

# Implantation of a novel synthetic scaffold for meniscus tissue regeneration

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## Introduction

Potentially detrimental outcome following partial meniscectomy is well established. A novel, biodegradable, porous, synthetic scaffold (Actifit™, Orteq Ltd) has been developed for the treatment of irreparable partial meniscus tears. It is implanted at the time of meniscus tissue removal and induces tissue ingrowth to replace surgically removed tissue.

## Materials and methods

A novel acellular synthetic scaffold for meniscal tissue regeneration, has been evaluated in a prospective multicenter, non-randomized study.

Fifty-two subjects with an irreparable partial medial or lateral meniscus tear, intact rim, presence of both horns and a stable, well-aligned knee have been treated. Tissue ingrowth was assessed by contrast enhanced magnetic resonance imaging (DCE-MRI) at 3 months (n=43), and 12 months, by gross examination (n=45) and histological examination of biopsies (n=45) collected during re-look arthroscopy. Clinical outcomes were assessed using the Visual Analog Scale (VAS), Knee and Osteoarthritis Outcome Score (KOOS), and International Knee Documentation Committee (IKDC) at baseline, 3, 6, 12 and 24 months.

## Subject population

- Skeletally mature, aged 16-50 years with partial, irreparable medial or lateral meniscal tears but with intact rim.
- Stable knee joint or scheduled for knee joint stabilization procedure within 12 weeks.
- ICRS classification Grade ≤ 2
- ≤3 previous surgeries on the involved meniscus.
- No significant malalignment, additional bone defects or advanced osteoarthritis of the knee.

## Assessments

- Pain and functionality using a Visual Analog Scale (VAS), the Knee Osteoarthritis Outcome Score (KOOS), the International Knee Documentation Committee (IKDC) score at baseline, 3, 6, 12 and 24 months post-surgery.
- Tissue ingrowth by dynamic contrast magnetic resonance imaging (DCE-MRI) at 3 months and by gross examination and histological analysis of biopsy samples during re-look arthroscopy at 12 months.
- Safety was monitored throughout the study.

## Interim results

### Baseline characteristics

	N=52
<b>Age</b>	
Mean ± SD	30.8 ± 9.4
<b>Sex</b>	
Male (n [%])	39 (75%)
Female (n [%])	13 (25%)
<b>Defect characteristics</b>	
Medial meniscus (n [%])	34 (65%)
Lateral meniscus (n [%])	18 (35%)
Longitudinal length (mean ± SD)	47.1 ± 10.0

### Clinical efficacy

46 subjects reached 12 months follow-up.

Mean change (95% confidence intervals) from baseline in clinical efficacy scores at 3, 6 and 12 months:

	VAS <sup>1</sup>	IKDC <sup>1</sup>
3 months	-18.7 (-26.3, -11.1)***	6.8 ( 1.2, 12.4)*
6 months	-21.0 (-28.6, -13.5)***	6.4 (10.5, 22.2)***
12 months	-21.2 (-29.2, -13.2)***	19.8 (13.1, 26.5)***

<sup>1</sup>LOCF (Last Observation Carried Forward)

Statistically significant change from baseline: \*P≤0.05; \*\*P≤0.01; \*\*\*P≤0.001

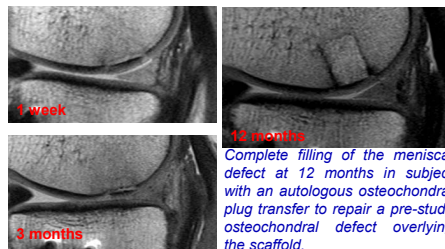
### KOOS<sup>1</sup>

Symptoms	3 months	6 months	12 months
	5.8 (-0.0, 11.7)	12.4 ( 6.9, 17.9)***	13.0 ( 6.7, 19.2)**
Pain	3 months	6 months	12 months
	12.8 ( 6.8, 18.9)***	14.8 ( 9.6, 20.0)***	16.5 (10.8, 22.2)***
Daily living	3 months	6 months	12 months
	8.0 ( 2.1, 14.0)**	11.3 ( 6.9, 15.8)***	13.6 ( 8.4, 18.9)***
Sport/recreation	6 months	12 months	
	21.8 (12.4, 31.2)***	26.1 (16.9, 35.4)***	
Quality of life	3 months	6 months	12 months
	8.7 ( 1.7, 15.7)*	13.9 ( 7.2, 20.6)**	19.4 (11.1, 27.6)***

<sup>1</sup>LOCF. Statistically significant change from baseline: \*P≤0.05; \*\*P≤0.01; \*\*\*P≤0.001

### Tissue ingrowth

- Evaluable DCE-MRI data are available for 43/52 (82.7%) subjects at 3 months.
- Increase of enhancement in the peripheral half of the implanted scaffold, and therefore evidence of tissue ingrowth into the scaffold in 35/43 (81.4%) subjects at 3 months post-implantation.



Complete filling of the meniscal defect at 12 months in subject with an autologous osteochondral plug transfer to repair a pre-study osteochondral defect overlying the scaffold.

### Re-look arthroscopy and histology

- Re-look arthroscopy data, histology results at 12 months are available for 45 subjects.
- All 45 biopsy samples showed fully vital material, with no signs of necrosis or cell death, illustrating biocompatibility and successful tissue ingrowth within the knee joint. No loose fragments of scaffold were identified in the tissue, demonstrating integrity of the implant.
- In addition to a fibrous capsule, three distinctly different layers (Figures 2 and 3) were observed based on the extracellular matrix (ECM) composition, cellular composition, and presence or absence of vessel structures:

**Layer 1:** 16/45: a vascularized, fibrotic layer mainly consisting of fibroblasts, with a dense ECM.

**Layer 2:** 41/45: an avascular "transition" layer consisting of a mixture of fibroblasts and fibrochondroblast-like cells of the oval subtype, and a loosely organized collagenous ECM.

**Layer 3:** 45/45: an avascular hypocellular layer consisting of fibrochondroblast-like cells of the rounded subtype with a matrix rich in fibrin.

### Safety

No serious adverse device effects and no device-related serious adverse events reported to date.

## Summary and conclusions

- Significant improvement compared to baseline in subjective outcome scores at 3, 6 and 12 months post-implantation, indicative of functional tissue ingrowth.
- Tissue ingrowth in 81.4% of subjects with evaluable DCE-MRI scans already at 3 months post-implantation.
- Histology data demonstrates that the scaffold induces regeneration of tissue with meniscus-like differentiation potential.
- No risks, other than the generally acknowledged risks associated with surgery, have been identified to date.

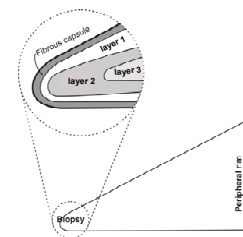


Figure 2: Cross-section of the scaffold meniscus free edge illustrating the biopsy site, and structure of the fibrous capsule and the three distinct layers observed in the biopsies.

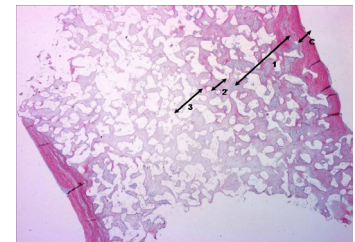


Figure 3: Sirius red stain (40x) with overlying vascularized fibrous capsule (C) and the 3 distinct layers observed in the biopsies (Layers 1, 2 and 3). Note mature collagen (deep red) decreasing when moving from the Capsule to Layer 3, illustrating the decrease in collagen towards the center of the biopsy.

- Layers 2 and 3 were characterized by the absence of vascular structures similar to the avascular part of the native human meniscus.
- The presence of fibrochondrocyte-like cells within a collagenous or fibrin-rich matrix indicates that the scaffold supports invading cells with meniscus-like differentiation potential.
- In Layer 3, cells with true chondroblastic features were observed (Figures 4 and 5).

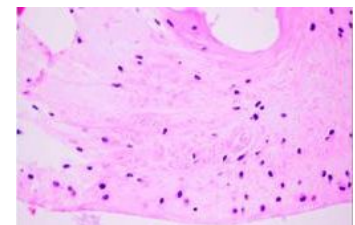


Figure 4: (H&E staining; 200x) Avascular tissue with more or less regularly distributed rounded and spindle shaped cells in an extracellular matrix with collagen deposition.

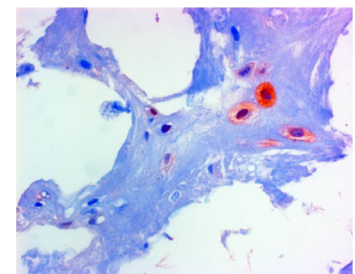


Figure 5: Immunohistochemistry (400x) with positive cartilage marker S100