*There were no significant differences between the treatment groups within the study arms.

**Patient Accounting for Chronic Study Arm Only**
The Patient Accounting information appears in the 510(k) submission, Appendix H, except for FDA calculations of "theoretically due" and "% follow-up" which were based on information provided in Table 6.

**Table 6: Information for Patients in Chronic Study Arm Only (Protocol 9602):**

| | Pre-Op | Post-Op | 6wk | 3mo | 6mo | 12mo | 24mo | 36mo | 48mo | 60mo | 72mo | 84mo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Theoretical (calculated)** | **87** | **87** | **86** | **85** | **82** | **81** | **80** | **80** | **66** | **52** | **42** | **35** |
| Actual | 87 | 87 | 85 | 84 | 80 | 73 | 68 | 38 | 27 | 25 | 24 | 18 |
| LTF | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 2 | 2 |
| Excluded | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 2 |
| Withdrew | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Not yet due | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 14 | 28 | 38 | 45 |
| Explants | 0 | 0 | 1 | 2 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Deaths | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| **% Follow-up (calculated)** | **100%** | **100%** | **99%** | **99%** | **98%** | **90%** | **85%** | **47%** | **41%** | **48%** | **57%** | **51%** |

**At the 3-7 year annual follow-up timepoints, there is approximately 50% of the data available. It is not clear how the missing data has impacted the presentation of the safety and effectiveness endpoints at time-points later than 24 months. The primary endpoint was a 24-month endpoint**

## Clinical Study Results

## Safety: For Chronic Arm of Study

(From 510(k), Appendices G, K, L, M, and N)

The following safety data was provided for the patients in the chronic arm of the IDE study.

Table 7: Safety Data – Chronic Study Arm

| | IN 510(K) | RESULTS IN 510(K) | |
|---|---|---|---|
| | | CS | CONTROL |
| **SAFETY** | | | |
| o Serum (Blood Analysis – ELISA – Antibody) | Appendix G | Not statistically significantly different | |
| o Adverse Events (AE) | | | |
| o Serious AE<br>▪ (total events/total patients);<br>▪ (events per patient/total patients) | Appendix K | 37/87 (43%);<br>21/87 (24%) | 23/69 (33%);<br>14/69 (20%) |
| o Serious Device Related AE<br>▪ (total events/total patients);<br>▪ (events per patient/total patients) | Appendix L | 14/87 (16%);<br>8/87 (9.2%) | 2/69 (3%);<br>1/69 (1.4%) |
| o Non Serious Device Related AE<br>▪ (total events/total patients);<br>▪ (events per patient/total patients) | Appendix L | 51/87 (59%);<br>29/87 (33%) | 5/69 (7%);<br>3/69 (4.3%) |
| o Non-serious AE<br>▪ (total events/total patients);<br>▪ (events per patient/total patients) | Appendix M | 241/87 (277%);<br>71/87 (82%) | 201/69 (291%);<br>49/69 (71%) |
| o All AE<br>▪ (total events/total patients);<br>▪ (events per patient/total patients) | Appendix N | 295/87 (339%);<br>74/87 (85%) | 240/69 (348%);<br>54/69 (78%) |

Note: In the table above, some of the Adverse Events were categorized as "device related" for the partial meniscectomy control by the sponsor although these patients did not receive a device.

**Summary of Adverse Events:**

(Summarized from information in 510(k), Appendices K, L, M, and N)

The following types of Adverse Events from the chronic study arm were reported in the 510(k) and summarized in Table 8 below.

Table 8: Adverse Events – Chronic Study Arm

| | Serious AEs | | Serious Device Related AEs | | Non-Serious Device Related AEs | | Non-Serious AEs | |
|---|---|---|---|---|---|---|---|---|
| | CS | Control | CS | Control | CS | Control | CS | Control |
| Surgery Op knee: | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 3 |
| Tear medial meniscus: | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| Swelling/Effusion: | 4 | 2 | 3 | 0 | 9 | 1 | 23 | 12 |
| Inflammation of Bone: | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Instability: | 2 | 0 | 1 | 0 | 2 | 0 | 5 | 6 |
| Pain | 5 | 2 | 4 | 0 | 14 | 0 | 54 | 37 |
| Loose bodies | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 |
| Fever | 1 | 1 | 1 | 0 | 0 | 1 | 3 | 1 |
| Redness | 1 | 0 | 1 | 0 | 2 | 0 | 3 | 0 |
| Infection | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 |

| | **Serious AEs (cont.)** | | **Serious Device Related AEs (cont.)** | | **Non-Serious Device Related AEs (cont.)** | | **Non-Serious AEs (cont.)** | |
|---|---|---|---|---|---|---|---|---|
| Wound related | 1 | 0 | 0 | 0 | 1 | 1 | 2 | 2 |
| Cyst | 1 | 0 | 1 | 0 | 1 | 0 | 2 | 1 |
| DVT | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| Synovitis/bursitis | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| Trauma Op knee | 0 | 1 | 0 | 0 | 0 | 1 | 7 | 8 |
| General Medical | 16 | 13 | 0 | 1 | 2 | 0 | 57 | 71 |
| Death | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Contralateral knee problem | 0 | 2 | 0 | 0 | 0 | 0 | 10 | 15 |
| Saphenous Nerve Injury | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 0 |
| Squeaking/Creaking | 0 | 0 | 0 | 0 | 5 | 0 | 8 | 0 |
| Stiffness | 0 | 0 | 0 | 0 | 3 | 0 | 4 | 2 |
| Numbness | 0 | 0 | 0 | 0 | 1 | 0 | 5 | 1 |
| Patello-femoral complaints | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 3 |
| Locking/catching | 0 | 0 | 0 | 0 | 2 | 0 | 4 | 6 |
| Torn implant | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Other | 0 | 0 | 0 | 0 | 1 | 0 | 8 | 6 |
| Plica | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| Lateral meniscus tear | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 |
| Implant fraying | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Popping/clicking | 0 | 0 | 0 | 0 | 1 | 1 | 4 | 4 |
| Delayed Healing | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Blister op site | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Impaired/decreased function | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Nausea/vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Tendonitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Splitting suture | 0 | 0 | 0 | 0 | 0 | 0 | 1 | |
| Reduced ROM | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 |
| OA/worsening OA op knee | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 |
| Immune reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Notch regrowth | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Painful hardware | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Tear at implant meniscus interface | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Unknown event | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Pain/stiffness | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Reinjury ACL | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Trauma/fall/MVA | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Sprained Knee | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| MCL tear/sprain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | | | | | | | | |
| Total | **37** | **25** | **14** | **2** | **51** | **5** | **241** | **201** |

The following "serious or clinically relevant" complications summary was provided in the JBJS Article (From 510(k), Appendix A (Tab E in Panel Pack)).

Table 9: Serious or Clinically Relevant Complications in the Study Knee

**TABLE IV Serious or Clinically Relevant Complications in the Study Knee***

| Complication | Collagen Meniscus Implant *(no.)* | Control *(no.)* |
|---|---|---|
| Pain | 2 | 7 |
| Swelling/effusion/redness | 4 | 1 |
| Instability | 1 | 0 |
| Infection/fever | 1 | 1 |
| Nerve injury/numbness | 1 | 1 |
| Deep vein thrombosis | 1 | 1 |
| Wound-related/other | 1 | 0 |
| Patellofemoral symptoms | 1 | 0 |
| Total | 12 | 11 |

*These complications were classified as serious or clinically relevant by the surgeon-investigator and required some form of treatment.

The presentation of "serious or clinically relevant complications" in the JBJS article provided in the 510(k), Appendix A (Tab E in Panel Pack) appears to provide different results/analysis compared to the presentation of "serious" and "serious device related" adverse events in Appendix K and L of the 510(k). Both summaries are presented for completeness.

**Explants:**
(From 510(k), Appendix O)

As summarized in Table 10 below, the sponsor identified 6 device explants in 5 CS patients enrolled in the chronic study arm, Protocol 9602.

Table 10: Explants – Chronic Study Arm

| Patient | Protocol | Time Post-Op | Reason for Explant |
|---|---|---|---|
| | | 3 weeks | Patient developed an infection that physician felt was seeded from the medial incision that was slow to close. |
| | | 3 months | Patient reported persistent pain and swelling after CS placement. Explant performed due to mechanical failure of the implant. Operative report indicated CS failed at midpole and was fragmented and resorbed. |
| | | 4 Months | At the 4 month time point – explant performed due to excessive pain. Removal classified as due to mechanical failure of the implant. Pathologist noted: "Meniscal tissue is not present." |
| | | 4 months | Used treadmill leading to mechanical failure of the implant. |
| | | 6 months | Implant failure and explanted due to severe pain/swelling |
| | | 6 months | Patient fell prior to the six week post-operative time point. Patient complained of increased pain and laxity of the joint after the fall. Patient underwent explant of the CS secondary due? to mechanical failure and PCL shrinkage procedure. |

## Effectiveness Endpoints: For Chronic Arm of Study Only

**VAS Pain Score, Lysholm Score (pain and function), Patient Self-Assessment:**
(From 510(k), Appendix A (Tab E in Panel Pack))

Table 11 captures the "clinical outcomes data at time of most recent follow-up" as outlined in Table III of the JBJS Article.

Table 11: Clinical Outcomes Data at Time of Most Recent Follow-up

TABLE III Clinical Outcomes Data at Time of Most Recent Follow-up

| | Acute Group | | Chronic Group | |
|---|---|---|---|---|
| | Collagen Meniscus Implant (N = 75) | Control (N = 82) | Collagen Meniscus Implant (N = 82) | Control (N = 69) |
| Visual analog scale pain score *(points)* | | | | |
| Mean change from preop. score | 16 | 21 | 18 | 18 |
| Mean score at time of last follow-up | 5 | 6 | 19 | 21 |
| Lysholm score *(points)* | | | | |
| Mean change from preop. score | 26 | 28 | 16 | 22 |
| Mean score at time of last follow-up | 90 | 87 | 79 | 78 |
| Patient self-assessment score *(points)* | | | | |
| Mean change from preop. score | 0.9 | 1.1 | 0.7 | 0.9 |
| Mean score at time of last follow-up | 1.6 | 1.6 | 1.9 | 2.1 |

**Evaluation of Chondral Surfaces**
(From 510(k), p.34)
Table 12 identifies the mean Outerbridge Scores for the patients in the chronic study arm.

Table 12: Mean Outerbridge Scores – Chronic Study Arm

| | | |
|---|---|---|
| Mean Outerbridge Scores:<br>(0-4 with 4 the most extensive damage to the articular surface) | CS:<br>Pre-op=1.5;<br>1-year re-look=1.3 | Control:<br>Pre-op=1.7;<br>No re-look performed |

On pp. 26-30 of the 510(k), the sponsor showed that the ReGen CS subjects in the chronic study group showed decreased pain, increased Lysholm knee function score, patient satisfaction, increased Tegner activity level, patient self-assessment, and tissue gain as compared to pre-operative or initial values but no significant differences compared to control.

**Amount of Meniscal Tissue at Baseline and at Re-Look Arthroscopy**
(From 510(k), Appendix A (Tab E in Panel Pack))
As denoted in Table 13 below, in Table II in the JBJS article, the sponsor provided their accounting of "meniscus remaining and defect filling" data.

Table 13: Menicus Remaining and Defect Filling - Acute and Chronic Study Arms

TABLE II Meniscus Remaining and Defect Filling

| | Acute Group | | Chronic Group | |
|---|---|---|---|---|
| | Collagen Meniscus Implant | Control | Collagen Meniscus Implant | Control |
| Percent meniscus remaining | | | | |
| No. studied | 75 | 82 | 85 | 69 |
| Mean and stand. dev. (%) | 51 ± 20 | 59 ± 19 | 37 ± 20 | 40 ± 22 |
| Percent defect filled | | | | |
| No. studied | 65 | | 76 | |
| Mean and stand. dev.* (%) | 45 ± 28 | 0† | 58 ± 27 | 0† |
| Percent tissue surface area | | | | |
| No. studied | 65 | 82 | 76 | 69 |
| Mean and stand. dev.* (%) | 73 ± 17 | 59 ± 19 | 73 ± 20 | 40 ± 22 |

*There was a significant difference ($p < 0.05$) between the treatment groups within the study arms. †The zero value was assumed on the basis of values for historical controls.

Note: Regarding "percent tissue surface area" for the control, these values were assumed to be equal to the baseline "percent meniscus remaining."

**Baseline Operative Information**
(From 510(k), p.32, Appendix I; Attachment C, Appendix B)
Baseline operative data indicate that for the ReGen CS patients, an average of 63% of meniscus tissue was removed during the partial meniscectomy in the chronic group leaving an average of 37% of their original meniscus volume remaining. For the control patients, an average of 60% of meniscus tissue was removed during the partial meniscectomy in the chronic group leaving 40% of their original meniscus volume remaining.

From the results presented, more native meniscus was removed in the CS device group, on average, as compared to the partial meniscectomy control group. Although the average amount of native meniscus remaining was 37%, 43% (37/87) of the tears in the treatment group had 20% or less of the native meniscus remaining, implying that there was 10% of the meniscus anteriorly and 10% posteriorly. Hence, in more than 40% of the cases, 80% or more of the meniscus was removed from patients in the CS group.

**Re-Look Arthroscopy Results**
(From 510(k), p.32-33)
The following information from the re-look arthroscopy was provided for the ReGen CS patients in the chronic study arm.

Of the 85 patients receiving the CS in the chronic study arm, 76 (89%) underwent second-look arthroscopy at approximately 12 months for the purpose of evaluating the status of the ReGen CS and the surrounding joint space. The remaining 9 patients (11%) were either lost to follow-up, explanted, or refused to allow the additional surgery. At the one-year relook, the surgeon documented that the CS patient had, on average, a total meniscus tissue volume of 73%.

(From 510(k), Attachment B, Appendix S)
The following additional information from the re-look arthroscopy including in Tables 14-18 was provided for the CS patients in the combined acute and chronic study arms.

Of the 162 patients receiving the CS device (both acute and chronic cases), 141 (87%) underwent second-look arthroscopy at approximately 12 months for the purpose of evaluating the status of the ReGen CS and the surrounding joint space. The remaining 21 patients (13%) were either lost to follow-up, explanted, or refused to allow the additional surgery. As presented in Table 14 below, the sponsor stated that during the re-look it was confirmed that the tissue in the area of defect where the CS was placed remained firmly attached to the host meniscus rim in 84% of the cases, with no evidence of migration or displacement. In the remaining 16% of cases, the device was not firmly attached to the host rim.

**Table 14: How Many Implant/New Tissue Complex Remaining Firmly Attached to Host Rim - Observed at Arthroscopic Re-look**

| Observation | Number of Cases | % of Total Cases with Relook (n=141) |
|---|---|---|
| Firmly attached | 119 | 84% |
| Not firmly attached | 22 | 16% |
| No response | 0 | 0% |
| Total | 141 | 100% |

As presented in Table 15 below, of the 141 CS patients who underwent the re-look arthroscopy procedure, 82% of those patients showed improvement or no change in the rating of the chondral surfaces in the involved compartment of the knee joint one year after implantation of the CS. In contrast, 18% showed worsening of their degenerative articular cartilage disease.

**Table 15: Changes in Involved Knee Compartment Noted in CS Cases at Re-look Procedure Compartment Observation Number of Cases % of Total Cases with Re-look**

| Compartment Observation | Number of Cases | % of Total Cases with Relook (n=141) |
|---|---|---|
| Compartment Unchanged | 83 | 59% |
| Compartment Improved | 33 | 23% |
| Compartment Worsened | 25 | 18% |
| No response | 0 | 0% |
| Total | 141 | 100% |

(From 510(k), Attachment B, Appendix T and U)
Of the 136 biopsies in 135 patients (one patient had biopsies at two timepoints), all underwent histological evaluation; however, only 81 (60% (81/136)) biopsies (from 80 patients) were confirmed to contain residual CS, whereas 40% did not. Of these 81 biopsy specimens, slight to marked cellular ingrowth was evident in 94% of 66 evaluable cases, and extracellular matrix organization at some level was seen in 97% of the evaluable cases. Inflammatory response was graded as minimal to none in 95% of evaluable specimens.

Histologic examination of the biopsied samples showed evidence of infiltration of the pores within the ReGen CS device with maturing connective tissue, best described as a fibrous connective tissue differentiating toward a fibrochondrocytic tissue. Most evaluable cases demonstrated some degree of CS assimilation into a newly developing fibrochondrocytic matrix. This assimilation was varied in type. According to the sponsor, most often the ReGen 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 ReGen CS.

The following tables provide data from the combined acute and chronic groups because this information was not provided separately, although only clearance of the chronic indication is being sought in the 510(k) submission.

Table 16:

**Cellular Ingrowth Observed in Cases with CMI Material in Biopsy Samples**

| Amount of Cellular Ingrowth | Number of Cases | Percentage |
|---|---|---|
| None | 4 | 6% |
| Slight | 19 | 29% |
| Marked | 13 | 20% |
| Marked with Cells Resembling Fibrochondrocytes | 30 | 45% |
| Total | 66* | 100% |

* 15 samples did not contain enough material to perform an evaluation of cellular ingrowth

Table 17:

**Extracellular Matrix Organization Observed in Cases with CMI Material in Biopsy Samples**

| Extracellular Matrix Organization | Number of Cases | Percentage |
|---|---|---|
| No matrix organization | 2 | 3% |
| Random organization | 17 | 26.6% |
| Sections of continuous chondroid matrix | 1 | 1.6% |
| Fibrocartilagenous tissue | 44 | 68.8% |
| Total | 64* | 100% |

*17 samples did not contain enough material to evaluate the extracellular matrix organization

Table 18:

**Inflammatory Response to CMI Observed in All Patients with Histology**

| Inflammatory Response | Number of Cases | Percentage |
|---|---|---|
| Minimal to None | 124 | 94.7% |
| Mild | 1 | 0.8% |
| Moderate | 1 | 0.8% |
| Severe | 2 | 1.5% |
| Missing | 3 | 2.2% |

Assuming that there is no regrowth of tissue after a partial meniscectomy procedure, the data has demonstrated that the ReGen CS device does act as a scaffold to allow for tissue ingrowth with minimal inflammatory response. Also, the majority of CS devices were firmly attached to the host rim. Of note was the fact that 16% of evaluated CS devices were not firmly attached to the host rim and 18% of knee compartments were determined to be worse than during the operative procedure at the time of the re-look arthroscopic procedure.

**Radiographic Evaluation – Changes from Pre-Op**
(From 510(k), Attachment C pp.24-25)

Results of the radiographic evaluation based on Fairbank parameters and osteophyte formation are shown in Table 19 below. Table 19 summarizes the changes in radiographic appearance from baseline for both the acute and chronic study arms. Although the subject 510(k) is only intended to support the chronic patient population, this data was not presented separately in the 510(k) submission. The IDE protocol defined osteophyte formation and changes in the Fairbank parameters of ridge formation, femoral condyle flattening and joint space narrowing as the appropriate measures to assess progression of degenerative changes in the knee. Assessments were made at 12 and 24 months.

The sponsor stated that "the value of the radiographic outcomes data is limited by several factors, including compliance with the submission of radiographs at all required time points, the varying quality of the radiographs from site to site and between time points, and the ability of all sites to provide long-standing views. The combination of these factors and the inability to provide a high level of control over the radiographic protocol prevents a side by side comparison to measure changes in joint space narrowing."

**Table 19: Radiographic Evaluation -Change from Pre-op for Combined Results from Acute and Chronic Study Arms**

| Parameter Evaluated | 12 Months | | | 24 Months | | |
|---|---|---|---|---|---|---|
| | CS | Control | p-value | CS | Control | p-value |
| Osteophyte formation worsens >= 1 grade | 15/64 (23%) | 16/66 (24%) | 1.00 | 19/72 (26%) | 26/78 (33%) | 0.38 |
| Fairbank – Ridge Formation worsens >= 1 grade | 5/64 (8%) | 1/64 (2%) | 0.21 | 10/71 (14%) | 7/73 (10%) | 0.45 |
| Fairbank – Flattening of femoral condyle worsens >= 1 grade | 16/64 (25%) | 20/64 (31%) | 0.56 | 25/71 (35%) | 25/73 (34%) | 1.00 |
| Fairbank – Joint space narrowing worsens >= 1 grade | 21/64 (33%) | 20/64 (31%) | 1.00 | 30/71 (42%) | 23/73 (32%) | 0.23 |

This information was not provided for the chronic patients alone. The percentage of patients (Combining Acute and Chronic groups) experiencing a change of one or more grades in osteophyte formation or Fairbank changes was not statistically significant between the CS and control at 12 or 24 months.

**Tegner Score/ Tegner Index**
(From 510(k), pp.36-37, Appendix A (Tab E in Panel Pack))
The sponsor stated that "Chronic patients who received the CS regained more of their lost activity level (42% for CS patients) than did the controls (29% for controls; p=0.02)." According to the JBJS journal article provided in the 510(k), Appendix A (Rodkey, JBJS) (Tab E in Panel Pack), this p-value of 0.02 was derived from a comparison of the Tegner Index between the two groups. The Tegner index was calculated from three Tegner activity scores (whose scale ranges from 0 to 10): pre-injury (based on patient recall of pre-injury status), pre-operative and post-operative.

The following additional information concerning mean scores (information on a per patient basis has not been provided) is provided in Table 20 to help evaluate the Tegner Activity Score.

Table 20: Activity Level (Tegner) – Chronic study arm:
TEGNER ACTIVITY LEVEL - MEAN SCORES FOR PROTOCOL 9602

| | N | Pre-Injury | N | Pre-operative | N | 12 Month | N | 24 Month |
|---|---|---|---|---|---|---|---|---|
| CS | 83 | 6.5 | 82 | 2.9 | 60 | 4.1 | 45 | 5.0 |
| CONTROL | 68 | 6.6 | 67 | 3.0 | 44 | 4.1 | 36 | 4.4 |

According to the approved IDE protocol, Tegner Index was not a pre-specified primary or secondary effectiveness endpoint. The related outcome "Tegner activity level" was actually collected as one of the thirteen "other information" (secondary) endpoints in addition to the primary effectiveness endpoints (i.e., pain, swelling, Lysholm knee function score, patient self assessment, and status of the implant using arthroscopy, histopathology, and radiographs). According to the protocol, a patient would be considered as a success at 24 months if the Tegner activity score was at least one grade level higher than the pre-op activity level (unless this would require them to exceed their pre-injury level). The JBJS article did not provide a statistical analysis for the dichotomized Tegner activity level according to the study protocol.

The sponsor stated on p.29 of the 510(k), the "clinical significance of the Tegner index has not been reported in the literature." According to the literature reference, the Tegner activity scale was designed as a score of activity level to complement other functional scores (e.g. the Lysholm knee score) for patients with ligamentous injuries. It does not appear to take into account that individuals may be able to participate at a higher level of activity but consciously choose not to or that some people will participate at a higher level of activity but with limitations. Therefore, it may be necessary to take these possibilities into consideration when relying on such a measure to establish clinical benefit of the CS device (as an add-on therapy to partial meniscectomy) as compared to the partial meniscectomy control therapy alone.

**Re-Operations**
(From 510(k), Appendix A (Tab E in Panel Pack))
As denoted in Table 21 below, in Table V in the JBJS article, the sponsor provided their accounting of the "re-operations" data from the IDE study.

Table 21: Reoperations

TABLE V Re-operations

| | Acute Group | | Chronic Group | |
|---|---|---|---|---|
| | Collagen Meniscus Implant (N = 5) | Control (N = 5) | Collagen Meniscus Implant (N = 8) | Control (N = 15) |
| Primary presenting symptom | | | | |
| Pain | 2 | 4 | 5 | 11 |
| Swelling/effusion | 1 | 0 | 2 | 1 |
| Stiffness/decreased motion | 1 | 0 | 0 | 0 |
| Locking/catching/popping | 0 | 0 | 1 | 2 |
| Instability | 1 | 1 | 0 | 1 |
| Primary surgical procedure performed | | | | |
| Explant of collagen meniscus implant | 1 | 0 | 2 | 0 |
| Repeat partial meniscectomy | 0 | 3 | 1 | 3 |
| Allograft meniscus transplant | 0 | 0 | 0 | 1 |
| High tibial osteotomy | 0 | 0 | 1 | 1 |
| Joint débridement/synovectomy/loose body removal | 3 | 1 | 4 | 9 |
| Ligament stabilization | 1 | 1 | 0 | 1 |

In the JBJS article analysis of the re-operations in Appendix A and Appendix J of the 510(k), the following re-operations were not included within Table V:

- 5 re-operations in the partial meniscectomy (control) patients; and
- 17 re-operations in the CS device patients

The following reasons were given in the 510(k) for removing these re-operations from the final counts. They were either:

1. A re-operation on the same patient (n=4 in CS group, n=5 in control group),
2. A procedure performed during the 1-year arthroscopic re-look (n=10 in CS group), or
3. The sponsor stated that the re-operation was not related to the meniscus (n=3, evaluation of saphenous nerve, excision of neuroma, and infection/device removal).

**Complete Table of Re-Operation Data**
The Survivorship Analysis and Reoperations for the JBJS Article (Chronic CS and Control Patients – Protocol 9602), from 510(k) Appendix A, is provided in Tab I of the Panel Pack.

**Summary of Re-Operation Data:**
Table 22 below summarizes both the comparative number of procedures and patients noted in the categories below. Note that FDA traditionally includes "procedure related events" as "device related" since the procedure is directly applicable to the device implantation. This data was originally provided in the 510(k) Appendix A and Appendix J.

Table 22: Number of additional procedures following index procedure for Chronic Study Arm (Protocol 9602)

| | CS | | Control | |
|---|---|---|---|---|
| | # Procedures | # Patients | # Procedures | # Patients |
| **Included:**<br>• Reoperations related to meniscal pathology or symptoms | 15 | 14 | 11 | 11 |
| **Included:**<br>• Reoperations – procedure related | 3 | 3 | 0 | 0 |
| **Excluded:**<br>• Reoperations related to protocol procedure only (2nd look); and/or<br>• Reoperations not procedure or device related | 9 | 7^ | 9 | 6^ |
| **Total Reoperations Included** | **18** | **17** | **11** | **11** |
| **Total Reoperations** | **27** | **24** | **20** | **17** |

^ Some patients had repeat/multiple operations

In determining procedures that FDA considered should be reported in the Table 22 above, the following criteria, which are consistent with FDA's usual procedure in determining safety outcomes, were applied:

- In the case of the control, a conservative approach was used in that anything that could be considered a failure of meniscectomy was included. This approach generally represents a worst-case scenario for the control. It is difficult to determine from the limited narratives whether the progression of pain was due to meniscectomy failure or progression of the overall disease process of osteoarthritis.
- Those procedures that occurred in the CS device group solely due to the protocol second-look arthroscopy and that included no other additional procedures were not considered reportable/included as additional procedures.
- If during the second look procedure, additional procedures were performed and accompanying meniscal or medial symptoms/pain were noted, then, the patient/procedure was considered to have had an additional procedure or re-operation.
- All explants were considered as procedure or device related and counted as re-operations.
- Additional procedures to repair or revise (smooth edges or repair tears in device) were considered as inclusive if done at "relook" as they were more than just biopsy. This approach was meant to be is a conservative approach.
- Patients experiencing new trauma prior to additional intervention were not considered to be related to index procedure for control or treatment group unless implant was mentioned as revised or explanted.

**Details of Summary Chart:**
**Table 23 below captures the specifics associated with the reoperations for the chronic arm patients in the IDE study.**

**Table 23: Reoperation procedures up to 60 months post index surgery Protocol 9602**

| | |
|---|---|
| **Included:**<br>• Reoperations related to meniscal pathology or symptoms | |

| | | |
|---|---|---|
| **Included**:<br>• Reoperations – procedure related<br><br>**Excluded**:<br>• Reoperations related to protocol procedure only (2nd look); and/or<br>• Reoperations not procedure or device related | | |
| **Total Procedures** | **27** | **20** |

**Note: (X2) and (X3) means patient had multiple re-operations and is included in category 2 or 3 times, respectively.**

**or CS Patients - Included**

**continued pain in index knee at re-look**
**explant**
**explant**
**explant due to septic joint at wound**
**explant - Protocol violation but this is a safety concern and should be considered per ITT analysis**
**explants - Protocol violation but this is a safety concern and should be considered per ITT analysis**

**CS Patients Excluded with Re-Operations Not Procedure or Device Related**

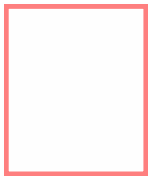
**lateral meniscectomy indeterminate as to cause**
**ACL repair**
**intervention following new trauma and continued pain**
**pes anserinus tendon release**
**lateral meniscus shaving**
**second & third procedure following new trauma**
**debridement of ACL graft and patellar chondroplasty**
**conservative classification as CS implant was revised this case is +/- for the implant but should at minimum be considered procedure related per conservative method detailed above**

*****Note for Control Patients - Included**

**High tibial osteotomy may be considered "related to failed meniscectomy as another method to treat medial arthritis but may not be related to meniscal pathology at all. For conservative purposes will include as a failure to treat pain**

******Notes for Control Patients Excluded with Re-Operations Not Procedure or Device Related**

**intervention following new trauma**
**second intervention following new trauma**
**third intervention following new trauma (>60 month timepoint)**
**intervention following new trauma**



**painful hardware**
**removal of painful hardware**
**second intervention following re-injury**
**third intervention following new trauma**
**fourth intervention for meniscal transplant (uncertain as to whether due to workman's compensation injury or prior condition)**

**Clinical Data Analysis Summary**

In your review of the clinical data, we would like you to consider the following issues in assessing whether use of the CS device, for the indication described above, affects the safety and effectiveness of the device as compared to the predicate devices.

- The JBJS article indicates that there was an improvement in the Tegner Index; however, it is unclear how this endpoint should be interpreted given that there was no prespecified hypothesis and, from our understanding of the literature, that there is no defined "clinical significance" for the Tegner Score when used in isolation as the Tegner Score is meant to '...complement other functional scores (e.g., the Lysholm knee score) for patients with ligamentous injuries.'

- Reoperation Analysis - Please note that within the published JBJS article the CS group showed a statistically significant advantage with respect to reoperation rate. The sponsor has excluded any patient from the reoperations rate if they were scheduled for a re-look (second look) arthroscopy and had an ancillary/additional procedure(s) performed. It should be noted that 1-year relook (second look) arthroscopy was required for the CS patients whereas it was not a requirement for the meniscectomy patients per the IDE protocol. FDA performed an independent analysis of the reoperations to determine whether or not we concurred with the exclusion of the subjects as was done during the JBJS analysis. From our analysis, we believe that there are several ways to determine the appropriateness of inclusion and exclusion of reoperations for the CS and control subjects. While the number of re-operations in FDA's analysis of the CS group exceeds that of the control (partial meniscectomy group), this number is considered to be a conservative approach for both groups. The procedures performed during the re-look appear to confound the interpretation of the re-operation data between the two groups.