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Successful Treatment of Painful Irreparable Partial Meniscal Defects With a Polyurethane Scaffold

Two-Year Safety and Clinical Outcomes

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Background: A novel, biodegradable, polyurethane scaffold was designed to fulfill an unmet clinical need in the treatment of patients with painful irreparable partial meniscal defects.

Hypothesis: The use of an acellular polyurethane scaffold for new tissue generation in irreparable partial meniscal defects provides both pain relief and improved functionality.

Study Design: Case series; Level of evidence, 4.

Methods: Fifty-two patients with irreparable partial meniscal defects (34 medial and 18 lateral, 88% with 1-3 previous surgeries on the index meniscus) were implanted with a polyurethane scaffold in a prospective, single-arm, multicenter, proof-of-principle study. Safety was assessed by the rate of scaffold-related serious adverse events (SAEs) and the International Cartilage Repair Society articular cartilage scoring system comparing magnetic resonance imaging (MRI) at 24 months to MRI at baseline (1 week). Kaplan-Meier time to treatment failure distributions were performed. Clinical outcomes were measured comparing visual analog scale, International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Score (KOOS), and Lysholm scores at 24 months from baseline (entry into study).

Results: Clinically and statistically significant improvements ($P < .0001$) compared with baseline were reported in all clinical outcome scores (baseline/24 months): visual analog scale (45.7/20.3), International Knee Documentation Committee (45.4/70.1), KOOS symptoms (64.6/78.3), KOOS pain (57.5/78.6), KOOS activities of daily living (68.8/84.2), KOOS sports (30.5/59.0), KOOS quality of life (33.9/56.6), and Lysholm (60.1/80.7), demonstrating improvements in both pain and function. The incidence of treatment failure was 9 (17.3%) patients, of which 3 patients (8.8%) had medial meniscal defects and 6 patients (33.3%) had lateral meniscal defects. There were 9 SAEs requiring reoperation. Stable or improved International Cartilage Repair Society cartilage grades were observed in 92.5% of patients between baseline and 24 months.

Conclusion: At 2 years after implantation, safety and clinical outcome data from this study support the use of the polyurethane scaffold for the treatment of irreparable, painful, partial meniscal defects.

Keywords: Actifit; meniscus; biodegradable scaffold; meniscectomy; polyurethane scaffold; partial meniscectomy; meniscal defect; irreparable meniscal defect

The importance of the menisci for a healthy, functional knee joint has been established.[28,31] Meniscus injuries are common, with tears occurring twice as frequently in the medial as in the lateral meniscus.[3] Annually, more than 1 million surgical procedures involving the meniscus are performed in the United States and more than 400,000 in Europe.[43] Rather than repair, most of these procedures involve resection of the damaged tissue (partial meniscectomy), the result of which is an increase of peak contact stresses between the articulating surfaces of the tibia and femur. This increase in contact stresses is directly proportional to the amount of removed meniscal tissue,[1] with a total removal of the menisci resulting in a 200% to 300% peak contact stress increase.[25] Moreover, these changes in load transmission alter the biological milieu of the articular cartilage and underlying subchondral bone, and although favorable results have been reported in the short term, meniscal tissue resection has been shown over time to lead to articular cartilage degeneration in addition to

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pain and decreased functionality.[5,7,15,20,27] In particular, irreparable partial tears in the avascular zone present a problem, and techniques involving scaffolds and advanced repair techniques have been called for.[9,12] It is understood that migration and colonization with precursor cells and proliferation of blood vessels eventually leading to the formation of organized meniscal tissue require the presence of a scaffold.[16,27]

A synthetic biodegradable polyurethane scaffold indicated for the repair of painful, irreparable partial meniscal defects (Actifit, Orteq Limited, London, United Kingdom) has been shown to support generation of new meniscus-like tissue. When attached to the vascularized portion of the meniscus, the scaffold acts as a template for proliferation and organization of cells with extracellular matrix formation within the interconnected, highly porous scaffold. Importantly, the scaffold is not designed to provide mechanical support to the knee joint; rather, it is anticipated that such a function will be provided by the new tissue generated after scaffold implantation. The scaffold slowly degrades and is replaced by regenerated tissue with meniscus-like characteristics.[44]

One-year clinical results reported in this journal by Verdonk et al[44] demonstrated tissue ingrowth into the scaffold at 3 months using dynamic contrast-enhanced magnetic resonance imaging (MRI). Moreover, ingrowth was also demonstrated at 12 months during gross examination at relook and in histologic results from 44 biopsies. No cartilage degeneration attributable to that of the scaffold was observed, the scaffold was shown to be biocompatible, and the regenerated tissue showed characteristics similar to those of native meniscal tissue.[44] The objectives of the study were to demonstrate safety, including the absence of adverse effects on the articular cartilage, and to show that tissue ingrowth into the scaffold provides a clinical benefit up to 24 months after surgery in the form of decreased pain and improved function compared with baseline.

METHODS

This study was a prospective, single-arm, multicenter proof-of-principle study designed to assess the safety and efficacy of the scaffold for the treatment of pain originating from a partial meniscal tear or meniscus loss requiring surgical intervention. All patients provided written informed consent, and the study was approved by all the appropriate ethics committees in 4 different European countries (Belgium, France, Germany, and Spain). Moreover, the study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and all applicable rules and laws including but not limited to the European Medical Device Directive, the Active Implants Directive, and the In Vitro Diagnostic Directive.

Overall Study Design and Methods

The methods of this study have been described by Verdonk et al[44]; therefore, only a summary of the methods is provided here. Fifty-two patients with irreparable meniscal defects of either the lateral or medial meniscus were enrolled into the study across 9 centers in Europe. All patients, except for 2 with an acute injury, suffered from postmeniscectomy symptoms and underwent debridement of the meniscal defect in a standard arthroscopic procedure, followed by implantation of the scaffold during the same procedure. In the case of the 2 patients with an acute meniscus injury, a partial meniscectomy was performed followed by implantation of the scaffold. Concomitant anterior cruciate ligament (ACL) reconstruction was permitted to stabilize the knee (up to 12 weeks after implantation); however, no other procedures were permitted during the index procedure.

The key inclusion criteria were (1) irreparable medial or lateral meniscal tear or partial meniscus loss, with intact rim; (2) skeletally mature male or female patients; (3) age 16 to 50 years; (4) stable knee joint or knee joint stabilization procedure within 12 weeks of index procedure; (5) International Cartilage Repair Society (ICRS) classification ≤ 2; (6) patient willing and able to give consent to participate in the clinical study, follow rehabilitation protocol, and attend all follow-up visits and procedures; and (7) no more than 3 surgeries on the involved meniscus. The key exclusion criteria were (1) total meniscus loss or unstable segmental rim defect, (2) multiple areas of partial meniscus loss that could not be treated by a single scaffold, (3) any significant malalignment (varus or valgus), (4) ICRS classification > 2, and (5) body mass index > 35.

To provide optimum conditions during the tissue healing and maturation process after implantation, all patients were required to follow a standardized rehabilitation protocol for 16 to 24 weeks. The rehabilitation protocol allowed no weightbearing until week 4, after which patients were

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allowed to begin partial weightbearing, which was gradually increased to full weightbearing at week 9. A gradual return to sports was allowed as of 6 months after the index surgery. Patients were assessed at 1 week; at 3, 6, and 12 months (which included relook arthroscopy and biopsy); and 24 months after the index surgery.

Efficacy Parameters

Patients were required to complete the visual analog scale (VAS) assessment of knee pain, the International Knee Documentation Committee (IKDC) subjective knee evaluation form, and the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Lysholm questionnaires at baseline (entry into study), 1 week (VAS only), and 3, 6, 12, and 24 months after implantation. One KOOS subscale, function in sports and recreation, was not collected at 3 months as patients were restricted from sports activities until 6 months after the index surgery under the rehabilitation protocol.

The VAS has been validated for use in patients with pain related to meniscus injuries of the knee.[10,17] Studies of the sensitivity of the VAS system have estimated that the minimum patient-perceived improvement, and hence minimum clinically significant change, is approximately 10 mm.[23,36]

The IKDC subjective knee evaluation form has been validated for use as an outcome measure for meniscus injuries of the knee.[6] Irrgang et al[18] suggested that a change in IKDC total score of at least 11.5 is necessary to distinguish a clinically relevant change between patients who have improved and those who have not.

The KOOS questionnaire has been validated in several different patient populations undergoing surgical procedures due to knee complaints.[33] Roos and Lohmander suggested that a change in a subscale score of >10 points represents a clinically significant change.[33]

Lysholm and Gillquist[26] (1982) developed the Lysholm Knee Scoring Scale for the follow-up of knee ligament surgery, with emphasis on the evaluation of symptoms of instability. It has been validated in a number of studies of patients with meniscal defects.[2,24] Briggs et al[2] (2006) suggest that a change in the overall score of at least 10 points should be considered clinically relevant.

Safety Parameters

Patients were carefully monitored throughout the study for adverse events (AEs). At each follow-up visit, patients were asked if they had experienced any AEs since the last assessment, and spontaneously reported AEs were also captured. All AEs were characterized by the investigator with respect to relationship (definite, probable, possible, unknown, or not related) to the scaffold and/or procedure. An AE was classified as a serious adverse event (SAE) if it led to death or a serious deterioration in the health of a patient that resulted in a life-threatening illness or injury, resulted in a permanent impairment of a body structure or a body function, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

A descriptive evaluation of time to treatment failure from the date of index surgery using Kaplan-Meier time to treatment failure distributions was performed. A treatment failure was deemed to have occurred if there was an additional surgical procedure on the index defect and if the surgeon decided that the need for such an additional surgical procedure was of unknown, possible, probable, or definite relationship to the scaffold and/or the index procedure. It should be noted that any additional surgical procedure taking place during the 12-month relook arthroscopy was therefore included as treatment failure in this analysis, even if the patient was asymptomatic.

The ICRS cartilage grade was determined by an independent radiographic reviewer, blinded to patient clinical data, using MRI at 1 week and at 3, 12, and 24 months after surgery. The 1-week MRI was used as baseline as this was the first protocol-stipulated MRI in the study. Details of the methodology and the results up to and including 12 months after surgery are discussed in Verdonk et al.[44]

Statistical Methods

In this observational noncomparative trial, the sample size of 50 patients was calculated to enable a meniscal repair failure rate of 20% to be estimated with a 95% confidence interval (CI) of 8.9% to 31.1%. Furthermore, lower failure rates could be estimated with greater precision.

All evaluations were based on all patients enrolled into the study and who were implanted with the scaffold. Evaluation of the primary safety end points included frequency of SAEs and AEs by relationship to the scaffold and/or procedure and time of onset after surgery. The ICRS cartilage classification at 24 months relative to 1 week was summarized descriptively.

Time to treatment failure was presented descriptively using Kaplan-Meier time to treatment failure distributions.

The last observation carried forward approach was used; that is, data from the last available follow-up visit were used in place of missing scores due to patient withdrawal, loss to follow-up, or nonevaluable VAS or other outcome questionnaire data.[8,14] Total clinical outcome scores were calculated according to standard formulae. Absolute and change from presurgery values were analyzed descriptively (including mean and 95% CI), and paired t tests to test the null hypothesis of mean change in outcome scores equal to zero were carried out for each outcome score at each follow-up assessment (a 2-sided $P < .05$ was considered statistically significant).

RESULTS

Patient Disposition

A total of 52 patients were treated with the polyurethane scaffold (intention-to-treat population). At the time of the 24-month postoperative visits, 38 remained in the study and 14 patients had withdrawn. Reasons for withdrawal were SAEs (6) and loss to follow-up (8) (see Table 1 for

TABLE 1
Patient Disposition[a]

Time Point	No. of Patients		Reason for Discontinuation
	In Study	Discontinued Since Previous Time Point	
Start of study	52	Not applicable	Not applicable
1 week	52	0	Not applicable
3 months	51	1	1 SAE, postoperative infection due to procedure
6 months	50	1	1 SAE, unicompartmental knee arthroplasty in patient not eligible for study (baseline ICRS = 3)
12 months	49	1	1 lost to follow-up
24 months	38	11	7 lost to follow-up; 3 SAEs, not eligible for study at baseline (meniscal allograft transplant, unstable knee resulting in scaffold dislocation, meniscus rim repair with implantation of a second scaffold); 1 SAE, nonintegration of scaffold, unknown relationship to scaffold or procedure

[a]ICRS, International Cartilage Repair Society; SAE, serious adverse event.

details). However, 1 patient who did not return for the follow-up visit at 24 months, and who therefore was considered lost to follow-up, provided 24-month outcomes questionnaire data. In addition, there were 24-month MRIs available for this same patient as well as for another withdrawn patient. Therefore, MRI data were available for a total of 40 patients, and clinical outcomes data were available for 39 patients.

Demographic Details and Baseline Meniscus Status

Patient demographics are set forth in Table 2. The patients were young, with a mean age at baseline of 30.8 (SD, 9.4) years, and three quarters were male. Most meniscal defects treated in this study were located in the medial meniscus, 34 of 52 (65.4%), and most defects were located in both the posterior and body region of the meniscus, 46 of 52 (88.5%), with just over half of these also involving the anterior region. In 17 of 52 (32.7%) cases, patients had ACL reconstruction in the index knee, either before or within 12 weeks of enrollment in the study. Although the study inclusion criteria required that patients have a continuous and stable meniscus rim as assessed during the index procedure, 4 of 52 (7.7%) did not meet these requirements (representing a departure from the protocol); however, they were included in the analysis as the study reports on the intention-to-treat population. Most defects were large, with 21 of 52 (40.4%) between 40 and 50 mm in length, 12 of 52 (23.0%) between 50 and 60 mm, and 10 of 52 (19.2%) 60 mm or more in length. The majority of patients, 46 of 52 (88.5%), had already undergone 1 or more previous procedures on the index meniscus (see Table 2 for details).

Clinical Outcomes Scores

Baseline clinical outcomes depict a study population with both pain and loss of function (Table 3). Clinically[‡‡] and statistically significant improvements from baseline in all clinical outcome scores (VAS, IKDC, KOOS, and Lysholm) were reported already at 6 months and thereafter at 12 and 24 months after index surgery compared with baseline (Table 3 and Figures 1 and 2).

Subgroup analyses were performed for age groups, gender, indication, and length of the meniscal defect. However, most likely due to the small sample size, no consistent trends were observed.

Treatment Failures

A treatment failure was deemed to have occurred if there was an additional surgical procedure on the index defect and the surgeon decided that the need for such an additional procedure was of unknown, possible, probable, or definite relationship to the scaffold and/or the index procedure. It should be noted that any additional surgical procedure taking place during the 12-month relook arthroscopy was therefore included as treatment failure in this analysis. A total of 9 (17.3%) treatment failures occurred during the study (see Table 4): 8 during the first year or at the protocol-stipulated relook surgery and only 1 in the second year of the study (Figure 3). Three (5.8%) treatment failures occurred in the medial meniscus, constituting 3 of 34 or 9% of medial implantations. They were considered related to the procedure and not to the scaffold and occurred within the first year or during relook surgery.

Of the 6 cases of treatment failure in the lateral meniscus, constituting 6 of 18 or 33% of lateral implantations, 1 was considered unrelated to the scaffold. In the remaining 5 lateral patients, the additional surgery was of unknown, possible, or definite relationship to the scaffold; of these, 3 patients had no symptoms, and the additional surgery was carried out during the relook arthroscopy. In 1 of the 2 remaining lateral patients, the additional surgical procedure was performed after relook arthroscopy (diagnostic arthroscopy for arthralgia, possibly related to the scaffold), and in the other lateral patient, the additional surgical procedure was performed before relook arthroscopy (an arthroscopy with suture removal for pain, possibly related to the scaffold).

[‡‡]References 2, 6, 18, 23, 24, 26, 33, 35, 36.

TABLE 2
Demographics (Intention-to-Treat Population)

Patient Characteristics	All Patients (n = 52)	
	n	%
Sex		
Male	39	75.0
Female	13	25.0
Age,[a] y	30.8 ± 9.4	
Meniscus		
Medial	34	65.4
Lateral	18	34.6
Involved knee		
Left	27	51.9
Right	25	48.1
Location of meniscal defect		
Posterior	2	3.8
Body	1	1.9
Posterior/body	22	42.3
Anterior/body	3	5.8
Posterior/body/anterior	24	46.2
Status of meniscus rim		
Continuous and stable	48	92.3
Not continuous and stable	4	7.7
Defect longitudinal length, mm		
<40	8	15.4
40 to <50	21	40.4
50 to <60	12	23.0
>60	10	19.2
Unknown	1	1.9
Anterior cruciate ligament (ACL) status prior to index surgery		
Native/normal	35	67.3
Reconstructed	17	32.7
ACL reconstruction during study		
During index procedure	2	3.8
After index procedure	1	1.9
Prior meniscal surgeries (involved meniscus)		
None	2	3.8
1	34	65.4
2	12	23.1
Unknown	4	7.7

[a]Data are mean ± SD.

Safety Assessments

A total of 71 AEs with a possible, probable, definite, or unknown relationship to the scaffold and/or procedure were reported. Only 5 of the 71 AEs (7.0%) were considered to be related solely to the scaffold. These included 3 instances of pain (1 probably, 1 possibly, and 1 definitely related), 1 case of effusion (probably related), and 1 case of swelling (unknown relationship to the device). Forty-one of 71 AEs (57.7%) were considered related solely to the procedure and 25 of 71 (35.2%) to both the scaffold and procedure. The most frequently reported related AEs included arthralgia, postprocedural pain and myalgia, joint effusion, and joint swelling. These AEs were expected as they are routinely reported after any knee surgery and typically occurred within 3 months of the index surgery or protocol-stipulated relook arthroscopy.

There were only 4 related AEs in 2 patients that occurred 3 months or longer after the protocol-stipulated relook surgery (pain and 2 AEs of effusion as a result of a loose cartilage flake from the central trochlea due to pre-index surgery–diagnosed chondromalacia in 1 patient and arthralgia in another patient).

Serious Adverse Events

There were 9 index knee–related SAEs reported during the study (5 in medial subjects and 4 in lateral subjects; incidence rate, 17.3%), of which 6 resulted in withdrawal (3 in medial subjects and 3 in lateral subjects). Of these 9 SAEs, 4 were considered unrelated to the scaffold and to the procedure; 4 were considered only procedure related; none were considered to be of a definite, probable, or possible relationship to the scaffold; and 1 was considered to be of unknown relationship to the scaffold and to the procedure (see Table 5). The latter was a scaffold removal performed at relook arthroscopy due to an almost completely nonintegrated scaffold. The patient was asymptomatic with no signs of inflammatory reaction to the scaffold and no evidence of cartilage damage observed in gross examination. Importantly, the biopsy specimen taken from the meniscus rim after removal of the nonintegrated scaffold material showed cell-populated scaffold material integrated with tissue and no inflammatory reaction to the scaffold. The integration failure was assumed to be due to lack of biological response.

Cartilage Status

Stable or improved cartilage status at 24 months was demonstrated in 92.5% (37/40) of patients compared with baseline status. Interestingly, in 7 patients, the cartilage score improved during the 24-month follow-up period. These included 1 patient with an ACL repair at approximately 3 months after index surgery and 1 patient with an osteochondral plug at 9 months after surgery for treatment of osteochondritis dissecans.

Worsening in cartilage status was observed in 3 patients. In 1 patient, a deterioration from grade 2 to a grade 3a occurred between 12 and 24 months in an area not in contact with the scaffold, and in 2 patients an overall worsening in cartilage status was observed between 1 week and 24 months. For each of these 3 patients, the worsening was not limited to the index compartment, was unrelated to the scaffold, and was considered to be due to preexisting conditions (see Table 6).

DISCUSSION

Efficacy Assessments

It is accepted that to treat the irreparable meniscus, a scaffold must be used to enable precursor cell migration and colonization and proliferation of blood vessels, which leads

TABLE 3
Clinical Outcome Scores, VAS Pain, IKDC, Lysholm, and KOOS From Baseline to 24 Months (LOCF, N = 52)[a]

Clinical Outcome Score	Baseline	6 Months	12 Months	24 Months
VAS pain	45.7 ± 26.2	24.7 ± 21.6	24.2 ± 24.7	20.3 ± 23.5
IKDC	45.4 ± 17.8	61.7 ± 19.9	65.5 ± 22.0	70.1 ± 23.0
Lysholm	60.1 ± 19.2	74.8 ± 16.6	77.2 ± 20.2	80.7 ± 19.5
KOOS				
Symptoms	64.6 ± 22.3	77.0 ± 16.6	77.9 ± 17.7	78.3 ± 18.5
Pain	57.5 ± 22.2	72.3 ± 18.7	74.6 ± 20.2	78.6 ± 22.5
Activities of daily living	68.8 ± 21.4	80.1 ± 16.2	82.8 ± 17.6	84.2 ± 21.2
Sports	30.5 ± 28.7	49.7 ± 33.5	54.5 ± 34.3	59.0 ± 33.4
Quality of life	33.9 ± 19.3	47.8 ± 20.3	53.5 ± 25.8	56.6 ± 24.2

[a]Data are means ± SD. IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LOCF, last observation carried forward; VAS, visual analog scale.

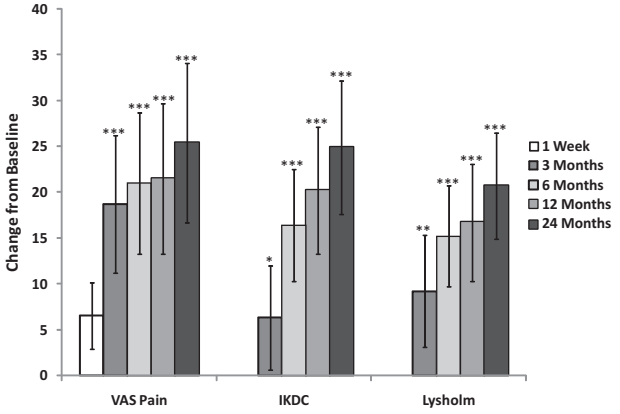

Figure 1. Improvements from baseline (last observation carried forward) in clinical outcomes VAS pain, IKDC, and Lysholm (mean ± 95% confidence interval; N = 52). *$P <$ .05. **$P <$ .005. ***$P <$ .0001. IKDC, International Knee Documentation Committee; VAS, visual analog scale.

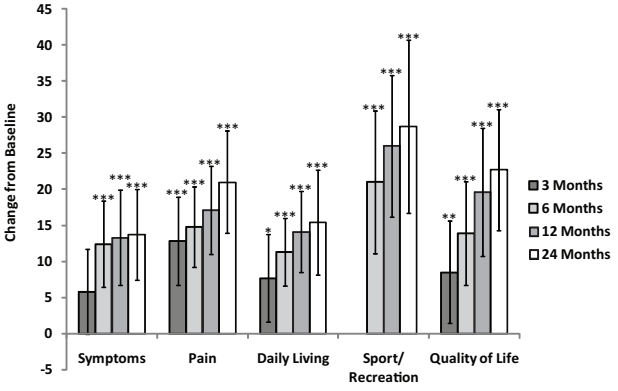

Figure 2. Improvements from baseline (last observation carried forward) in KOOS subscales (mean ± 95% confidence interval; N = 52). *$P <$ .01. **$P <$ .05. ***$P <$ .0001. KOOS, Knee Injury and Osteoarthritis Outcome Score.

to the formation of organized meniscal tissue.[16,27] Studies with first-generation scaffolds such as the cohort study reported by Zaffagnini et al[46] showed no significant differences in VAS and IKDC scores at 5-year follow-up evaluations and in Tegner scores at either 5- or 10-year follow-up evaluations in patients implanted with a medial collagen meniscus implant compared with controls who underwent a partial medial meniscectomy. At 10-year follow-up evaluations, there were significant differences in VAS pain, IKDC score, medial joint line height, and medial joint side-to-side differences in the collagen meniscus implant group. The medial joint changes were quantitatively assessed on radiographs and indicate that a meniscus implant can prevent the degenerative changes to joint space that typically occur after a partial meniscectomy. In the conclusion of their article, the authors recommend the use of scaffolds for irreparable meniscal defects and state that "the use of a scaffold to regrow meniscal tissue would help to maintain patient activity level for a longer time while protecting the joint against pain and degeneration."[46]

In this study population, which consisted of patients with medial and lateral meniscal tears (34 medial, 18 lateral), all of the clinical outcome measures, including VAS, IKDC, all 5 KOOS subscale scores, and Lysholm, showed increasing improvement over baseline at each successive follow-up (1 week and 3, 6, and 12 months) evaluation to 24 months. Furthermore, all clinical outcome scores reached clinical and statistical significance compared with baseline by the 6-month follow-up evaluation.

This is the first study we are aware of that incorporated more than 2 validated outcomes scores to assess functionality and, therefore, the clinical benefit of using a scaffold for tissue regeneration in irreparable partial medial and lateral meniscal defects. The consistency and cross-corroboration of the VAS, IKDC, KOOS, and Lysholm efficacy results, accompanied by clinically and statistically significant improvements from baseline in all clinical outcome measures at all follow-up time points, support the effectiveness of the polyurethane scaffold. In this study, the VAS pain score improvements are particularly robust as they occurred at the same time as the sports and recreation score improved, suggesting sustained pain relief in combination with increased activity levels. In addition, the largest

TABLE 4
Treatment Failures[a]

Intervention	Relationship to Device
Medial meniscus	
<3 months after index surgery	
Postoperative infection within 1 week of index surgery	NR
3-12 months after index surgery	
Unicompartmental knee arthroplasty due to ongoing pain in patient with severe osteoarthritis	NR
During relook arthroscopy	
Dislocation of tissue/scaffold construct after uncontrolled twisting of the index knee	NR
Lateral meniscus	
<3 months after index surgery	
Arthroscopic removal of suture due to pain	NR
3-12 months after index surgery	
Arthroscopic removal of suture due to pain	Unknown
During relook arthroscopy	
2 cases of debridement of nonintegrated scaffold material	Definite
All-inside suture added to small tear in tissue/scaffold construct	Definite
After relook arthroscopy, 24 months after index surgery	
Arthroscopy for diagnostic purposes due to pain	Possible

[a]NR, not related.

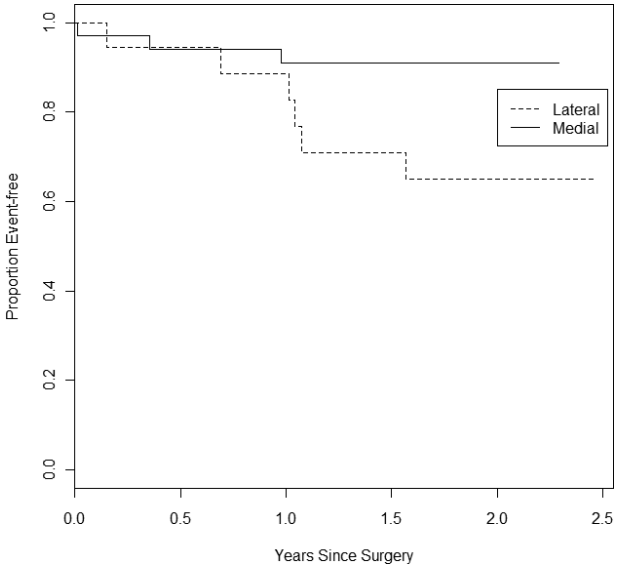

Figure 3. Time to treatment failure by meniscal defect.

improvement overall was observed in the KOOS subscale of function in sport and recreation. This particular result on the KOOS subscale of function in sport and recreation subscale at 6, 12, and 24 months is a particularly important outcome for young, athletically active individuals and contrasts with the findings of Stein et al,[42] who showed a loss in sports activity level based on the Tegner score at 3.4 and 8.8 years in patients who had undergone partial meniscectomy and meniscal repairs.

The numerical scores and changes in clinical outcomes experienced by the patients are shown in Table 3 and in Figures 1 and 2, respectively. All improvements at the last study follow-up were clinically and statistically significant. The magnitude of these changes was generally at least twice that which is considered clinically relevant for a patient in the literature.[2,18,23,29,36]

Although patients had not had any rehabilitation for approximately 18 months, their clinical outcome scores continued to improve. The observation of continued pain reduction even as functionality improved shows sustained pain relief despite increased activity levels and is another result of particular interest in this study.

Safety Assessments

Rodkey et al[32] reported a 9.5% reoperation rate in a randomized controlled trial involving the collagen meniscus implant and that most nonprotocol-stipulated surgery occurred before 24 months. The study population (patients with chronic injuries) was similar to those seen in this study, albeit in somewhat older patients (mean age, 38 vs 30.8 years) and only in the medial indication. Treatment failures that took place during the protocol-stipulated relook arthroscopy were not included,[19] unlike in this study. In this study, all but 1 treatment failure, which occurred between 12 and 24 months, took place before or during the 12-month protocol-stipulated relook surgery. Three treatment failures occurred in patients implanted with the medial scaffold (5.8%), and 6 treatment failures occurred in patients implanted with the lateral scaffold (11.5%). The treatment failure criteria were deliberately strict with a view to capturing all additional procedures that took place. In the lateral indication, however, it should be pointed out that 2 of the treatment failures (see Table 4) involved problems with the suture material rather than the scaffold, and 2 events were discovered during the planned study relook arthroscopy in asymptomatic

TABLE 5
Description of Each SAE Related to the Index Knee and Relationship to Device and Procedure as Assessed by the Investigating Surgeon[a]

SAE	Relationship to Device
Medial meniscus	
<3 months after index surgery	
Postoperative infection within 1 week of index surgery	NR
3-12 months after index surgery	
Treatment of preexisting osteochondritis dissecans using mosaicplasty	NR
Unicompartmental knee arthroplasty due to ongoing pain in patient with severe osteoarthritis	NR
During relook arthroscopy	
Removal of dislocated tissue/scaffold construct after uncontrolled twisting of the index knee	NR
After relook arthroscopy, 24 months after index surgery	
Repair of chondromalacia using microfracture	NR
Lateral meniscus	
3-12 months after index surgery	
Pain and swelling treated with suture removal	NR
During relook arthroscopy	
Meniscus allograft transplant in patient with nonintact meniscus rim at time of index surgery	NR
Debridement of nonintegrated scaffold material	Unknown
After relook arthroscopy, 24 months after index surgery	
Tear of tissue/scaffold construct in front of popliteal hiatus in patient with nonintact meniscus rim at time of index surgery	NR

[a]All serious adverse events (SAEs) were resolved with treatment. NR, not related.

TABLE 6
International Cartilage Repair Society Cartilage Classification as Determined by MRI; Change at 24 Months Compared With Baseline

Change in Cartilage Score Between Baseline and 24 Months	n	%
Improved	7	17.5
No change	30	75.0
Worsened	3	7.5
Total[a]	40	

[a]Patients with evaluable anatomic magnetic resonance images (MRIs) at both assessments.

patients. The overall combined treatment failure rate of 17.3% in this study compares favorably to reoperation rates presented in the short term for meniscal repair procedures[30] and includes patients who were considered to be protocol violators.

In the present study, a higher failure rate for patients with repair in the lateral compartment was observed than for patients with repair in the medial compartment, 6 of 18 (33%) versus 3 of 34 (9%). However, this was not unexpected as the lateral meniscus can be viewed as the more challenging application. Higher stresses are observed on the lateral plateau,[1,11,40,45] and the lateral meniscus has been shown to carry 70% of the load in the lateral compartment, whereas the medial meniscus carries only 50% of the load in the medial compartment.[39] Importantly, increased risk of rapid degeneration and significantly worse outcomes are observed after lateral meniscectomy, highlighting the need for a treatment solution for this specific indication.[13,21,22,29,41] Nevertheless, should the device fail, a patient is left with the same treatment options as he or she had before the index surgery. Therefore, it could be concluded that the greatest potential risk in the case of treatment failure is an additional arthroscopic procedure. Finally, it should also be noted that >30% of the lateral compartment failures were in patients who were protocol violators, which underlines the importance of adhering to the indications for use of the scaffold.

The AE rates in this study compare favorably with those previously reported for partial meniscectomy.[34,38] The most frequently reported AEs of arthralgia, postprocedural pain and myalgia, joint effusion, and joint swelling are commonly reported after a surgical knee procedure.[4,37] The majority of AEs occurred either during or within 3 months of the index surgery or the protocol-stipulated relook arthroscopy. The SAEs in the index knee were 17.3%, and there was only 1 SAE in which the relationship to the scaffold could not be excluded (integration failure with unknown relationship to the scaffold and the procedure).

The 24-month safety cartilage status data presented in this article build on the 12-month data already published. At 24 months, 92.5% (37/40) of the patients had improved or stable scores as compared with baseline on MRI, suggesting a possible chondroprotective effect and demonstrating that the polyurethane scaffold is safe and does not cause cartilage damage.

Limitations

A limitation of this study is the absence of randomization with a control arm of patients undergoing partial

meniscectomy without implantation of a polyurethane scaffold, which prevents direct comparisons of the 2 treatment options. The study population was too small and heterogeneous to fully evaluate the benefit of the polyurethane scaffold in a detailed subgroup analysis. Finally, to minimize potential bias resulting from loss to follow-up, the last recorded response was used in lieu of missing outcomes data.

CONCLUSION

Already at 6 months, consistent, clinically and statistically significant improvements in all clinical outcome scores (VAS, IKDC, KOOS, and Lysholm) have been demonstrated, which provide strong evidence of the potential clinical benefit that the polyurethane scaffold can provide to a patient group for whom only restricted treatment options currently exist. The degree of improvement continued, remaining clinically and statistically significant as compared with baseline, at the 24-month follow-up visit. The treatment failure rate of 17.3% compares favorably to reoperation rates presented in the short term for meniscal repair and included patients who departed from the protocol. There were no unanticipated adverse device effects and no SAEs with a direct relationship to the scaffold, although 1 patient had an SAE with an unknown relationship to the scaffold. Stable or improved ICRS cartilage grades were observed in 92.5% of patients between baseline and 24 months, demonstrating that the polyurethane scaffold does not harm the cartilage. Nevertheless, long-term follow-up, preferably in the form of a controlled study, is required to confirm a potential chondroprotective effect.

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REFERENCES

1. Baratz ME, Fu FH, Mengato R. Meniscal tears: the effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. *Am J Sports Med*. 1986;14(4):270-275.
2. Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. *J Bone Joint Surg Am*. 2006;88(4):698-705.
3. Campbell SE, Sanders TG, Morrison WB. MR imaging of meniscal cysts: incidence, location, and clinical significance. *AJR Am J Roentgenol*. 2001;177(2):409-413.
4. Cole BJ, Carter TR, Rodeo SA. Allograft meniscal transplantation: background, techniques, and results. *Instr Course Lect*. 2003;52:383-396.
5. Cox JS, Nye CE, Schaefer WW, Woodstein IJ. The degenerative effects of partial and total resection of the medial meniscus in dogs' knees. *Clin Orthop Relat Res*. 1975;109:178-183.
6. Crawford K, Briggs KK, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the IKDC score for meniscus injuries of the knee. *Arthroscopy*. 2007;23(8):839-844.
7. Englund M, Roos EM, Roos HP, Lohmander LS. Patient-relevant outcomes fourteen years after meniscectomy: influence of type of meniscal tear and size of resection. *Rheumatology (Oxford)*. 2001;40:631-639.
8. European Medicines Agency. Points to consider on missing data from the Committee for Proprietary Medicinal Products of the European Medicines Agency (EMEA). Available at: http://www.emea.europa.eu/pdfs/human/ewp/177699EN.pdf. Accessed January 31, 2011.
9. Fetzer GB, Spindler KP, Amendola A, et al. Potential market for new meniscus repair strategies: evaluation of the MOON cohort. *J Knee Surg*. 2009;22(3):180-186.
10. Flandry F, Hunt JP, Terry GC, Hughston JC. Analysis of subjective knee complaints using visual analog scales. *Am J Sports Med*. 1991;19(2):112-118.
11. Fukubayashi T, Kurosawa H. The contact area and pressure distribution pattern of the knee: a study of normal and osteoarthrotic knee joints. *Acta Orthop Scand*. 1980;51(6):871-879.
12. Ghadially FN, Wedge JH, Lalonde JMA. Experimental methods of repairing injured menisci. *J Bone Joint Surg Br*. 1986;68(1):106-110.
13. Hede A, Larsen E, Sandberg H. The long term outcome of open total and partial meniscectomy related to the quantity and site of the meniscus removed. *Int Orthop*. 1992;16:122-125.
14. Herman A, Botser IB, Tenenbaum S, Chechick A. Intention-to-treat analysis and accounting for missing data in orthopaedic randomized clinical trials. *J Bone Joint Surg Am*. 2009;91(9):2137-2143.
15. Higuchi H, Kimura M, Shirakura K, Terauchi M, Takagishi K. Factors affecting long-term results after arthroscopic partial meniscectomy. *Clin Orthop Relat Res*. 2000;377:161-168.
16. Hoben GM, Athanasiou KA. Meniscal repair with fibrocartilage engineering. *Sports Med Arthrosc*. 2006;14(3):129-137.
17. Höher J, Münster A, Klein J, Eypasch E, Tiling T. Validation and application of a subjective knee questionnaire. *Knee Surg Sports Traumatol Arthrosc*. 1995;3(1):26-33.
18. Irrgang JJ, Anderson AF, Boland AL, et al. Responsiveness of the International Knee Documentation Committee subjective knee form. *Am J Sports Med*. 2006;34(10):1567-1573.
19. Jacques L, Syrek Jensen T, Salive ME, O'Connor D, Schafer J. Coverage decision memorandum for collage meniscus implant (CMI). CAG 00414N, dated 25 May 2010. Available at: http://www4a.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=337&ncdver=1&NCAId=235&ver=10&NcaName=Coll agen+Meniscus+Implant&IsPopup=y&bc=AAAAAAAAIBAA&.
20. Jaureguito JW, Elliot JS, Lietner T, Dixon LB, Reider B. The effects of arthroscopic partial lateral meniscectomy in an otherwise normal knee: a retrospective review of functional, clinical, and radiographic results. *Arthroscopy*. 1995;11(1):29-36.
21. Johnson RJ, Kettelkamp DB, Clark W, Leaverton P. Factors affecting late results after meniscectomy. *J Bone Joint Surg Am*. 1974;56:719-729.
22. Jorgensen U, Sonne-Holm S, Lauridsen F, Rosenklint A. Long-term follow-up of meniscectomy in athletes: a prospective longitudinal study. *J Bone Joint Surg Br*. 1987;69:80-83.
23. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J*. 2001;18(3):205-207.

24. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. *J Bone Joint Surg Am*. 2004;86(6):1139-1145.
25. Kurosawa H, Fukubayasi T, Nakajima H. Load-bearing mode of the knee joint: physical behavior of the knee joint with or without menisci. *Clin Orthop Relat Res*. 1980;149:283-290.
26. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med*. 1982;10(3):150-154.
27. McCarty EC, Marx RG, DeHaven KE. Meniscus repair: considerations in treatment and update of clinical results. *Clin Orthop Relat Res*. 2002;402:122-134.
28. McDermott ID, Amis AA. The consequences of meniscectomy. *J Bone Joint Surg Br*. 2006;88(12):1549-1556.
29. McNicholas MJ, Rowley DI, McGurty D, et al. Total meniscectomy in adolescence: a thirty-year follow-up. *J Bone Joint Surg Br*. 2000;82:217-221.
30. Paxton ES, Stock MV, Brophy RH. Meniscal repair versus partial meniscectomy: a systematic review comparing reoperation rates and clinical outcomes. *Arthroscopy*. 2011;27(9):1275-1288.
31. Rodkey WG. Basic biology of the meniscus and response to injury. *Instr Course Lect*. 2000;49:189-193.
32. Rodkey WG, DeHaven KE, Montgomery WH III, et al. Comparison of the collagen meniscus implant with partial meniscectomy: a prospective randomized trial. *J Bone Joint Surg Am*. 2008;90(7):1413-1426.
33. Roos EM, Lohmander LS. The Knee Injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
34. Roos EM, Ostenberg A, Roos H, Ekdahl C, Lohmander LS. Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. *Osteoarthritis Cartilage*. 2001;9(4):316-324.
35. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS): development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88-96.
36. Roytman TM, Kitagawa KM, Yamamoto LG. Minimum perceived VAS differences at an interval of 7 days. *Pain Clinic*. 2006;18(2):119-121.
37. Scheller G, Sobau C, Bülow JU. Arthroscopic partial lateral meniscectomy in an otherwise normal knee: clinical, functional, and radiographic results of a long term follow up study. *Arthroscopy*. 2001;17(9):946-952.
38. Schimmer RC, Brülhart KB, Duff C, Glinz W. Arthroscopic partial meniscectomy: a 12-year follow-up and two-step evaluation of the long-term course. *Arthroscopy*. 1998;14(2):136-142.
39. Seedhom BB, Dowson D, Wright V. Functions of the menisci: a preliminary study. *J Bone Joint Surg Br*. 1974;56:381-382.
40. Seedhom BB, Hargreaves DJ. Transmission of the load in the knee joint with special reference to the role of the menisci, part II: experimental results, discussion and conclusions. *Eng Med*. 1979;8(4):220-228.
41. Simpson DA, Thomas NP, Aichroth PM. Open and closed meniscectomy: a comparative analysis. *J Bone Joint Surg Br*. 1986;68:301-304.
42. Stein T, Mehling AP, Welsch F, von Eisenhart-Rothe R, Jager A. Long-term outcome after arthroscopic meniscal repair versus arthroscopic partial meniscectomy for traumatic meniscal tears. *Am J Sports Med*. 2010;38(8):1542-1548.
43. Verdonk PCM, Van Laer MEE, Verdonk R. Meniscus replacement: from allograft to tissue engineering. *Sports Orthop Traumatol*. 2008;24(2):78-82.
44. Verdonk R, Verdonk P, Huysse W, Forsyth R, Heinrichs E-L. Tissue ingrowth after implantation of a novel, biodegradable polyurethane scaffold for treatment of partial meniscal lesions. *Am J Sports Med*. 2011;39(4):774-782.
45. Walker PS, Erkman MJ. The role of the menisci in force transmission across the knee. *Clin Orthop Relat Res*. 1975;109:184-192.
46. Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, et al. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: a minimum 10-year follow-up study. *Am J Sports Med*. 2011;39(5):977-985.