Polyurethane Implant (ACTIFIT)

7

Rene Verdonk

7.1 Basic Science

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7.1.1 Introduction

Increased awareness of potentially detrimental outcomes following partial meniscectomy led to the development of a novel meniscal scaffold, Actifit™, by Orteq Bioengineering. It received the CE Mark in July 2008 for treatment of medial or lateral irreparable partial meniscal tears. Actifit™ consists of highly interconnected porous synthetic material (Fig. 7.1) enabling tissue ingrowth. Over time, transformation into meniscus-like tissue takes place as the implant slowly degrades. Furthermore, Actifit™ is made of an aliphatic polyurethane, which provides optimal mechanical strength, biocompatibility, porosity, safe degradation and ease of use required for the indication. It is available in two shapes, medial and lateral (Fig. 7.2).

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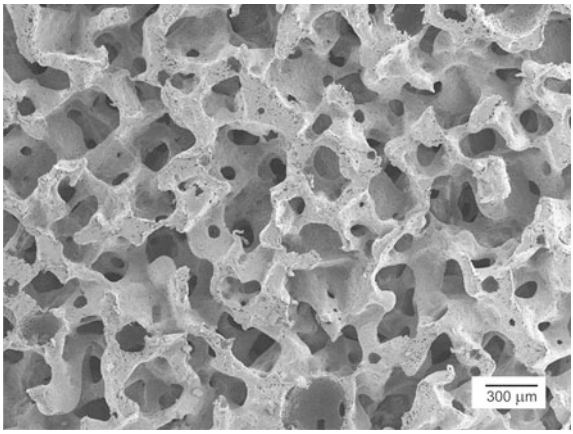

Fig. 7.1 Scanning electron micrograph of the porous structure of Actifit™

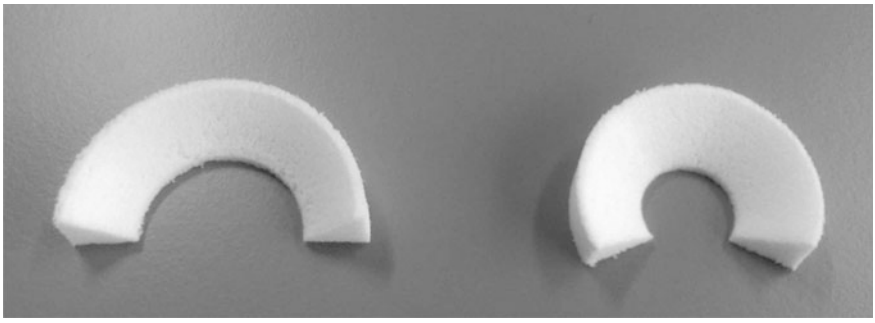

Fig. 7.2 Medial and lateral Actifit™

7.1.2 Background

Development of the meniscal scaffold started in the 1980s. Scaffold materials made of various synthetic polymers were tested in animal studies as meniscal repair or meniscal replacement material [1–22]. Based on these studies, a set of requirements for the optimal implant with respect to pore size, porosity, rate of degradation, degradation products, mechanical properties, and importantly ease of use in an arthroscopic procedure were developed. With respect to the mechanical properties, a high suture pull-out strength and sufficient stiffness became essential. Synthetic polymers currently used as biodegradable polymers for implantable devices are mainly copolymers based on lactide, ε-caprolactone, glycolide and trimethylene carbonate, and cannot fulfill all these requirements.

Polyurethanes are a class of materials with properties ranging from very brittle and hard to very tough, soft and tacky, and viscous [14]. The molecular structure can be tuned and consequently also the mechanical properties and rate of degradation. They are composed of alternating polydisperse blocks of soft and hard

segments (Fig. 7.3). These qualities combined with excellent biocompatibility make polyurethanes one of the most promising synthetic biomaterials [23]. Apart from the Orteq implant, marketed polyurethanes all contain (aromatic) diisocyanate moieties, which may yield a small amount of toxic diamines upon degradation. Although it has never been proven that toxic diamines are released or that such a release would cause problems, and aromatic polyurethanes have successfully been implanted in dogs as meniscal reconstruction material in the past [1–4, 7–11, 17, 18, 20–22, 24], the possibility of toxic amine release has given polyurethanes a negative perception. Therefore, it was decided to focus on polyurethanes based on 1,4-butanediisocyanate [16, 25–33]. Upon degradation, this aliphatic polyurethane will release 1,4-butanediamine, also known as putrescine, already naturally present in the body.

7.1.3 A New Synthetic Polymer

The Actifit™ polymer consists of two components, polyester (soft segments) and polyurethane (hard segments), specifically developed and tuned for meniscal application [29]. The soft segment, 80 % of the polymer, is a biodegradable polyester, poly (ε-caprolactone). It provides flexibility and determines the degradation rate. The semi-degradable, semicrystalline, polyurethane hard segments (20 % of the polymer) are of uniform size and provide mechanical strength.

Poly (ε-caprolactone) (lines in polymer chain in Fig. 7.3) is a degradable polyester found in several implantable biodegradable medical devices, mainly sutures (Monocryl by Ethicon; Caprosyn by Tyco Healthcare) and coatings of sutures (Vicryl and Panacryl by Ethicon; Dexon and Polysorb by Tyco Healthcare). The polyurethane hard segments (white boxes in polymer chain in Fig. 7.3) contain two 1,4-butanediisocyanate (BDI) and one 1,4- butanediol (BDO) moieties and are designed to be very small (2–3 nm), i.e. approximately 5,000 times smaller than a human cell.

In order to obtain a polyurethane with excellent mechanical properties comparable to the properties of aromatic polyurethanes, the conventional polyurethane synthesis process had to be changed [25]. The polyurethane is made without a catalyst, which contributes to the polymer biocompatibility. The absence of a

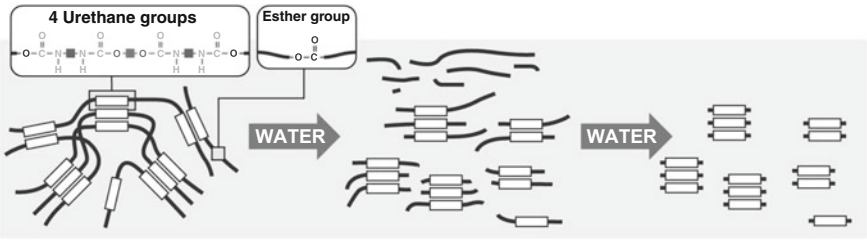

Fig. 7.3 Hydrolysis of the Actifit™ polyurethane

catalyst also contributes to the uniformity of the hard segments, and therefore to the mechanical properties of the polyurethane [29].

7.1.4 Degradation

The Actifit™ polyurethane has a very low degradation rate. The degradation mechanism takes place in the presence of water through hydrolysis of the ester bonds in the poly (ε-caprolactone) soft segments (Fig. 7.3). The polyurethane hard segments are more stable than the polycaprolactone segments and remain after hydrolysis of polycaprolactone. It is expected that these segments do not degrade in when integrated in. In case the polyurethane segments are phagocytized by macrophages (or giant cells), the hard segments degrade safely. This was determined in scientific studies of a polyurethane with similar polyurethane hard segments [34, 35] and was confirmed in Orteq's biocompatibility testing program on hard segments [36].

Degradation of the polycaprolactone segments is expected to take 4–6 years. In-vitro degradation testing (at 37 °C in phosphate buffer at pH 7.4) showed that after 1.5 years the molecular weight of the polyurethane decreased to 50 % of its original molecular weight while the implant weight was not reduced [16].

The biocompatibility of identified degradation products has either been tested by Orteq, or extensive documentation of their nontoxicity in the quantities released was already available. An overview of the tests performed is shown in the next section [37–39].

7.1.5 Preclinical Biocompatibility and Animal Testing

Orteq has completed a number of biocompatibility tests on the Actifit™ implant and on hard segments (Table 7.1). Actifit™ has passed all tests.

Two dog (beagles) studies were performed with the Actifit™ material [24, 40]. In the first study Actifit™ was implanted following total meniscectomy [24]. The follow-up period was 6 months. The implant horns were fixed on the tibial plateau with sutures pulled through drill holes in the tibia. Total meniscectomy served as control. In the second study Actifit™ was implanted for 6 and 24 weeks, with total meniscectomy and native menisci as controls [40]. The Actifit™ implants were fully integrated into the tissue without capsule formation, and the immunological response was very mild, not exceeding grade I. Histological examination of the tissue ingrowth disclosed formation of meniscus-like tissue containing proteoglycans and type II collagen (Fig. 7.4). A chondroprotective effect was not expected nor observed, due to limitations of the animal model. Nevertheless, it was hypothesized that absence of chondroprotection could be implant material-related [24]. No definite conclusions could be drawn since in this particular model the tibial plateaus were severely damaged due to technical issues in the group

Table 7.1 Tests Orteq has performed on Actifit™

Testing requirements	Relevant standards
Cytotoxicity	ISO10993-05
Sensitization	ISO10993-10
Intracutaneous irritation	ISO10993-10
Acute systemic toxicity	ISO10993-11
Combined subchronic toxicity and local tolerance (implant and hard segments)	ISO 10993-06 and ISO10993-11
Combined chronic toxicity and local tolerance (implant and hard segments)	ISO 10993-06 and ISO10993-11
Genotoxicity: bacterial reverse mutation	ISO10993-03
Genotoxicity: chromosomal aberration test in mammalian cell in vitro	ISO10993-03
Genotoxicity: mouse bone marrow micronucleus	ISO10993-03
Wear debris on small particles rabbit knee	ISO10993-06 (adapted)

receiving the implant. In a subsequent, recent sheep study Actifit™ was implanted after partial meniscectomy, with partial meniscectomy serving as control [41]. The material was found not to negatively affect the articular cartilage. In addition, the friction coefficient of the Actifit™ did not appear to be significantly different from that of native meniscus after 3 months.

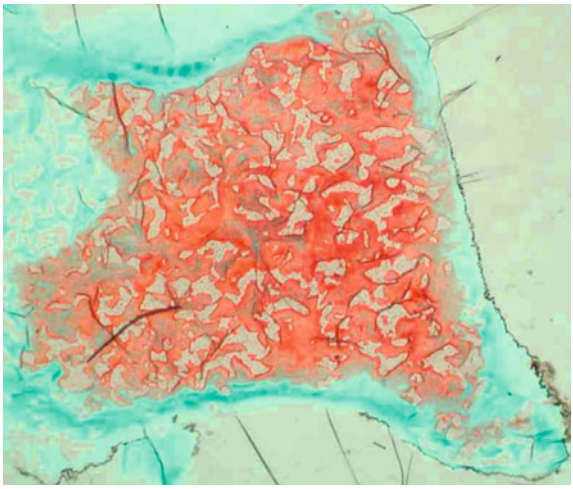

Fig. 7.4 Light micrograph of the posterior part of an Actifit™ implant, 24 months after implantation in a dog. *White areas* polymer; *green areas* fibrous tissue mainly containing type I collagen; *red areas* fibrocartilage-like tissue containing proteoglycans and mainly type II collagen

7.1.6 Clinical Results

Clinical results for Actifit™ showed significant improvement from baseline at 3, 6 and 12 months postimplantation, as evidenced by the Visual Analogue Scale (VAS), and the International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome (KOOS) and Lysholm scores. DCMRI scans showed tissue ingrowth in 85.7 % of subjects already at 3 months postimplantation, while biopsies at 12 months showed cells with meniscus-like differentiation potential [42]. In conclusion, Actifit™ is a novel, biocompatible, polymer device specifically designed for use as a matrix for tissue ingrowth to treat irreparable meniscal defects.

7.2 Technique and Results

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7.2.1 Introduction

Pain and other short and long-term sequelae of irreparable meniscal tears remain a challenge for the orthopedic community and there is a genuine need for an approach which will offer patients and surgeons new acceptable treatment options.

Orteq Ltd (London UK) has developed a polyurethane scaffold, Actifit®, for blood vessel ingrowth and meniscal tissue regeneration intended for the treatment of irreparable, painful meniscus tears and meniscal tissue defects. It is available in the medial and lateral configurations (Fig. 7.5). Criteria for use include an intact meniscal rim and sufficient tissue in the anterior and posterior horns to permit fixation of the scaffold. Other requirements include a well aligned and stable knee joint, an ICRS classification grade ≤ 3, a body mass index <35 kg/m^2 and the non-presence of systemic disease or infection sequelae.

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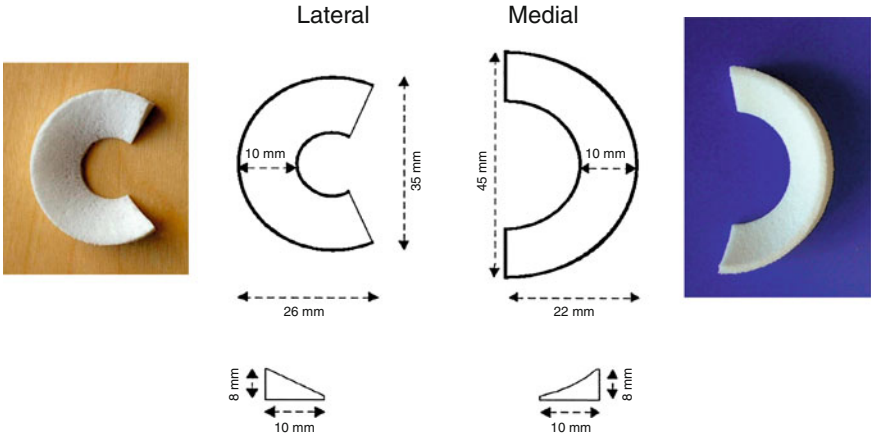

Fig. 7.5 The Actifit® meniscal scaffold comes in medial and lateral configurations

7.2.2 Implantation Procedure, Post-operative Care and Rehabilitation

7.2.2.1 Implantation Procedure

Implantation of the Actifit® meniscal scaffold is performed arthroscopically using standard surgical arthroscopic knee procedures and equipment. Detailed instructions and related warnings and precautions are set out in the Instructions for Use accompanying the device.

Using spinal or general anaesthesia at the discretion of the orthopaedic surgeon the implantation of the Actifit® meniscal scaffold is usually performed under tourniquet conditions. Thigh fixation may be used for appropriate valgus stress positioning.

Prior to implantation of either the medial and lateral scaffold, cartilage status and meniscal wall remnant status and integrity should be assessed. In the case of the lateral meniscus, meniscal wall integrity across the hiatus popliteus is essential for secure fixation and optimal tissue regeneration. All pathological cartilage and ligamentous findings should be carefully recorded.

In the case of a tight medial compartment, the medial collateral ligament (MCL) can be distended using the outside-in puncture method. Under valgus stress, and directed by the inside arthroscopic light, the surgeon is able to bring a needle in the posteromedial side of the knee joint into joint. The MCL is sensed and allows for progressive pie-crusting of the ligament until the appropriate opening is obtained.

The inside-out pie crusting release technique as described by Steadman can also be used. Under arthroscopic control, the posteromedial corner of the knee joint is visualised. Using the Steadman pick, the MCL can be reached and progressively

disrupted in order to open the knee joint appropriately until visualisation is obtained.

In the lateral compartment progressive pie-crusting release techniques as described above and used in the medial compartment are not possible because of anatomical considerations; however, lateral compartment narrowing is rare.

To facilitate healing, the meniscal rim can be punctured for vascular access channels and gentle rasping of the synovial lining is recommended. After debridement and preparation, the defect should reach into the red–red or red-white zone, approximately 1–2 mm from the synovial border. The defect should thereafter be measured along its inner margin using the meniscal ruler and meniscal ruler guide which accompany the Actifit® device.

The Actifit® meniscal scaffold should be measured and cut using a scalpel (Fig. 7.6). Sterility should be continually maintained. Care should be taken not to undersize the device. For the purpose of achieving a snug fit into the defect, the length of the scaffold should be oversized by approximately 10 %, i.e. 3 mm for small defects (<3 cm) and approximately 5 mm for large defects (≥3 cm). It is recommended that the anterior side be cut at an angle of 30–45° for easier suturing (Fig. 7.7).

For the implantation 2–3 small incisions for anteromedial and anterolateral portals are needed. An arthroscopic central transpatellar tendon portal is optional. For easy insertion of the scaffold, we recommend that the relevant portal is sized sufficiently to approximately the size of the little finger. In addition, a posteromedial or posterolateral incision may be required if an inside-out meniscal fixation technique is used.

Although the Actifit® material is easy to manipulate and is strong and flexible, it should be handled with care. The tailored Actifit® scaffold can be introduced into the knee joint through the anteromedial or anterolateral portal using a non cannulated tissue tension grasper such as the Acuflex Grasper Tissue Tensioner™ (Smith and Nephew) (Fig. 7.8). Marking the cranial and caudal scaffold surface

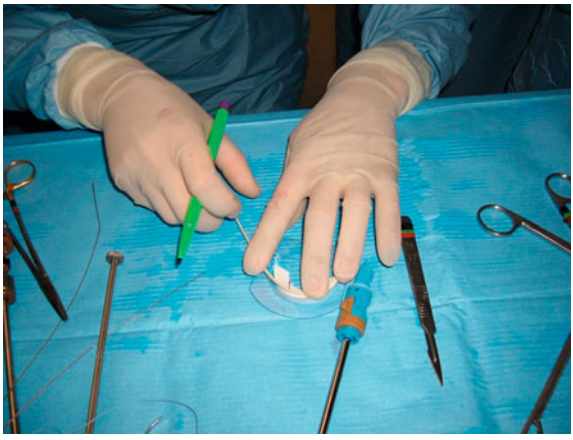

Fig. 7.6 The Actifit meniscal scaffold is tailored using a scalpel for a snug fit to the meniscus defect

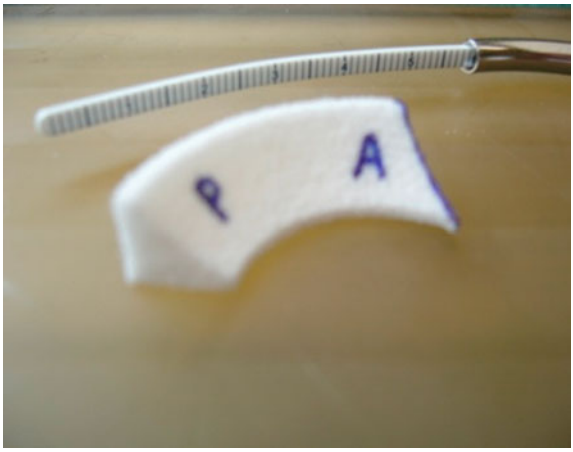

Fig. 7.7 The anterior side should cut at an angle of 30–45° for easier suturing

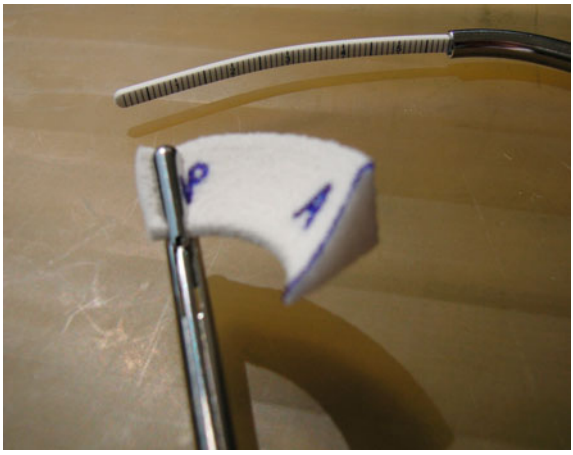

Fig. 7.8 The scaffold device should be manipulated using a blunt nose grasper. It is useful to mark the cranial and caudal meniscal scaffold surface

helps to avoid problems in positioning. The Actifit® scaffold should be clamped at the posterior part of the scaffold and placed into the knee joint through the anteromedial or anterolateral portal. To ensure a good initial position of the scaffold and facilitate fixation, a vertical holding suture may be placed in the native mensicus tissue to bring the scaffold through the eye of this holding suture.

Fixation of Actifit® is accomplished by suturing the scaffold to the native meniscus tissue. Standard commercially available size 2.0 non-resorbable sutures, such as polyester or polypropylene and braided or monofil sutures are recommended. Which suturing techniques are used depends on the location of the defect and the surgeon's experience and preference. All-inside suturing is commonly used for the posterior horn and posterior part of the rim. All-inside, inside-out and outside-in techniques may be used for the middle and anterior part of the rim.

Horizontal sutures with an outside-in technique are commonly used for the anterior horn.

Fixation should start with a horizontal all-inside suture from the posterior edge of the scaffold to the native meniscus. Suturing should be secure; however, sutures must not be over-tightened as they may alter and indent the surface of the scaffold. The distances between the sutures should be kept to approximately 0.5 cm (Fig. 7.9a). Each suture should be placed at one-third to one-half of the scaffold's height, as determined from the lower surface of the scaffold (Fig. 7.9b). Suturing through the musculus popliteus are not detrimental to later function.

Once sutured in place if required, the scaffold may be further trimmed and fine-tuned intra-articularly using a basket punch. Stability of the fixation is tested using the probe and carefully moving the knee through a range of motion (0–90°).

7.2.2.2 Post Operative Care

Following implantation of the Actifit® scaffold, pain and thromboprophylactic medications are administered at the surgeon's discretion and would be those typically administered following classic meniscal suturing.

Dependent upon the meniscal scaffold stability as determined at the end of the surgical procedure, a rigid removable brace may be used over a compression bandage in the first week post-implantation.

7.2.2.3 Post Operative Rehabilitation

Following implantation of the Actifit® scaffold the recommended post operative rehabilitation protocol should be strictly followed to ensure optimum conditions for healing and to protect the newly formed fragile tissue from potentially harmful stresses whilst tissue remodelling and maturation processes are ongoing during the

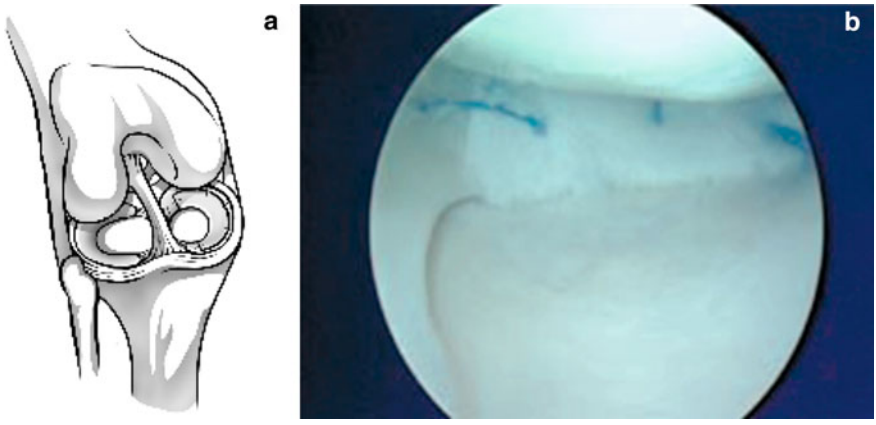

Fig. 7.9 **a** The distances between the sutures should approximately 0.5 cm. **b** Each suture should be placed at one-third to one-half of the scaffold height determined from the lower surface of the scaffold in order to allow proper fixation

first 3 months post-surgery. It is important that the rehabilitation protocol is reviewed and approved to be suitable for the patient in question by the responsible orthopaedic surgeon and carried out under the supervision of a professional physiotherapist.

Non weight-bearing is recommended until 4 weeks post-surgery. Partial weight bearing is permitted from 4 weeks onward with a gradual increase in loading up to 100 % load at 9 weeks post-implantation, at a rate of 10 kg per week for patients weighing ≤60 kg and 15 kg per week for patients weighing ≤90 kg, and without the use of the unloader brace from week 14 onwards.

Under the rehabilitation protocol, motion is initiated immediately after implantation, with bending up to 30° with full extension permitted in weeks 1 and 2. Flexion is increased to 60° in week 3, and to 90° in weeks 4 and 5. From week 6 onwards, flexion is further increased until a full range of motion is achieved; however, forceful movements should be avoided. Light exercise, including isometric quadricps exercises, mobilsation of the patella, heel slides, quad sets, anti-equinus foot exercises and Achilles tendon stretching, is advised from week 1. As of 9 weeks, additional exercises, including increased closed hamstring exercises, lunges between 0 and 90°, proprioception exercises, dynamic quadriceps expercises and use of a home trainer, are indicated. Increased open and closed exercises, jogging on level ground, plyometris and sports-related exercises without pivot are recommended from week 14 onwards. Hydrotherapy and swimming (crawl and headstroke) can commence 24 weeks post-implantation. Gradual resumption of other sports is generally commenced as of 6 months at the discretion of the responsible orthopaedic surgeon; however, contact sports should be resumed only after 9 months.

7.2.3 Clinical Results

Safety, performance and efficacy results to support use of the Actifit® scaffold in the treatment of painful irreparable meniscal defects were obtained from a prospective, non-randomised, single-arm, clinical investigation conducted at 9 orthopaedic centres of excellence located throughout Europe. Patients recruited (N = 52) had an irreparable medial or lateral meniscus tear or partial meniscus loss, intact rim, presence of both horns and a stable well-aligned knee.

Thirty-four patients were treated with a medial meniscal scaffold and 18 patients were treated with a lateral meniscal scaffold. Demographics and baseline characteristics were representative of the population for which Actifit® is intended. The mean patient age was 30.8 ± 9.4 years and 75 % were male. The mean longitudinal defect length was 47.1 ± 10.0 mm.

The study follow-up period was 24 months and the study has been reported in the American Journal of Sports Medicine [43].

7.3 Safety Results

Nine index knee-related Serious Adverse Events (SAEs) were reported in the study (five in the medial and four in the lateral indication. Three of these in the medial indication and three in the lateral indication resulted in withdrawal. Four of the nine SAEs were reported as unrelated to the scaffold and to the procedure; four were reported as procedure related; none were reported as having a definite, probable, or possible relationship to the Actifit® scaffold.

One SAE was reported as having an unknown relationship to the Actifit® scaffold and to the procedure. This was the removal of an almost completely nonintegrated scaffold, which took place at the protocol stipulated relook arthroscopy. The patient was asymptomatic and importantly no signs of inflammatory reaction to the scaffold and no evidence of cartilage damage were observed during gross examination. A biopsy specimen taken from the meniscus rim post removal of the nonintegrated scaffold material showed cell-populated scaffold material integrated with tissue. No inflammatory reaction to the scaffold was observed in the biopsy. It was concluded that the integration failure was most likely due to lack of biological response.

Cartilage scores in the index compartment were assessed at 3, 12 and 24 months post-implantation using anatomic MRI scans. Stable or improved cartilage status at 24 months was demonstrated in 92.5 % (37/40) of patients compared with baseline status.

7.3.1 Efficacy Results

Pain and functionality were assessed using validated clinical outcome scores. The Visual Analog Scale (VAS), was used for knee pain, at 3, 6, 12 and 24 months post-implantation. The International Knee Documentation Committee (IKDC), the Lysholm score, as well as the Knee and Osteoarthritis Outcome Score (KOOS) were used to assess functionality.

For functionality on IKDC and Lysholm scores and for pain (VAS), statistically and clinically significant improvements from baseline to 24 months were reported at 3, 6, 12 and 24 months post implantation ($p < 0.05$).

Statistically and clinically significant improvements ($p < 0.05$) were also reported for the five KOOS subcomponents: for pain, activities of daily living and quality of life at 3, 6, 12 and 24 months, and for sports/recreation and symptoms at 6, 12 and 24 months post implantation.

7.3.2 Evidence of New Tissue Formation

Tissue ingrowth into the Actifit® scaffold was assessed during the protocol stipulated relook arthroscopy at 12 months (n = 44) by gross examination and histological examination of biopsies from the inner free edge of the implanted scaffold.

Presence of vital tissue with no necrosis or cell death and hence consistent with biocompatibility of the scaffold was observed in all 44 biopsies at 12 months. Moreover, the histology data suggested an ongoing process of regeneration, remodelling and maturation towards tissue resembling the human meniscus.

Tissue ingrowth was also assessed at 3 months post-implantation by evidence of vascularisation in the scaffold using diagnostic contrast enhanced MRI (DCE-MRI) (n = 43). All scans were assessed for neovascularisation in the peripheral half of the scaffold meniscus.

At 3 months post-implantation, early evidence of tissue ingrowth was observed on DCE-MRI in the peripheral half of the scaffold, in 35 of 43 (81.4 %) patients.

7.3.3 Conclusion

No safety concerns, other than those generally acknowledged with this type of surgery, were identified. Importantly, no safety issues related to the device, including cartilage damage or inflammatory reaction to the Actifit® scaffold or its degradation products, were observed. Efficacy data showed significant (statistical and clinical) improvement from pre-operative status for the subjective clinical outcome scores as of 3–24 months post-implantation. The 24-month clinical results provide strong evidence of the safety and efficacy of the Actifit® scaffold treatment option for a patient group for whom currently only restricted treatment options are available. In addition, compared to partial meniscectomy, treatment of irreparable meniscus defects with the Actifit® scaffold has the benefit of promoting new tissue generation.

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