



# New and Emerging Techniques - Surgical

Horizon Scanning Report

## Collagen Meniscal Implants

July 2004



**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**

New and Emerging Techniques - Surgical  
Horizon scanning reports are for information  
only



**Royal Australasian  
College of Surgeons**

Online ISBN: 1-74186-102-0

Publications Approval Number: 3927

© Commonwealth of Australia [2004]

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the *Copyright Act 1968*, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney-General's Department, Robert Garran Offices, National Circuit, Barton ACT 2600 or posted at <http://www.ag.gov.au/cca>

## Table of Contents

---

Introduction.....	1
Background.....	1
Background to the Condition.....	1
Description of the Technology.....	2
Treatment Alternatives.....	3
Existing Comparators.....	3
Clinical Outcomes.....	4
Effectiveness.....	4
Safety.....	5
Potential Cost Impact.....	6
Cost Analysis.....	6
Ethical Considerations.....	6
Informed Consent.....	6
Access Issues.....	6
Training and Accreditation.....	6
Training.....	6
Clinical Guidelines.....	7
Limitations of the Assessment.....	7
Search Strategy Used for Briefing.....	7
Availability and Level of Evidence.....	8
Sources of Further Information.....	8
Impact Summary.....	9
Conclusions.....	9
References.....	9
Appendix A: Table of Key Efficacy and Safety Findings – Case Series Studies.....	11



# Introduction

---

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) in conjunction with the Royal Australasian College of Surgeons has undertaken a Horizon Scanning Report to provide advice on the state of play of the introduction and use of collagen meniscal implants.

ReGen Biologics Inc. provide a collagen meniscal implant for meniscal repair and regeneration. The procedure is nearly established in Australia.

This Horizon Scanning report provides an assessment of the current state of development of collagen meniscal implants, present use, the potential future application of the technology, and likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with collagen meniscal implants.

## Background

---

### Background to the Condition

The knee joint is one of the most complex and most heavily loaded joints of the body. Up to five times body weight is acting on each knee during walking and running, and up to ten times during jumping or falling (Messner and Goa 1998).

Each knee joint contains two menisci, lateral (outer) and medial (inner). These crescent-shaped structures are attached to the tibial plateau and occupy the space between the femur (thigh bone) and the tibia (shin bone) (Messner and Goa 1998).

The menisci play many important roles, including friction reduction, load transmission, joint lubrication, shock absorption, and joint stability (Rodkey and Steadman 2003). Meniscal injuries most commonly occur through rotational movements of the loaded knee joint, for example, during rapid changes of direction or falls. Damage or tears to the menisci frequently causes pain and considerable restriction of movement.

Simple tears in the tissue can be sutured, however many meniscal injuries are so severe that suturing is not possible (Rodkey *et al.* 1999). For these injuries, the current treatment of choice involves either partial or total meniscectomy (removal of the meniscus). However, the loss of meniscal tissue may frequently lead to various derangements of the knee including osteoarthritis and irreversible joint damage, such that patients may require an artificial knee joint in the long term (Stone *et al.* 1997; Messner and Goa 1998; Rodkey *et al.* 1999).



## Description of the Technology

### *The Procedure*

Collagen scaffolds are implanted into the knee to support the regeneration of new meniscal tissue (Stone *et al.* 1997). These resorbable implants have been moulded to approximate the shape of a normal human knee meniscus and are made from purified type I collagen fibres isolated from bovine Achilles tendons (Rodkey and Steadman 2003).

The implants are placed using an arthroscopic surgical procedure. In what is essentially a meniscectomy, the damaged meniscal tissue is removed by debridement until healthy vascularised tissue is reached. In those cases where debridement does not reach vascularised tissue, a bleeding bed is created by perforating the rim of the meniscus. An implant of suitable dimension is then sutured into place on the meniscal rim (Stone *et al.* 1997; Rodkey *et al.* 1999).

### *Intended Purpose*

The collagen meniscal implant has been developed in an attempt to restore knee function in patients with irreparably damaged or surgically removed meniscal tissue with the ultimate goal of preventing or minimising progressive joint disease (Stone *et al.* 1997; Rodkey *et al.* 1999). The collagen implants are also intended to help regenerate new meniscal tissue, rather than simply replace the meniscus as would be done in a meniscal transplant (Rodkey *et al.* 1999).

### **Indications**

The current indications for collagen meniscal implantation include irreparable injury or partial loss of menisci in a normally aligned knee (Stone *et al.* 1997; Rodkey *et al.* 1999). The involved knee should be ligamentously stable or able to be stabilised at the time of surgery.

Collagen meniscal implantation should not be performed in patients with full thickness meniscal defects, inflammatory or systemic disease (e.g. gout), known collagen allergies or autoimmune disease (Rodkey *et al.* 1999).

### *Clinical Need and Burden of Disease*

In the USA in 2002, approximately 780,000 partial meniscectomies were performed (Bisbee 2003). Dr. Bisbee estimates about one-third of these would be eligible for medial collagen meniscal implantation and potential demand is likely to grow by 5 to 10% a year. In 2002/2003, 462 arthroscopic meniscectomies of the knee (with repair) were performed in the public health system in New Zealand (NZHIS 2004). Assuming there is a similar burden of disease and demand in Australia, about 17,000 patients a year could be eligible for medial collagen meniscal implantation.



Partial or total meniscectomy without some form of meniscal replacement may eventually require total knee joint replacement. A Canadian evaluation of 14,391 knee debridement procedures found that almost 10% of patients required total knee replacement within one year of debridement (Wai *et al.* 2002). Collagen meniscal implantation may be able to prevent a proportion of knee replacements.

### ***Stage of Development***

Collagen meniscal implants are manufactured by ReGen Biologics, Inc., New Jersey, USA. (ReGen Biologics, <http://www.regenbio.com>). No other meniscus implants are currently available or are being tested in clinical trials (Bisbee 2003).

The implants have been approved for use in Australia, Europe, Chile and are selectively available in Canada. They are not currently approved for use in the USA but are being used within a multicentre RCT (see *Sources of Further Information*).

Current plans are to submit an application to the FDA for its consideration at the end of 2004. The process of review by the FDA is uncertain, but ReGen expects that the FDA will issue its ruling in 2005

(<http://www.regenbio.com/patients/international/clinical.msp>).

The collagen meniscal implant is distributed by the Centerpulse Orthopaedics unit of Zimmer Holdings, Inc.

Only three published studies relating to the use of collagen meniscal implants in humans were identified. However diffusion of this technology may increase once the results of the FDA trials are released.

## **Treatment Alternatives**

---

### **Existing Comparators**

Small, unstable tears in the periphery of the meniscus may be sutured (meniscus repair). However treatment of severe meniscal injury usually involves excision of the damaged tissue, either partly or completely (partial or complete meniscectomy). In complete meniscectomy of the knee, the entire meniscus is removed, whereas in partial meniscectomy, only the torn portion of the meniscus may be excised, leaving the remainder of the meniscus intact (Messner and Gao 1998).

Many different materials have been evaluated for prostheses to replace lost or damaged menisci, including artificial materials, autogenous tissue (graft tissue obtained from oneself) and allograft tissue (graft tissue obtained from another person, usually a cadaver donor) (Rodkey *et al.* 1999). [Transplantation using menisci from organ donors is reviewed in another ASERNIP-S Horizon Scanning Report, *Meniscal transplantation*; see [http://www.surgeons.org/asernip-s/net-s/information/meniscal\\_transplantation.htm](http://www.surgeons.org/asernip-s/net-s/information/meniscal_transplantation.htm)].



# Clinical Outcomes

---

## Effectiveness

### Knee function and activity

In two case series (Rodkey *et al.* 1999; 8 patients and Stone *et al.* 1997; 10 patients), knee function and activity improved after collagen meniscal implants.

In Rodkey *et al.* (1999), knee function at five to six years after collagen meniscal implantation was less than that reported for one and two years postoperatively but still improved compared to preoperative knee function (mean Lysholm score of 93.5 at two years and 88 at five to six years compared to mean 75.3 preoperatively). In the same study, Tegner knee activity scores continued to improve over the five to six year follow-up period. In Stone *et al.* (1997), knee scores (test not stated) also improved over three years following collagen meniscal implantation.

### Pain

In Rodkey *et al.* (1999), pain scores were better at one to two years postoperatively than preoperative scores, although the five to six year scores were slightly worse than those at one to two years (n=8; mean score 7 at one year, 2 at two years, 11 at five to six years; compared to mean 23 preoperatively – on a VAS of 100). One of the eight patients reported worse pain after the operation. Stone *et al.* (1997) reported improved pain scores three years postoperatively (n=9, mean 0.6 at three years compared to mean 2.2 preoperatively, with 3 representing severe pain). In Vaekenstedt *et al.* (1998), one out of five patients had persistent pain in the medial knee compartment one year postoperatively, and another patient had mild pain.

### Return to Activities

In Rodkey *et al.* (1999), all eight patients had returned to daily living activities at three months and were fully active by six months postoperatively and in Vaekenstedt *et al.* (1998), all five patients returned to daily activities from three months to one year postoperatively.

### Deficit Filling

In Rodkey *et al.* (1999), the mean preoperative meniscal deficit was 62% (range 35% to 85%) (n=8). At follow-up (either six months, n=6 or one year, n=2), mean meniscal deficit filling was 80% (range 70% to 90%) in 6/8 patients and 70% (range 40% to 100%) in 2/8 patients. At six years postoperative the mean deficit filling was 70% (range not stated) for all eight patients.

### Disease Progression

In Rodkey *et al.* (1999), postoperative radiographic analysis at one and two years did not indicate increased degenerative joint disease or further joint space narrowing.



## Relook Arthroscopy/Reoperation

Relook arthroscopy at either six months (n=6) or one year (n=2) indicated new tissue regeneration and the formation of a stable interface with host tissue in all eight patients (Rodkey *et al.* 1999). There was no sign of wear particles, synovitis, inflammation, or abrasion to the articular surface at six months (n=6) but one patient had some fragmentation to the posterior implant surface at one year (n=2). At five to six years follow-up, the tissue appeared stable and virtually unchanged from the initial relook in all eight patients.

In Stone *et al.* (1997), two patients (n=9, 22%) underwent reoperation following relook arthroscopy (one at 19 months postoperatively due to traumatic tear of the involved medial meniscus; one at 21 months postoperatively due to degeneration of lateral joint space and pain).

## Range of Motion

Vaeckenstedt *et al.* (1998) reported that all five patients had full range of knee motion (from 3 months to one year postoperatively).

## Safety

### Complications

In Rodkey *et al.* (1999), no serious or life-threatening complications were reported five to six years postoperatively (n=8). Excessive scar formation was present at nine months postoperatively in one patient, who underwent joint debridement. In Stone *et al.* (1997), mild transient effusions were reported in seven patients (70%; n=10), with symptoms resolving spontaneously within three to fourteen days postoperatively.

### Inflammatory/Immunological Reactions

In Rodkey *et al.* (1999), there were no inflammatory cells, evidence of immunological reaction or infection in any of the biopsy samples taken at either six months or one year (n=8). Similar results were reported in Stone *et al.* (1997), although no time period was stated (n=10). Rodkey *et al.* (1999) reported no 'significant' increase in antibodies to the collagen implants in any patient (up to one year postoperatively) while Stone *et al.* (1997) reported no formation of antibodies to the collagen implants in any patient (time period to testing not stated). Hypersensitivity to the implants was detected in three patients (n=8, 37.5%) at 12 weeks but not at 26 weeks or 52 weeks postoperatively (Rodkey *et al.* 1999). No hypersensitivity to the implants was reported (n=10) by Stone *et al.* (1997) (time period to testing not stated).



## Potential Cost Impact

---

### Cost Analysis

Costs of the collagen meniscal implants and the implantation procedure were not available.

As implantation is an additional step once meniscectomy has been performed, resources required for collagen meniscal implants will be greater than for knee meniscectomy.

If collagen meniscal implants prove to be effective in the treatment of meniscal injuries and/or prevention of degenerative joint disease, their use is likely to become common practice following meniscectomy.

The impact on the health system resulting from the cost of the implants will need to be assessed against the potential gain in reducing degenerative joint disease and the future need for total joint replacement.

## Ethical Considerations

---

### Informed Consent

Although collagen meniscal implants have been approved for sale within Australia, the use of the implants is essentially experimental and should be subject to written informed consent by patients.

### Access Issues

Since collagen meniscal implants are of bovine origin, there may be some cultural and religious issues to consider.

No significant access issues are anticipated.

## Training and Accreditation

---

### Training

Training and accreditation for the implantation of collagen meniscal implants should not be significantly different to that required for the use of other prostheses of the meniscus. However specific training guidelines are not available and may need to be developed if collagen meniscal implants are to become widely used in Australia.



## Clinical Guidelines

No clinical guidelines for the use of meniscal prostheses in Australia were located.

## Limitations of the Assessment

---

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of collagen meniscal implants, their present and potential use in the Australian public health system, and future implications for the use of this technology.

## Search Strategy Used for Briefing

Database	Platform	Searched/edition
MEDLINE	Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Medline	searched 4 March 2004
EMBASE	Ovid	searched 4 March 2004
Current Contents	Web of Science	searched 10 March 2004
Australasian Medical Index		Searched 5 March 2004
The Cochrane Library	<a href="http://www.update-software.com/clibng/cliblogon.htm">http://www.update-software.com/clibng/cliblogon.htm</a>	Issue 1 2004
NHS Centre for Research and Dissemination (UK)	<a href="http://144.32.228.3/scripts/WEBC.EXE/nhscred/newsearch">http://144.32.228.3/scripts/WEBC.EXE/nhscred/newsearch</a>	searched March 4 2004



NHS Health Technology Assessment (UK)	<a href="http://www.ncchta.org/">http://www.ncchta.org/</a>	searched 4 March 2004
National Research Register (UK)	<a href="http://www.doh.gov.uk/research/nrr.htm">http://www.doh.gov.uk/research/nrr.htm</a>	searched 4 March 2004
Google	<a href="http://www.google">http://www.google</a>	searched 9 March 2004
INAHTA	<a href="http://www.inahta.org/publication.html">http://www.inahta.org/publication.html</a>	searched 4 March 2004
Meta-Register of Controlled Trials	<a href="http://www.controlled-trials.com">www.controlled-trials.com</a>	searched 9 March 2004

Abbreviations: NHS, National Health Service; UK, United Kingdom

Search terms used included collagen; menisci\*; tibia\*; prothes\*; implant\*, knee

## Availability and Level of Evidence

There is very little evidence available in the literature on the efficacy and safety of collagen meniscal implants, with almost no evidence on long-term outcomes.

Specific issues include:

- Only three case series with small numbers (23 patients in total) were located
- It is likely that all the studies were funded by the manufacturer of collagen meniscal implants (ReGen Biologics, Inc). Dr Rodkey, the Chief Scientific Officer with ReGen, is an investigator on two of the three published studies.
- Patient characteristics (e.g. degree of morbidity) varied within and between studies
- Results of trials are pending (see below)

## Sources of Further Information

---

A national multicentre (14 centres) Food and Drug Administration approved randomised controlled trial of 288 patients comparing collagen meniscal implants and standard surgical meniscectomy has been conducted in the US. The trial was open to both male and female patients, aged between 18 to 60 years of age with irreparable medial meniscus cartilage tear. This study was funded by ReGen biologics, the manufacture of collagen meniscal implants, with the results yet to be published (Rodkey *et al.* 1999; <http://www.regenbio.com/products/cmi.msp>; and personal communication (3 February 2004) from Evelyne Hasler, PhD, Senior Product Manager Sports Medicine, Centerpulse Orthopedics Ltd.). Publication may be expected after the company makes its submission to the FDA (currently scheduled for 2004).

A multicentre European trial in Germany, Spain, Italy, Belgium, Austria, Switzerland and France comprising 68 patients was completed in 2000. This study was sponsored by Centerpulse Orthopaedics, the distributor of ReGen biologics collagen meniscal implants



outside the US. This study resulted in the European Conformité Européene Mark for collagen meniscal implants. However the results are yet to be published. A five year follow-up of patients is planned (<http://www.regenbio.com/products/cmi.msp>).

## Impact Summary

---

Of the order of 17 000 patients a year in Australia could be considered for collagen meniscal implants. This is likely to increase with an ageing population. Each procedure will incur greater costs than at present due to the cost of the implant and the additional procedures over and above those required for meniscectomy. However a proportion of future total knee replacements may be able to be avoided.

Collagen meniscal implants may allow people with knee injuries to remain active for longer by preventing degenerative changes which lead to osteoarthritis.

## Conclusions

---

Three small case series indicate that collagen meniscal implants can improve knee function and reduce pain, without resulting in a significant level of short-term complications and without inducing immunological reactions. However these results need to be validated by the recently completed RCTs. Reliable information on requirement for reoperation, length of rehabilitation and longer term sustainability and safety of the implants is not yet available.

If the initially promising results are confirmed, collagen meniscal implants are likely to be an option for patients with meniscal injuries not able to be repaired by suture.

## References

---

Bisbee GE. ReGen Biologics, Inc. (RGI). *The Wall Street Transcript* October 2003 ([www.twst.com](http://www.twst.com))

Messner K, Gao J. The menisci of the knee joint: anatomical and functional characteristics, and a rationale for clinical treatment. *Journal of Anatomy* 1998; 193: 161-178.

NZHIS. NMDS public hospital data. Wellington. New Zealand Health Information Service 2004.



- Rodkey WG, Steadman JR, Li S-T. A clinical study of collagen meniscus implants to restore the injured meniscus. *Clinical Orthopaedics and Related Research* 1999; 367S (Supplement); S281-292.
- Rodkey WG, Steadman JR. Collagen meniscus implants: multicenter clinical trial results and long term follow up [abstract #30]. *Arthroscopy: the Journal of Arthroscopic and Related Surgery* 2003; 19(6 Suppl 1): 16-17.
- Stone KR, Steadman JR, Rodkey WG, Li S-T. Regeneration of meniscal cartilage with use of a collagen scaffold: analysis of preliminary data. *Journal of Bone and Joint Surgery* 1997; 79(12): 1170-1177.
- Vaeckenstedt J, Wirz D, Herr A, Friederich NF. First experiences with a collagen meniscus implant [abstract]. *Annales de la Société Française d'Arthroscopie* 1998 [http://www.sofarthro.com/ANNALES/ANNALES\\_1998/CONFERENCES/vaeckenstedt](http://www.sofarthro.com/ANNALES/ANNALES_1998/CONFERENCES/vaeckenstedt) [accessed 30 September 2003]
- Wai EK, Kreder HJ, Williams JI. Arthroscopic debridement of the knee for osteoarthritis in patients fifty years of age or older: utilization and outcomes in the Province of Ontario. *Journal of Bone and Joint Surgery - American Volume* 2002; 84-A: 17-22.



## Appendix A: Table of Key Efficacy and Safety Findings - Case Series Studies

Study Details	Key Efficacy Findings	Key Safety Findings
<p><b>Rodkey <i>et al.</i> 1999, USA (includes Rodkey and Steadman 2003)</b></p> <p>8 patients (phase II trial)</p> <p><u>Follow-up:</u> 5 to 6 years postoperative (no loss to follow-up)</p> <p><u>Selection criteria:</u> patients with irreparable injury or previous loss of the medial meniscus between 18 to 50 years of age.</p> <p><i>Continued over...</i></p>	<p><u>Mean (range) Lysholm knee score:</u> (questionnaire to assess knee function)</p> <p>Preoperative 75.3 (range 52 to 97)</p> <p>1 year postoperative 89.4 (range 73 to 100) (7/8 (87.5%) improved score; 1/8 (12.5%) lower than preoperative score)</p> <p>2 years postoperative 93.5 (range 79 to 100) (8/8 (100%) improved score)</p> <p>5 to 6 years postoperative 88 (no range reported)</p> <p><u>Mean (range) Tegner activity score:</u></p> <p>Before injury 7.4 (range 5 to 10)</p> <p>Preoperative 3.5 (range 1 to 5)</p> <p>1 year postoperative 4.8 (range 2 to 7) (4/8 (50%) improved score; 4/8 unchanged from preoperative score)</p> <p>2 years postoperative 5.3 (range 3 to 8) (7/8 (87.5%) improved score; 1/8 (12.5%) lower than preoperative score)</p> <p>5 to 6 years postoperative 6 (no range reported)</p> <p><u>Patient self-assessment score (1 normal; 4 severely abnormal):</u></p> <p>Preoperative 2.4 (range 2 to 3)</p> <p>1 year postoperative 1.8 (range 1 to 2) (4/8 (50%) improved score; 4/8 unchanged from preoperative score - patients had assessed knees as nearly normal preoperatively)</p> <p>2 year post-operative 1.6 (range 1 to 2) (5/8 (62.5%); 3/8 (37.5%) unchanged from preoperative score - patients had assessed knees as nearly normal preoperatively)</p> <p>5 to 6 years postoperative 1.9 (range not stated)</p> <p>8/8 (100%) returned to daily activities by 3 months 8/8 (100%) returned to full activity at 6 months</p> <p><u>Mean pain during activities of daily living (VAS 100mm; 0 no pain and 100 being the worst pain):</u></p> <p>Preoperative 23</p> <p>1 year postoperative 7.1</p>	<p><u>Complications attributed to CMI:</u></p> <p>No serious or life-threatening complications related to CMI at 5-6 years postop</p> <p>1/8 (12.5%) excessive scar formation at 9 months after CMI - patient underwent relook arthroscopy and joint debridement</p> <p><u>Late complications:</u></p> <p>1/8 (12.5%) painful plica - 32 months relook arthroscopy showed no change &amp; patient refused biopsy</p> <p><u>Histology (biopsy specimens):</u></p> <p>No inflammatory cells or evidence of immunologic reaction or infection (6 month and 12 month biopsy samples)</p> <p><u>Immunology:</u></p> <p>No 'significant' increase in antibodies to collagen implant in any patient at 1, 6, 12, 26 weeks and 1 year postoperative</p> <p>Hypersensitivity to collagen implant was detected 3/8 (37.5%) patients at 12 weeks but not at 26 and 52 weeks postop</p>



	<p>2 years postoperative 1.8</p> <p><u>Pain continued:</u> (7/8 (87.5%) improved from preoperative (results remained stable or improved over 1 to 2 years postoperatively); 1/8 (12.5%) worse pain than preoperatively (pain improved over 1 to 2 years postoperatively without additional treatment) 5 to 6 years postoperative 11</p> <p><u>Mean (%) preoperative meniscus deficit:</u> 6/8 patients: 61% (range 35% to 85%) 2/8 patients: 65% (range 50% and 80%) (8/8 patients: 62%)</p> <p><u>Mean (%) postoperative meniscus deficit filling:</u> 6/8 patients 6 months: 80% (range 70% to 90%) 2/8 patients 1 year: 70% (100% and 40%) 77.5% (n=8) 5 to 6 years postoperative 70% (n=8)</p> <p><u>Radiographic analysis:</u> Comparison of pre and postoperative radiographs at 1 and 2 years revealed no increased degenerative joint disease or further joint space narrowing</p> <p><u>Sequential MRI scan:</u> 6 weeks postoperative - CMI and new tissue complex appeared to be smaller than expected for the normal medial meniscus &gt; 6 weeks postoperative - no apparent change or loss of new tissue</p> <p><u>Relook arthroscopy:</u> 6/8 patients 6 months postoperative - new tissue regeneration present (variable degree of maturity) and stable interface with host meniscus rim in all cases. No evidence of wear particles, synovitis, inflammation, or abrasion to the articular surface 2/8 patients 1 year postoperative - new tissue regeneration present and stable interface with host meniscus rim in both patients but 1/2 patients had some fragmentation of the posterior horn Tissue appeared stable 5 to 6 years postoperative in all patients</p>	
--	--	--

Abbreviations: CMI, collagen meniscal implant; MRI, magnetic resonance imaging; VAS, visual analogue scale



## Appendix A: Table of Key Efficacy and Safety Findings - Case Series Studies

Study Details	Key Efficacy Findings	Key Safety Findings
<p><b>Stone <i>et al.</i> 1997, USA</b></p> <p>10 patients (phase I trial)</p> <p><u>Follow-up:</u> 36 months (1/10 loss to follow-up at 3 months)</p> <p><u>Selection criteria:</u> patients with an irreparable tear of meniscal cartilage or major loss of meniscal cartilage in a stable or stabilised knee. Patients were excluded if they had previous treatment with collagen or an allergy to collagen, a concomitant injury of the contralateral knee, inflammatory arthritis, or severe degenerative osteoarthritis. Patients were not excluded for having had previous knee surgery.</p> <p><i>Continued over...</i></p>	<p><u>Relook and biopsy:</u>            3/9 at 3 months postoperative            6/9 at 6 months postoperative            2/9 patients underwent reoperation (1 at 19 months postoperative due to traumatic tear of the involved medial meniscus; 1 at 21 months postoperative due to degeneration of lateral joint space and pain)</p> <p><u>Mean activity score (1 strenuous activity; 5 inability to perform sports activity):</u>            Before injury 1.5 (time period not stated)            Preoperative 3.0            6 months postoperative 2.4            12 months postoperative 2.2            24 months postoperative 2.0            36 months postoperative 1.9</p> <p><u>Mean pain score (1 no pain; 3 severe pain):</u>            Preoperative 2.2            36 months postoperative 0.6</p> <p><u>Mean knee rating:</u> (1 normal knee; 3 abnormal knee)            12 months postoperative 3.0            24 months postoperative 2.0            36 months postoperative 1.4</p> <p><u>Mean score one-leg-hop test:</u>            6 months postoperative 90% of uninvolved limb            12 months postoperative 94% of uninvolved limb</p> <p>9/9 patients who completed the study stated improvement and that they would have the procedure again if the circumstances were similar            3 months postop - substantial amount of remaining collagen implant and some new collagen            6 months postoperative – increase in amount of new collagen (immature in appearance with few fibrocartilage sections)</p>	<p><u>Complications:</u>            7/10 patients (70%) mild, transient effusions (resolved spontaneously within 3 to 14 days postoperative)</p> <p><u>Note:</u> 1/10 patient lost to follow-up at 3 months postoperative due to pain caused by operation and personal reasons</p> <p><u>Histology (biopsy specimens):</u>            No inflammatory cells or evidence of immunologic reaction noted (time period not stated)</p> <p><u>Immunology (time period not stated):</u>            No formation of antibodies to collagen implant in any patient            No hypersensitivity to collagen implant detected</p>



	<p><u>Radiographic analysis:</u> 36 months postoperative – no major change in joint space height compared with preoperative joint space height</p> <p><u>Sequential MRI scan (3, 6, 12 and 36 months):</u> Evidence of ongoing ingrowth, regeneration overtime Joint fluid in all patients with physiological limits Interface between host meniscal rim and implant-regenerated tissue complex less distinct with time</p>	
--	---	--



## Appendix A: Table of Key Efficacy and Safety Findings - Case Series Studies

Study Details	Key Efficacy Findings	Key Safety Findings
<p><b>Vaeckenstedt <i>et al.</i> 1998, Switzerland</b></p> <p>5 patients</p> <p><u>Follow-up:</u> up to 12 months</p> <p><u>Selection criteria:</u> patients less than 50 years of age with meniscal tear unsuitable of suturing in a stable or stabilised knee and no relevant cartilage damage.</p>	<p><u>Full range of motion:</u> 3 months 1/1 6 months 2/2 12 months 2/2</p> <p><u>Patient outcome:</u> 1/5 (20%) no complaints at 3 months 1/5 (20%) persistent pain in medial knee compartment at 12 months 2/5 (40%) returned to daily activities with mild pain in medial knee compartment 1/5 (20%) fully active but with severe pain in medial knee compartment</p>	<p>None reported</p>