Protocol title:

A Prospective Multicenter Open-label Randomized Controlled Trial of Agili-C™ vs. Surgical Standard of Care (SSOC) for the Treatment of Joint Surface Lesions of the Knee

Protocol number: CLN0021 Rev 2

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1. Investigator Agreement

In applying to be an Investigator for the clinical study of the CartiHeal's Agili-C device I understand that I must comply with this Agreement as a condition for conducting clinical studies with this device, which is limited to investigational use.

1. I am submitting with this signed statement a summary of my education and experience.

2. I understand I must abide by the following conditions governing my receipt and use of the Agili-C for clinical study:

   a) CartiHeal is required to furnish me with full information concerning the preclinical investigations that justify clinical studies, together with fully informative material describing any prior investigations, any side effects and any precautions to be taken into account in the course of the clinical study.

   b) I am required to maintain adequate records regarding all devices received and used by me including any serial numbers, dates, and quantities. If the clinical study is terminated, suspended, discontinued, or completed, or as otherwise requested by SciVance Consulting, I am to return to the sponsor, any unused supplies unless other arrangements are made.

   c) I am required to prepare and maintain adequate, accurate and complete patient case histories, including all required Case Report Forms as specified in the study protocol, and to record all observations and other data pertinent to the clinical study of each patient enrolled as a study subject in the clinical investigation of the Agili-C.

   d) I understand I am to furnish my records of the clinical study to the Sponsor including reports which I agree to submit at prescribed intervals as required and to comply with all related record and report requirements and conditions of approval as established by the Institutional Review Board/Research Committee/Ethical Committee (IRB/RC/EC), 21 C.F.R. Part 56, and the IDE regulation.

   e) I agree to maintain records of the disposition of the device and the case histories for a minimum period of two years following the latter of: (1) the date the records are no longer required for supporting an application for clearance or approval of the device or (2) the date the clinical study is discontinued.

f) Upon the request of an authorized employee of the FDA, I will make records related to the clinical study available for inspection and copying. The patients' names need not be divulged unless the records of a particular individual require a more detailed study or unless there is a reason to believe that the records do not represent actual cases studied or do not represent actual results obtained.

g) I certify that the Agili-C for clinical study will be provided only to patients under my personal supervision. I certify that each additional investigator has read this Agreement and agreed to comply with its terms.

h) I further certify that the Agili-C will not be supplied by me to any investigator with patients not properly enrolled in this investigational study.

i) I certify I will inform any patients involved in the clinical study, including representatives of such patients, that the Agili-C is being used for clinical studies for the treatment of joint surface lesions of the knee. In accordance with 21 C.F.R. Part 50, prior to including any patient as a subject in this investigation, I will obtain the informed consent of the patient or her representatives for the implantation and the study of the Agili-C and for the subsequent submission of the patient's medical data to the Sponsor.

3. I agree that the Agili-C will be used by me in accordance with the SciVance Consulting's Investigational Plan (protocol) and in accordance with the FDA regulations defining the procedure, conditions and requirements applicable to the investigational studies for medical devices under 21 C.F.R. Part 812. No implantation of the Agili-C will be performed until all personnel have been properly trained.

4. Any and all deviations from the approved protocol that affect the rights, safety or welfare of the patients or affect the scientific validity of the study must have prior approval of FDA unless there is an emergency as defined in 21 C.F.R. § 812.150(a)(4). I will not proceed with a non-emergency deviation from the protocol without SciVance Consulting and FDA approval. I will report all deviations from the protocol and all complications to the designated CRO for this study.

5. If applicable, I am submitting with this statement all information regarding investigational studies or research in which I participated as an investigator, that were terminated on the

order of a Sponsor, an IRB, or the FDA prior to their intended termination. I have checked here whether I have ☐ or have not ☐ participated in such terminated studies.

6. Prior to initiating the study, I will provide the SciVance Consulting with a written disclosure of any financial interest including, but not limited to, cash payments, stock, stock options, patents or other proprietary interests in the SciVance Consulting or study monitor, in accordance with 21 C.F.R. Part 54.

7. I understand that SciVance Consulting is required by law to discontinue shipments of Agili-C to me during the clinical study if I fail to comply with the Investigational Plan or any FDA regulations or conditions of approval applicable to the study, as well as requiring me to return all devices and materials supplied by SciVance Consulting for use in the investigational procedure.

8. I understand that I may not begin this study until both FDA and IRB approval of the study protocol have been obtained and until I have provided the Sponsor with a copy of the written IRB approval. While the study is ongoing, I will cooperate with SciVance Consulting and its clinical and medical monitors in the conduct of the study.

I agree to conduct the investigation in accordance with this Agreement, the investigational plan, all applicable FDA regulations, and any conditions of approval imposed by the reviewing IRB or FDA.

NAME:_____

SIGNED:_____
(Investigator)

DATE:_____

SIGNED PAGE OF PRINCIPAL INVESTIGATOR AGREEMENT IS ATTACHED

NAME:_____

SIGNED:_____
(Company Representative)

DATE:_____

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3. Study Protocol Synopsis

Protocol No.:	CLN0021
Sponsor:	Elaine J. Whitmore, Ph.D. SciVance Consulting 7113 River Club Blvd. Bradenton, Florida 34202
Title:	A Prospective Multicenter Open-label Randomized Controlled Trial of Agili-C™ vs. Surgical Standard of Care (SSOC) for the Treatment of Joint Surface Lesions of the Knee
Study Device:	Agili-C™ is a porous scaffold designed for the treatment of joint surface lesions of the knee
Study Phase:	Pivotal Study
Study Type:	Interventional
Indication for Use:	The Agili-C™ scaffold is indicated for the treatment of an ICRS grade III or above knee-joint surface lesion(s), with a total treatable area of 1-7cm^2 and without severe osteoarthritis (Kellgren-Lawrence grade 0-3)
Study Design:	Number of Centers: up to 30 The subjects in the study will be randomized by site using variable block sizes. The subjects in the study will be stratified by extent of osteoarthritis, defined dichotomously by the Kellgren–Lawrence grade: • Strata I: 0 & 1 • Strata II: 2 & 3 The study will recruit and take place in US and OUS sites Allocation: 2:1 (Agili-C™:SSOC) Masking: Open-Label, adaptive design with interim analyses
Estimated Enrollment:	250 - 500 subjects, depending on results of interim analyses

Study Population:	Patients with joint surface lesions of the knee
Study Arms:	Experimental: Agili-C™ Control: Surgical Standard of Care
Surgical Standard of Care Modalities as per Algorithm (Control)	Surgical Care Modalities are chosen according to algorithm: • Debridement (Deb.) • Microfracture (MFX)
Follow up:	24 months per subject
Primary Study Objectives:	To evaluate the superiority of Agili-C™ vs. SSOC
Primary Endpoint:	Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports)
Safety Endpoint:	Adverse events, including serious adverse events, reoperations and revisions, up to 24 months
Confirmatory Secondary Endpoints:	This trial will have one primary endpoint and 4 confirmatory secondary endpoints for labeling purposes. These will be tested sequentially and Type I Error controlled hierarchically. Trial success will be declared if the primary endpoint has been met. Additional labeling claims will be made for confirmatory secondary endpoints met in sequence following success on the primary endpoint • Change from baseline to 24 months in KOOS Pain subscore • Change from baseline to 24 months in KOOS QOL subscore • Change from baseline to 24 months in KOOS ADL subscore • Overall KOOS responder rate (defined as an increase from baseline to 24 months of ≥ 30 points on overall KOOS)

Additional Secondary Endpoints:	• Percentage of Articular Defect Fill according to MRI at 12, and 24 months • Change from baseline in average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) at 6, 12, and 18 Months • Change from baseline in IKDC Subjective Knee Evaluation at 12, 18, and 24 Months • Change from baseline in Tegner score at 12, 18, and 24 Months • Change from baseline QOL as measured by SF-12 v2 at 6, 12, 18, and 24 Months • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with chondral lesions • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with osteochondral lesions • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with single lesion • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with multiple lesions • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients without osteoarthritis (K/L 0-1) • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with osteoarthritis (K/L 2-3) • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with total lesion(s) size ≤3cm²

	• Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with total lesion(s) size >3cm² • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients without previous ligament reconstruction • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with intact meniscus • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with previous partial meniscectomy • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with concomitant partial meniscectomy • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in active patients • Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in non-active patients
Inclusion Criteria:	1. 21 -75 years 2. Up to 3 treatable joint surface lesion(s), ICRS Grade III or above, on the femoral condyles and/or trochlea 3. Symptomatic total treatable area 1-7 cm^2. Asymptomatic lesions will not be included in the calculation 4. Must be physically and mentally willing and able to comply with the post-operative rehabilitation protocol and scheduled clinical and radiographic visits

	5. Signed and dated the IRB/Ethics Committee approved Informed Consent Form and HIPPA (if applicable) 6. Non-responsive to physical therapy for at least 3-4 weeks
Exclusion Criteria:	1. KOOS Pain Subscale score at baseline is less than 20 or more than 65 (scale: maximum pain =0, pain free =100) 2. Bony defect depth deeper than 8mm, according to baseline MRI/X-ray/arthroscopy 3. Articular cartilage lesions in the tibia or the patella, ICRS grades IVa or above 4. Osteoarthritis of the index knee graded 4 according to the Kellgren-Lawrence Grading 5. Significant instability of the index knee according to IKDC Knee Examination Form 2000, Grade C (abnormal) or D (severely abnormal) 6. Malalignment more than 8 degrees varus OR 8 degrees valgus according to standing X-ray 7. Lack of functional remaining meniscus, at least 5mm rim at the end of the procedure 8. Meniscal transplantation in the past 6 months 9. Any known tumor of the index knee 10. Any known history of intra-articular or osseous infection of the index knee 11. Any evidence of active infection anywhere in the body. Urinary Tract Infection (UTI) patients can be included following antibiotic treatment, and provided that two consecutive cultures are negative (taken within at least 2 weeks of each other) 12. Any known history of inflammatory arthropathy or crystal-deposition arthropathy

	13. Any known systemic cartilage and/or bone disorder, such as but not limited to, osteoporosis, chondrodysplasia or osteogenesis imperfecta 14. Body Mass Index (BMI) > 35 15. Chemotherapy in the past 12 months 16. Any previous surgical cartilage treatment (such as: microfracture, ACI, OATS, etc.) in the index knee within the last 6 months 17. Any previous ligamentous repair or malalignment correction in the index knee within the last 6 months 18. History of allergic reaction or intolerance of materials containing calcium carbonate or hyaluronate 19. Patient who is pregnant or intends to become pregnant during the study 20. History of any significant systemic disease, such as but not limited to: HIV, hepatitis, HTLV, syphilis, and coagulopathies 21. Known substance or alcohol abuse 22. Participation in other clinical trials within 60 days prior to the study or concurrent with the study 23. Known insulin dependent diabetes mellitus 24. Unable to undergo either MRI or X-ray 25. Use of anticoagulation medication or antiaggregant medication; however up to 100 mg Acetylsalicylic acid (ASA) daily is allowed 26. Previous intra-articular steroid injection within the last 1 month 27. Prisoners 28. Uncontained lesion - Lack of vital bone wall, at least 2mm thick, completely surrounding the lesion - based on MRI/X-ray/arthroscopy 29. Inability to position the implant 2mm recessed relative to the articular surface - based on MRI/X-ray/arthroscopy

Methods:	• Candidates will be evaluated by the investigator based on an MRI (NMT one year old), X-ray (AP and Lateral; NMT one year old), clinical history and physical examination
	• Prior to Screening, the candidate will sign and date the ICF using the IRB/EC approved form in accordance with local regulations
	• Following signing of the informed consent, subjects will undergo Initial Screening using study questionnaires.
	• The investigator will send the MRI and X-ray (AP and Lateral) for off-site evaluation, by an independent radiologist, in order to determine the level of osteoarthritis according to Kellgren-Lawrence grade.
	• In cases of K/L <4 and absence of clear exclusion criteria on MRI (as determined off-site), subjects will undergo Final Screening via Arthroscopy, not more than 90 days after Initial Screening. Arthroscopic findings will verify the subject's eligibility for study enrollment, and if found eligible will be Enrolled into the study and Randomized intra-operatively into either Agili-C™ or SSOC
	• During the course of the procedure, mechanical-symptom generating lesions will be managed (such as synovectomy, loose body removal and partial menisectomy)
	  ○ Agili-C™: Agili-C™ implantations will be performed via an arthrotomy or mini-arthrotomy procedure, using a designated surgical toolset
	  ○ SSOC: microfracture and/or debridement procedures will be performed arthroscopically according to standard practice
	• Ligamentoplasty is not allowed concomitantly

	• Follow-up will be performed at 2 weeks and at 3, 6, 12, 18 and 24 months post-procedure to evaluate the patient's knee condition and clinical health • Questionnaires will be completed at baseline and at 6, 12, 18 and 24 months and yearly thereafter, until the last patient exits the study at 24 months • Anterior-Posterior (A/P) and Lateral knee X-rays will be taken at 2 weeks and at 6, 12, 18 and 24 months post procedure • MRI according to specific protocol will be performed at 12 and 24 months. Additionally, MRI will be performed at 3 and 6 months for an initial cohort of at least 25 patients per study group • Drug use will be recorded at each visit, including pain medication • Patients that drop out or withdraw consent will not be replaced.
Statistical Considerations:	See Section 13
Off-site Imaging Analysis:	X-ray - Kellgren–Lawrence grade MRI – Evaluation of baseline criteria and Defect Fill

4. List of Abbreviations

- ACL = Anterior Cruciate Ligament
- ADL=Activities of Daily Life
- AE = Adverse Event
- AIC = Akaike information criterion
- ASA= Acetyl Salicylic Acid
- CFR= Code of Federal Regulations
- CIP = Clinical Investigation Plan (protocol)
- CKC = closed kinetic chain
- CPM = Continuous Passive Motion
- CRA = Clinical Research Associate
- CRF = Case Report Form
- EAC = Endpoint Adjudication Committee
- EC = Ethics Committee
- FU = Follow up
- FAS= Full analysis Set
- FDA = Food and Drug Administration
- GCP = Good Clinical Practice
- HA = Hyaluronic Acid
- ICRS = International Cartilage Repair Score
- IEC = Independent Ethics Committee
- IFU= Information for User
- IKDC = International Knee Documentation Committee
- IRB= Institutional Review Board
- KOOS = Knee injury and Osteoarthritis Outcome Score
- LFC = Lateral Femoral Condyle
- LV = Last Visit
- MCID= Minimum Clinically Important Difference
- MCL = Medial Collateral Ligament

- MCSD= Minimal Clinically Significant Difference
- MFC = Medial Femoral Condyle
- MMRM = Mixed-Effect Model Repeated Measure
- mITT= Modified intention to treat population
- MPFL = Medial Patellofemoral Ligament
- MRI= Magnetic resonance imaging
- NMT = Not More Than
- NSAIDs=Non-Steroidal Anti-Inflammatory Drugs
- OA = Osteoarthritis
- OATS = Osteoarticular Transfer System
- OKC = Open kinetic chain
- OUS = Outside United States
- PCL = Posterior Cruciate Ligament
- PPS= Per Protocol Analysis Set
- PSR = Periodic Summary Report
- PRO = Patient Reported Outcome
- ROM = Range of motion
- SAE = Serious Adverse Event
- SD = Source Documents
- SDV = Source Document Verification
- SSOC = Surgical Standard of Care
- Trial Cohort = Patient Group for Efficacy Evaluation
- USADE = Unanticipated Serious Adverse Device Effect
- US = United States

5. Background and Rationale

The development of the Agili-C™ implant was based on the innovative concept of using two well-known FDA-approved devices to create a scaffold for treating joint surface lesions.

5.1 Joint Surface Lesions

Joint surface lesions (JSL) involving the articular cartilage and the subchondral bone are a common clinical problem in orthopedics. JSL can be superficial, partial thickness cartilage defects, which do not involve the subchondral bone, and full thickness lesions which cross the osteochondral junction[1]. Lesions of the joint surface remain a major clinical challenge, due mainly to the poor self-healing ability of articular cartilage. If left untreated, these joint surface lesions can lead to secondary osteoarthritis (OA). Hence, symptomatic chronic full-thickness defects of the knee joint surface require intervention for symptom relief and to prevent possible evolution towards OA. JSLs are very common, being reported in about 20% of all arthroscopic procedures[2,3]. JSLs are clinically important as they can be symptomatic and disabling, with pain and/or locking of the joint, and can lead to further cartilage loss and development of OA[4].

The natural history and consequence of JSLs in established OA joints has also been investigated. Davies-Tuck et al. prospectively recorded chondral lesions in a cohort of patients with osteoarthritis[5]. In this cohort, chondral injuries worsened in 81% of the cases and improved in only 4% over 2 years. In a similar prospective study, Wluka et al. showed that the presence of cartilage defects in patients with established symptomatic OA was associated with disease severity and was a predictor of joint replacement within 4 years[6].

In summary, JSLs can complicate and accelerate the course of OA. Thus, their treatment may be of functional benefit to the patient.

5.2 Coral Based Scaffolds

Coralline skeletal material is composed of calcium carbonate in the crystalline form of aragonite. These biomaterials provide a three-dimensional (3D) structure with mechanical properties and high interconnected macroporosity (between 100 and 200 µm) required for vascular tissue ingrowth[7]. These characteristics are thought to confer aragonite its osteoconductive ability and make it suitable for bone repair. The calcium carbonate structures are gradually resorbed and replaced by functional bone tissue.

Coral derivatives are commonly used as a bone graft substitute and bone void fillers. Several products are FDA-cleared, for example, Pro-Osteon 200R (Biomet, K000515) and BoneMedik (Metabiomed, K070897) are biocompatible bone substitutes based on natural coral.

5.3 The Role of Hyaluronic Acid in Mechanical Lubrication

Hyaluronic acid (HA) is routinely used for viscosupplementation in OA. The HA added to the top of Agili-C™ provides mechanical lubrication.

5.4 Device Description

Agili-C™ is a porous scaffold designed for the treatment of knee-joint surface lesions. Agili-C™ consists of a porous, interconnected calcium carbonate (aragonite) derived from purified, inorganic coral exoskeleton (Figure 1). The lower part of the implant is composed of inorganic aragonite and the top of the implant is mechanically modified with drilled channels (Figure 2). Histology performed by an independent laboratory in a series of preclinical studies confirmed the regeneration of hyaline cartilage, as demonstrated by the presence of collagen type II and aggrecan, and the lack of collagen type I in the repaired tissue, alongside the reconstruction of the subchondral bone.

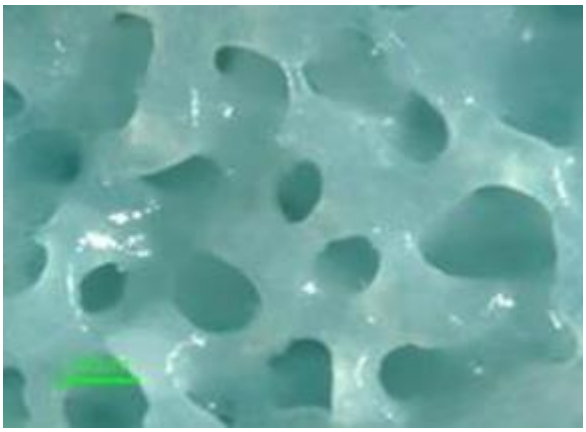

Figure 1: Coral exoskeleton

Agili-C™ is supplied sterile in various sizes from 6-20mm in diameter and 8-15mm in length, conically shaped (2°chamfer/morse), enabling treatment of different sized lesions. The implant is intended for single use only, and should not be re-sterilized. Agili-C™ implantation should only be performed by qualified surgeons. Single or multiple implants can be used in the same joint.

Figure 2: Agili-C™ implant

5.5 Mode of Operation

The Agili-C™ implant is composed of calcium carbonate in aragonite crystalline form. The implant is intended to treat knee-joint surface lesions. The Agili-C™ implant exhibits a combination of interconnected porous architecture and crystalline structure. This study is

intended to demonstrate the superiority of the Agili-C™ when compared to SSOC in the treatment of joint surface lesions.

5.6 Device Traceability

Each Agili-C™ implant is identified by a lot number, serial number and expiration date. The Sponsor will keep records to document the physical locations of all investigational devices from shipment of investigational devices to the investigation sites until their return or disposal. Device usage will be documented by Principal Investigator in the patient's medical chart and on the study CRF.

6. Justification for Study Design

6.1 Study Design

The current study compares the efficacy and safety of the Agili-C™ implant to Surgical Standard of Care treatment in patients suffering from joint surface lesions of the knee. The patient population is heterogeneous, involving different kinds of joint surface lesions: focal lesions, osteochondral defects and mild to moderate osteoarthritis, including multiple defects.

6.2 Current Treatment Options

The patient population in the study may suffer from a diversity of joint surface lesions. Currently, no gold standard treatment exists which is applicable for all types of joint surface lesions. Small focal defects are frequently treated by microfracture, while large, multiple and diffuse lesions are typically treated by debridement.

As shown in a series of clinical studies OUS, the Agili-C™ implant offers the potential to treat a wide range of joint surface lesions, such as: focal defects, large and degenerative lesions, osteochondral defects and mild to moderate osteoarthritis.

6.3 Control Group Treatment Algorithm

As no single, current therapy can be used as a single comparator for the treatment of the above described defect range, the most appropriate approach is to compare the device with the current general practice (e.g. Surgical Standard of Care) that includes two surgical options: Debridement and Microfracture – according to the following algorithm (Figure 3):

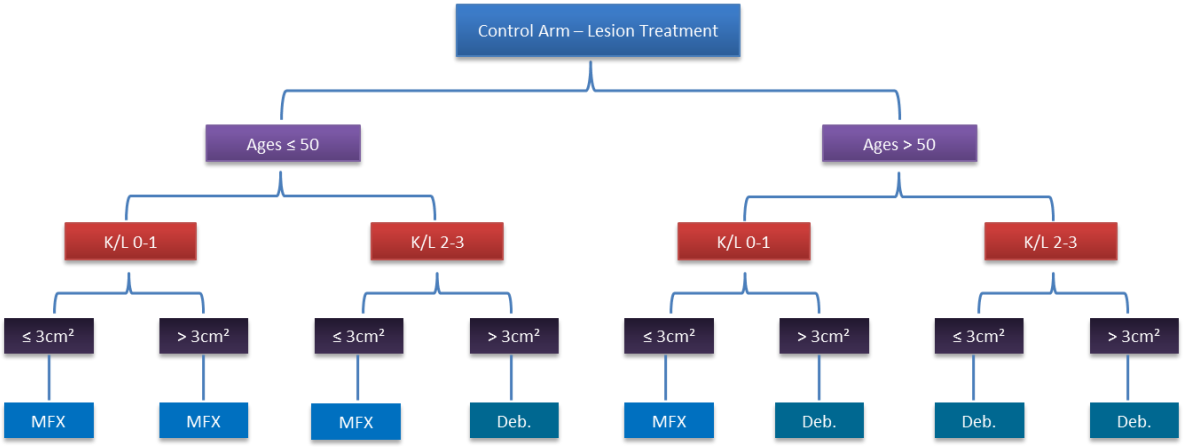

Figure 3: Control Group Treatment Algorithm

In accordance with this algorithm, in two subgroups there is a possibility for mixed treatment in the same joint, according to the lesion's size. For example, a male patient, 42 years old, with K/L=3 and two symptomatic lesions: one lesion - 1.4cm^2 on the trochlea, and another lesion - 5.2cm^2 on the medial condyle, will be treated with MFX in the small lesion and debridement in the large lesion.

6.4 Flow Chart

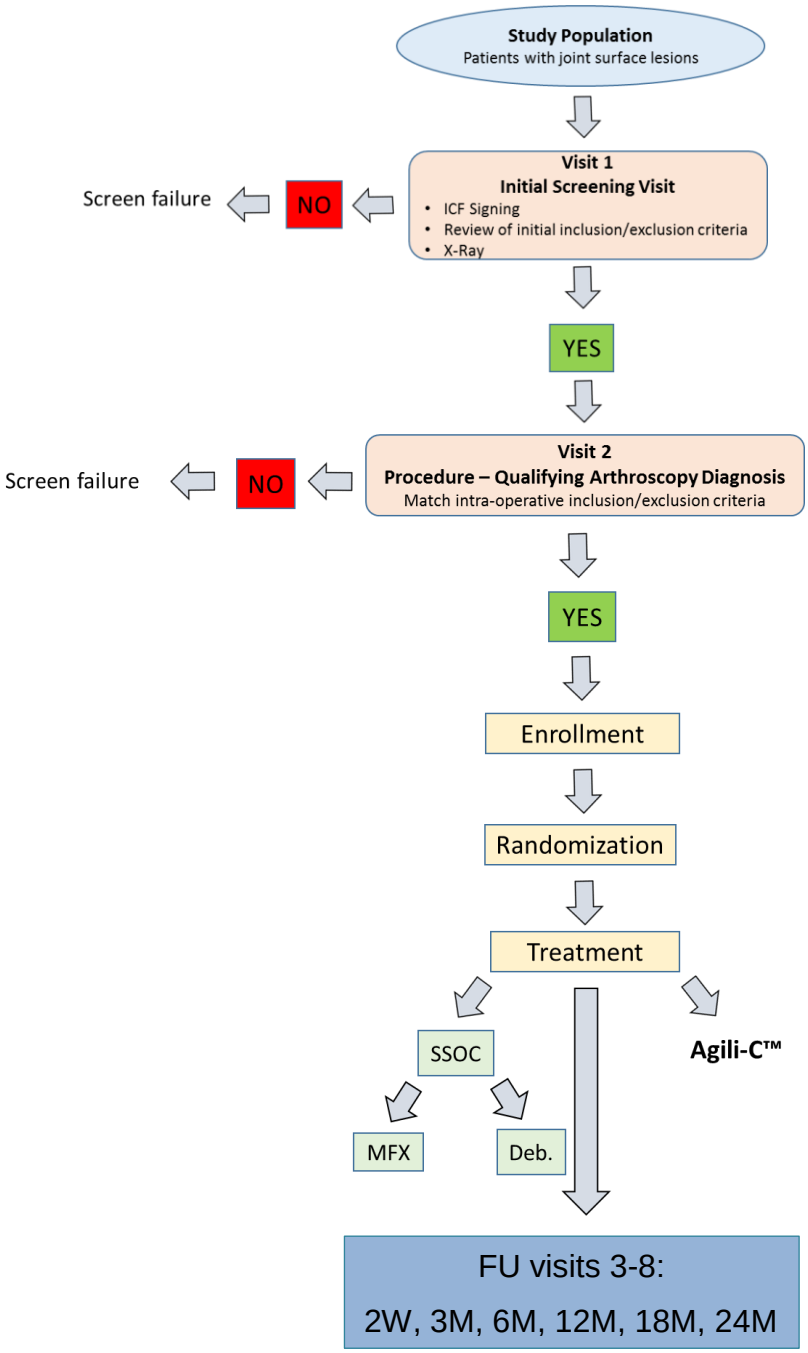

Figure 4: Study Flowchart

6.5 Study Objective

To evaluate the superiority of Agili-C™ vs. SSOC

6.6 Clinical Hypotheses

The underlying clinical hypothesis of this study is that the Agili-C™ implant is superior to SSOC according to the overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) at 24 months relative to baseline.

6.7 Overall Study Design

This is a prospective, multicenter, open-label, randomized, and controlled trial of Agili-C™ vs. SSOC for the repair of joint surface lesions. Candidates will be evaluated by the investigator based on an MRI and X-ray (NMT one year old), clinical history and physical examination. Prior to Screening, the candidate will sign and date the ICF. Following signing of the informed consent, subjects will undergo Initial Screening using study questionnaires. The PI will send the candidate's MRI and standing X-ray for on off-site K/L assessment. In case of K/L<4 and absence of clear exclusion criteria as seen on baseline MRI, not more than 90 days after Initial Screening, subjects will undergo Final Screening via Arthroscopy. Arthroscopic findings will verify the subject's eligibility for study enrollment, and if found eligible will be enrolled into the study and randomized intra-operatively into either Agili-C™ or SSOC. Agili-C™ implantations will be performed via an arthrotomy or mini-arthrotomy procedure, using a designated surgical toolset. In SSOC, microfracture and/or debridement procedures will be performed arthroscopically according to standard practice. Follow-up will be performed at 2 weeks and at 3, 6, 12, 18 and 24 months post-procedure to evaluate the patient's knee condition and clinical health. Questionnaires will be completed at baseline and at 6, 12, 18 and 24 months and yearly thereafter until the last patient exits the study at 24 months. Anterior-Posterior (A/P) and Lateral knee X-rays will be taken at 2 weeks and at 6, 12, 18 and 24 months post procedure. MRI according to specific protocol will be performed at 12 and 24

months. Additionally, MRI will be performed at 3 and 6 months to an initial cohort of at least 25 patients per study groups.

6.8 Patient Population

The patient population is composed of patients with joint surface lesions of the knee.

6.9 Indication for Use

The Agili-C™ scaffold is indicated for the treatment of an ICRS grade III or above knee-joint surface lesion(s), with a total treatable area of 1-7cm^2 and without severe osteoarthritis (Kellgren-Lawrence grade 0-3).

6.10 Number of Subjects

250 - 500 subjects. The design incorporates multiple interim analyses to determine the appropriate sample size (e.g. a “Goldilocks” strategy, see Broglio et al)

6.11 Number of Centers, Randomization and Allocation

Number of Centers will be up to 30.

The subjects in the study will be randomized by site using variable block sizes.

The subjects in the study will stratified by extent of osteoarthritis, defined dichotomously by the Kellgren-Lawrence grade:

- Strata I: 0 & 1
- Strata II: 2 & 3

The study will recruit subjects in US and OUS sites.

6.12 Treatment Groups

- Experimental: Agili-C™
- Control: Surgical Standard of Care (SSOC)

6.13 Inclusion Criteria

1. 21 – 75 years
2. Up to 3 treatable, joint surface lesion(s), ICRS Grade IIIa or above, on the femoral condyles or trochlea
3. Symptomatic total treatable area 1-7 cm^2. Asymptomatic lesions will not be included in the calculation
4. Must be physically and mentally willing and able to comply with the post-operative rehabilitation protocol and scheduled clinical and radiographic visits
5. Signed and dated the IRB/Ethics Committee approved Informed Consent Form and HIPPA if applicable
6. Non-responsive to physical therapy for at least 3-4 weeks

6.14 Exclusion Criteria

1. KOOS Pain Subscale score at baseline is less than 20 or more than 65 (scale: maximum pain =0, pain free =100)
2. Bony defect depth deeper than 8mm, according to baseline MRI/X-ray/arthroscopy
3. Articular cartilage lesions in the tibia or the patella, ICRS grade IVa or above
4. Osteoarthritis of the index knee graded 4 according to the Kellgren-Lawrence Grading
5. Significant instability of the index knee according to IKDC Knee Examination Form 2000, Grade C (abnormal) or D (severely abnormal)
6. Malalignment more than 8 degrees varus OR 8 degrees valgus according to standing X-ray
7. Lack of functional remaining meniscus, at least 5mm rim at the end of the procedure
8. Meniscal transplantation in the past 6 months
9. Any known tumor of the index knee
10. Any known history of intra-articular or osseous infection of the index knee

11. Any evidence of active infection anywhere in the body. Urinary Tract Infection (UTI) patients can be included following antibiotic treatment, and provided that two consecutive cultures are negative (taken within at least 2 weeks of each other)
12. Any known history of inflammatory arthropathy or crystal-deposition arthropathy
13. Any known systemic cartilage and/or bone disorder, such as, but not limited to, osteoporosis, chondrodysplasia or osteogenesis imperfecta
14. BMI > 35
15. Chemotherapy in the past 12 months
16. Any previous surgical cartilage treatment (such as: microfracture, ACI, OATS, etc.)in the index knee within the last 6 months
17. Any previous ligamentous repair or malalignment correction in the index knee within the last 6 months
18. History of allergic reaction or intolerance of materials containing calcium carbonate or hyaluronate
19. Patient who is pregnant or intends to become pregnant during the study
20. History of any significant systemic disease, such as, but not limited to, HIV, hepatitis, HTLV, syphilis, and coagulopathies
21. Known substance or alcohol abuse
22. Participation in other clinical trials within 60 days prior to the study or concurrent with the study
23. Known insulin dependent diabetes mellitus
24. Unable to undergo either MRI or X-ray
25. Use of anticoagulation medication or antiaggregant medication; however up to 100 mg Acetylsalicylic acid (ASA) daily is allowed
26. Previous intra-articular steroid injection within the last 1 month
27. Prisoners
28. Uncontained lesion - Lack of vital bone wall, at least 2mm thick, completely surrounding the lesion - based on MRI/X-ray/arthroscopy

29. Inability to position the implant 2mm recessed relative to the articular surface - based on MRI/X-ray/arthroscopy

6.15 Risks

The Agili-C™ implant is designed to treat joint surface lesions. The device is a biodegradable implant. The PI must be a qualified orthopaedic surgeon that has undergone pre-procedure training by the Sponsor. Following are risks that may occur while using the device:

- Improper implantation due to incorrect surgical technique and not according to the IFU.
- Creation of an improper implantation site may lead to implant breakage, instability, implant loosening and device failure.
- The defect site must exhibit vital bone on its entire circumference otherwise implant integration may not occur.
- Incorrect orientation of implant positioning may lead to improper healing.
- The implant must be inserted into the defect in a pressed fit manner. Non-press fit positioning may lead to failure due to lack of implant integration.
- Implantation using a non-designated surgical toolset may lead to implant fracture or misplacement.
- Incorrect use of the surgical toolset can lead to bone breakage, damage to neurovascular structures, bone cyst formation or improper implantation site creation. The surgeon must take into consideration the joint geometry especially with regard to notch, lateral and trochlear lesions. If there is a chance of bone wall violation during creation of the implantation site the implant should not be used.
- The device is composed of a porous brittle material, applying excess mechanical pressure during insertion may lead to implant breakage and particle generation. Particulate debris may cause an inflammatory response.
- If the implant is inserted at or above the articular cartilage, damage to the counter or adjacent tissue can occur, as well as particulate debris generation and synovitis.

- Protruding edges, if left untreated, may lead to injury of nearby tissue. It is required that all implant sharp edges be removed, breakage of protruding edges may lead to fragment or particulate debris generation which may require removal.
- Idiosyncratic rejection reaction.
- Multiple implants may impinge, leading to implant fracture, bone fracture particulate debris and implant loosening and bone cysts may develop.
- Effusion, swelling, pain, synovitis, and systemic fever can occur due to infection, pseudo-septic reactions, reactive arthritis or aseptic arthritis.
- Inflammation might lead to degeneration of other articular surfaces, as well as ligament laxity and joint deformity. Large joint effusion might impact venous return and lead to leg edema. The neurovascular structures might be compromised.
- Suboptimal tissue ingrowth might occur: e.g. partial ingrowth, overgrowth, fibrous tissue ingrowth or partial coverage of the implant.
- Chronic pain reactions including complex regional pain syndrome might ensue.
- Implantation within avascular necrosis or cyst may lead to lack of implant integration and implant failure.
- Entrapment of soft tissue between the implant and the bone during implantation may lead to small gap followed by penetration of synovial fluid, lack of integration and cyst formation.
- Muscle atrophy.

These risks can be reduced significantly when the procedure is performed by a qualified orthopedic surgeon adhering to the IFU, trained in the use of the investigative device.

6.16 Potential Benefit of the Study Device

Proper use of the study device may provide reduction in pain and improved function with the concomitant improvement in quality of life and daily activities. However, participants in the study may experience no direct benefit, although the findings from the investigation may benefit future patients with similar conditions.

7. Response Measures

7.1 Safety Measures

Adverse events, including serious adverse events, reoperations and revisions, up to 24 months

7.2 Study Arms

7.2.1. SSOC Group

In the SSOC group, due to variety of pathologies, two surgical options are available to provide ideal treatment options. As part of the enrollment process, all patients will undergo arthroscopy. Patients will be treated by MFX and/or Deb (Figure 3) as described in Section 8.3, the surgical technique is according to standard of practice. All symptomatic lesions in the joint should be treated.

7.2.2. Agili-C™ Group

Agili-C™ is intended to be implanted following arthroscopy via a mini-arthrotomy or arthrotomy approach, using the designated surgical tools and surgical technique described in Appendix 6. The size of the implant(s) will be determined according to the size of the lesion(s) by the investigator according to the following algorithm (Figure 5):

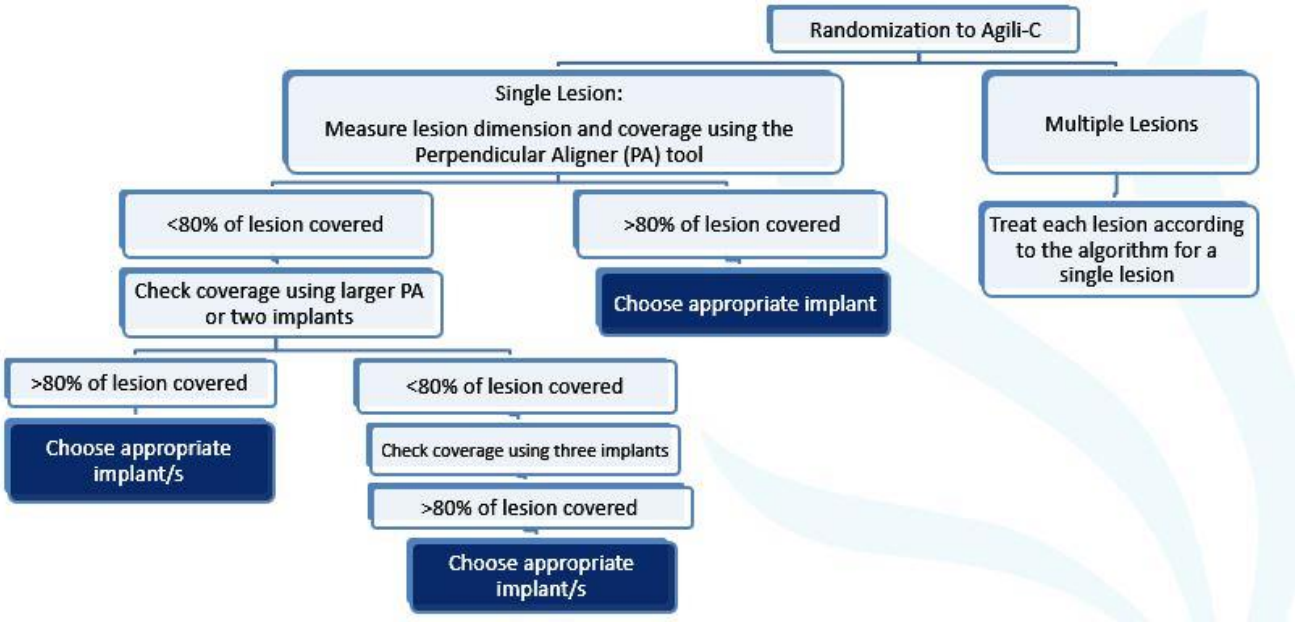

Figure 5: Implant Size Algorithm

7.3 Concomitant Procedures

Non-lesion related concomitant procedures, such as synovectomy, partial meniscectomy, high tibial osteotomy (HTO) and loose body removal are allowed, however ligamentoplasty is not allowed as concomitant; applicable for both treatment groups.

In case an HTO is performed concomitantly, the type of procedure and fixation technique will be documented. Additionally the amount of HTOs will be stratified between the treatment arms.

8. Study Methods and Procedure

8.1 Introduction

Prior to enrollment of any study subjects, the PIs will undergo Agili-C™ specific surgical training to familiarize themselves with the Agili-C™ implantation, as well as training on the use of the various PROs and scales and other specifics of the protocol. Weight bearing X-ray imaging will be performed according to protocol in Appendix 4.

During the course of the study, subjects will be instructed to report any unusual signs or symptoms to the PI (or designee), who will solicit and record information about Adverse Events and Serious Adverse Events (AEs/SAEs), concomitant medications, therapies, and treatments. All reported AEs/SAEs will be documented on the appropriate case report form.

8.2 Subject Entry Procedures

8.2.1 Informed Consent Form and Subject Privacy

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject who has a knee surface lesion. Prior to any study-related procedures, the subject must sign an IRB/EC approved ICF and HIPPA Form (if applicable). If any new relevant information becomes available, the Sponsor will provide an updated ICF and HIPAA forms for IRB review and approval. The subject should personally sign and date the ICF and HIPAA forms. Upon signing the Informed Consent Form and authorization forms, the subject is considered to be a consenting individual in the study and receives a Subject Number that will be used on all documentation for the subject throughout the study.

After signing the Informed Consent Form, the consenting individual can then proceed with the screening evaluation. Surgery (Visit 2) must be performed within 1-90 days of signing the Informed Consent Form. During this period, if the subject decides to withdraw consent, the

subject will then be considered as a screen failure. This will be captured in the screening log as well as in the CRF End/Exit form.

8.2.2 Withdrawal Criteria

The subject has the right to withdraw from the study at any time without consequences, as indicated in the Patient Informed Consent documentation.

8.3 Study Visits

8.3.1 Screening Visit (Visit 1)

Following signing an informed consent, as described in section 10.2.1, candidates will undergo Initial Screening that includes lesion(s) assessment according to MRI and X-ray (not more than 1 year old), clinical history, physical examination and Patient Reported Outcome (PRO). A standing X-ray will be sent off-site for Kellgren–Lawrence evaluation to exclude K/L grade 4. The PI will be informed regarding subject eligibility according to K/L grade.

Initial Screening Visit (Visit 1) Activities:

1. Sign Informed consent
2. Assign Patient Number
3. Perform clinical examination
4. Review standing X-ray (AP and lateral, NMT 1 year old)
5. Review MRI (NMT 1 year old)
6. Record Medical history
7. Determine initial eligibility according to available inclusion/exclusion criteria
8. The investigator will complete:
    a. IKDC Knee Examination Form 2000
    b. ICRS Knee History Registration
9. The patient will complete the following questionnaires:

a. KOOS subscales
b. Tegner score
c. SF-12 Health Survey (v2)
d. ICRS Cartilage Injury Standard Evaluation Form 2000
e. 2000 IKDC Subjective Knee Evaluation Form

10. Analgesic, anti-inflammatory and prescription medication recording
11. The patient's MRI and standing X-ray (AP and lateral) will be sent off-site for OA evaluation according to Kellgren-Lawrence (K/L) score. In case of K/L < 4 (e.g. not severe OA) and absence of clear exclusion criteria as seen on the baseline MRI the PI will be informed that the patient is eligible for the study and the patient will continue to Visit 2.

In case of bilateral symptomatic knees, it is recommended that the most symptomatic knee be chosen for treatment in the study, as long as the inclusion/exclusion criteria are met. In case of equally symptomatic knees, the Investigator and the subject will determine which knee will be treated in the study. The knee that does not enter the study can be treated according to general practice. If during Visit 2 (Final Screening/Procedure Visit (arthroscopy)), the knee chosen is found to not meet the inclusion/exclusion criteria, the patient will be determined to be intra-op ineligible and not be included in this study for both knees.

8.3.2 Final Screening/Procedure Visit (Visit 2)

- Between 1 to 90 days after initial screening, subjects will undergo Final Screening (Visit 2) via arthroscopy. If found eligible, the subject will be enrolled into the study and randomized intra-operatively into either Agili-C™ or SSOC. Stratification will be performed based on K/L score performed off-site.
- For the SSOC group, lesion treatment will be determined according to subject's age, lesion size and K/L grade (Table 1) as per the control group selection algorithm (Figure 3).

Table 1: SSOC Sequence of Selection Criteria

Criteria	Initial Screening, at site (Visit 1)	X-ray evaluation, off-site (Visit 1)	Arthroscopy & Final Screening, at site (Visit 2)
Age	X		
K/L grade		X	
Lesion Size			X

Final Screening/Procedure Visit (Visit 2) Activities:

1. Review of inclusion/exclusion criteria
2. Arthroscopy
3. Final enrollment
4. Randomization
5. Treatment (Agili-C™/ SSOC)
6. Film procedure
7. Analgesic, anti-inflammatory and prescription medication recording
8. Record AEs/SAEs
9. Complete surgery debriefing forms

Arthroscopy Procedure

The arthroscopy procedure will be conducted according to hospital practice. Once subjects have fulfilled all the inclusion and none of the exclusion criteria, they will be enrolled into the study and randomized. The arthroscopy procedure should be video recorded and documented post-procedure by the PI or study team on the relevant CRF assessment forms. The following structures should be carefully assessed by visualization and palpation:

- Synovia
- Patellar surface
- Trochlea surface

- Medial and lateral condylar surface
- Medial and lateral tibial surface
- Medial and lateral meniscus
- Cruciate ligaments

Additionally, each lesion, regardless if symptomatic or not and if treated or not, should be documented according to the following parameters: location, severity (ICRS grade) and size (maximum length and maximum width). A company representative will be allowed to participate in the arthroscopy and to film the procedure.

Post-Procedure Treatment

Recommended treatment for both groups is per the recommended rehabilitation protocol, see Appendix 7.

8.3.3 Two weeks post-procedure ± 1.5 week (Visit 3)

1. Record Adverse events
2. Analgesic, anti-inflammatory and prescription medication recording
3. X-ray (AP and lateral)

8.3.4 Three months post procedure visit ± 2 weeks (Visit 4)

1. Analgesic, anti-inflammatory and prescription medication recording
2. Record AEs/SAEs
3. MRI will be performed at 3 months to an initial cohort of at least 25 patients per study groups to evaluate presence of cysts

8.3.5 Six months post-procedure ± 4 weeks (Visit 5)

1. Weight bearing X-ray (AP and lateral)
2. The investigator will complete the IKDC Knee Examination Form 2000
3. The patient will complete the following questionnaires:
    a. KOOS subscales
    b. Tegner score
    c. SF-12 Health Survey (v2)
    d. 2000 IKDC Subjective Knee Evaluation Form
4. Analgesic, anti-inflammatory and prescription medication recording
5. Record AEs/SAEs
6. MRI will be performed at 6 months to an initial cohort of at least 25 patients per study groups to evaluate presence of cysts

8.3.6 Twelve months post-procedure ± 8 weeks (Visit 6)

1. MRI according to CartiHeal protocol
2. Weight bearing X-ray (AP and lateral)
3. The investigator will complete the IKDC Knee Examination Form 2000
4. The patient will complete the following questionnaires:
    a. KOOS subscales
    b. Tegner score
    c. SF-12 Health Survey (v2)
    d. 2000 IKDC Subjective Knee Evaluation Form
5. Analgesic, anti-inflammatory and prescription medication recording
6. Record AEs/SAEs
7. Off-site Defect fill evaluation (per MRI)

8.3.7 18 months post-procedure ± 8 weeks (Visit 7)

1. Weight bearing X-ray (AP and lateral)
2. The investigator will complete the IKDC Knee Examination Form 2000
3. The patient will complete the following questionnaires:
    a. KOOS subscales
    b. Tegner score
    c. SF-12 Health Survey (v2)
    d. 2000 IKDC Subjective Knee Evaluation Form
4. Analgesic, anti-inflammatory and prescription medication recording
5. Record AEs/SAEs

8.3.8 24 months post-procedure ± 8 weeks (Visit 8)

1. MRI according to CartiHeal protocol
2. Weight bearing X-ray (AP and lateral)
3. The investigator will complete the IKDC Knee Examination Form 2000
4. The patient will complete the following questionnaires:
    a. KOOS subscales
    b. Tegner score
    c. SF-12 Health Survey (v2)
    d. 2000 IKDC Subjective Knee Evaluation Form
5. Analgesic, anti-inflammatory and prescription medication recording
6. Record AEs/SAEs
7. Off-site Defect fill evaluation (per MRI)

8.3.9 Annual post 24 months visits ± 8 weeks (until last patient reaches 24 months)

1. Weight bearing X-ray (AP and lateral)
2. The investigator will complete the IKDC Knee Examination Form 2000

3. The patient will complete the following questionnaires:
    a. KOOS subscales
    b. Tegner score
    c. SF-12 Health Survey (v2)
    d. 2000 IKDC Subjective Knee Evaluation Form
4. Analgesic, anti-inflammatory and prescription medication recording
5. Record AEs/SAEs

9 Study Schedule

Table 2: Study Schedule

Procedures	**Screening Visit**	**Final Screening/ Procedure Visit**	**2 week Post-Procedure Visit (± 1.5 weeks)**	**3 [μ], 6^, 12 and 18 Months Post-Procedure Visit (± 8 weeks)**	**24 Months Post-Procedure Visit (± 8 weeks)**	**Annual Post-24 months Visit[$] (12 months ± 8 weeks)**	**Unscheduled Visit**
Number of Visit	Visit 1	Visit 2	Visit 3	Visits 4-7	Visit 8	Visits 9+	
Obtain Informed Consent	X						
Assignment of Subject Number	X						
Review Inclusion/ Exclusion criteria	X	X (intra operative)					
BMI	X[@]						
Medical History	X						
Baseline MRI	X*						
MRI according to CartiHeal protocol				X**	X**		X***
Defect Fill Evaluation according to MRI, off-site				X[**,∞]	X**		
Baseline standing X-ray (AP & Lateral)	X*						
Weight bearing AP & Lateral X-ray			X[#]	X[∞]	X		X***

Procedures	**Screening Visit**	**Final Screening/ Procedure Visit**	**2 week Post-Procedure Visit (± 1.5 weeks)**	**3 [μ], 6^, 12 and 18 Months Post-Procedure Visit (± 8 weeks)**	**24 Months Post-Procedure Visit (± 8 weeks)**	**Annual Post-24 months Visit[$] (12 months ± 8 weeks)**	**Unscheduled Visit**
IKDC Knee Examination form 2000 (Surgeon)	X			X[∞]	X		X
OA Classification Kellgren-Lawrence score, off-site	X						
ICRS Cartilage Injury Standard Evaluation Form 2000 (Subject)	X						
ICRS Knee History Registration (Surgeon)	X						
SF-12 v2	X			X[∞]	X	X	
2000 IKDC Subjective Knee Evaluation Form	X			X[∞]	X	X	
KOOS Subscales	X			X[∞]	X	X	
Tegner score	X			X[∞]	X	X	
mICRS cartilage injury mapping and classification		X					
Arthroscopy and randomization		X					
Analgesic, anti-inflammatory and prescription medicine recording	X	X	X	X	X	X	X
AEs/SAEs		X	X	X	X	X	X
Tissue biopsy with histology							X****
Video recording		X					X

@ Weight and Height, only at screening

X-ray may be performed lying down or standing, per patient comfort

* Screening MRI and X-ray must not be older than 1 year** MRI and Defect Fill evaluation is performed at 12 and 24 months. Additionally, MRI will be performed at 3 and 6 months to an initial cohort of at least 25 patients per study groups to evaluate presence of cysts

*** MRI and X-ray will be performed according to PI decision

**** According to PI decision if surgery is performed. The biopsy will be sent to a central lab.

$ Annual visit until last patient out

μ The 3 month visit may take place ±2 weeks

^ The 6 month visit may take place ±4 weeks

°° Not applicable for the 3 months visit

9.1 Unscheduled Visit

Each time the subject returns to the study site, the PI (or designee) will solicit and record information about AEs, concomitant medications and therapies. All applicable procedures should be performed including MRI and X-ray (according to PI's decision).

9.1.1 Unscheduled Visit without Surgery

Unexpected symptoms might lead to an unexpected visit. In such visits, the following should be performed:

1. Investigator completes the IKDC Knee Examination Form 2000
2. Analgesic, anti-inflammatory and prescription medication recording
3. Record AEs/SAEs

9.1.2 Unscheduled Visit with Surgery

In case of a secondary procedure, the following should be performed:

1. Investigator completes the IKDC Knee Examination Form 2000
2. ICRS cartilage repair assessment form
3. Record AEs/SAEs
4. Analgesic, anti-inflammatory and prescription medication recording
5. Tissue and/or implant removal and histology (if relevant)
6. Video recording of the procedure with images captured

The study protocol does not require a tissue biopsy. If clinically required, the tissue should be sent to a central lab for histological assessment as determined by the Sponsor. The Sponsor should be notified in advance and a Sponsor's representative will be allowed to participate in the procedure and film it.

9.2 Compliance with Protocol

The PI is responsible for compliance with the protocol at the investigational site. The PI is also responsible for reporting all issues of protocol non-compliance to the respective IRB/EC and to the Sponsor. A representative of the Sponsor will make frequent contact with the PI and research staff and will conduct regular monitoring visits at the site to review subject and device accountability records for compliance with the protocol, e.g., subject eligibility criteria, randomization assignments, concomitant and subsequent procedures performed and follow-up visit schedule.

9.3 Discontinued Subjects

The Principal Investigator will record on the CRF and will report to the Sponsor and the IRB/EC the reasons that subjects discontinue from the study, including subjects who sign the Informed Consent Form but do not proceed to randomization.

9.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site should be terminated, the Sponsor will provide notification in accordance with 21 CFR and will advise the FDA, PIs, IRB/ECs, and appropriate institutional officials. The report will include the IDE number, the full name of the research protocol, the name(s) of the clinical investigators and the reason(s) for the suspension or termination.

Conditions that may warrant termination of the study or site include, but are not limited to:

1. Any unanticipated problems involving risks to human subjects or others
2. Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or
3. Any suspension or termination of IRB approval
4. Study completion

9.5 Study Duration

Study participation for an individual subject is expected to last 24-26 months, including the time to randomization and treatment (including arthroscopy) and the 24-month follow-up period. Study duration at each investigational site may last up to 3 to 5 years including recruitment phase, follow-up and close out. Study participation may be 2-5 years total as follow up will include the time period until last patient out. Therefore study duration is estimated between 2 - 5 years per patient.

9.6 Documentation

All tests will be performed prior to implantation procedure as required by the study protocol. Device handling will be recorded. The standard treatment and care provided to all subjects, alongside the application of the study device, will be performed and recorded in the subject's medical files and on the appropriate study CRF.

9.7 Deviations from Study Protocol

Any deviations from the study protocol should be notified to the Sponsor, documented on study deviation forms, and reported to the IRB/EC as required by local regulations.

10 Post-Trial Device Availability

Each SSOC treated patient will have the option to receive the Agili-C™ device free of charge for a period of 2 years after the 24 months visit. For a US SSOC the device will be available only after PMA approval. This option will be offered upon request and regardless of the patient's scores at the end of the study. This option will not be considered "cross-over" as it occurs following patient study completion and would only be offered after product approval. Under these circumstances, the PI will fill an exit form prior to the patients receipt of the device.

11 Safety and Medical Device Vigilance

All adverse events occurring during the study will be recorded on the appropriate case report form page by the investigator. The nature, severity and relation of the adverse event to the study device will be documented. If an adverse event occurs, the first concern will be the safety of the study participants. All AEs occurring during the study will be followed throughout the study until resolved or stabilized or until follow-up is no longer possible.

12 Definitions

12.1 Adverse Event (AE)

AE is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation. An AE can therefore be any unintended sign, symptom, disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device. The following should be reported as AE:

- Untoward medical conditions or signs or symptoms that were absent before starting study treatment.

- Untoward medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory findings.
- Clinical signs or symptoms that require therapy.

12.2 Serious Adverse Events (SAE)

A SAE is an adverse event that:

- Led to a death
- Led to a serious deterioration in the health of the subject that:
  - Resulted in a life-threatening illness or injury.
  - Resulted in a permanent impairment of a body structure or a body function.
  - Required in-patient hospitalization or prolongation of existing hospitalization.
  - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-adverse events (e.g. cosmetic surgery or diagnostic procedure) are not considered serious adverse events.

12.3 Unanticipated Serious Adverse Device Effect (USADE)

USADE is defined as a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or other study related documents and that is device related.

Note: Anticipated adverse events expected (with relation to the device and its designated toolset) are detailed in section (14.8, 14.9).

12.4 Adverse Events Classification

AEs reported by the subject or observed by the investigator will be individually listed on an adverse event form in the CRF as follows: the specific event or condition, whether the event was present pre-study, the dates and times of occurrence, duration, severity, relationship to study device and/or procedure, specific countermeasures, and outcome.

Note: Event which was present pre-study is not considered as an adverse event unless it has worsened since the enrolment to the study.

All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

12.5 Intensity/Severity Definition

The intensity or severity of the AE will be characterized as follows:

Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.

Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.

12.6 Relationship to Investigative Device or SSOC

The Investigator and Medical Director will separately evaluate and document the relationship between an AE or SAE to the investigative device or the SSOC according to the parameters defined in Table 3. In case of disagreement between the investigator's evaluation and the Medical Director's evaluation, an independent evaluator, a physician, well versed in safety assessments of medical device clinical trials, will evaluate the case and determine the relationship between an AE or SAE to the investigative device or the treatment procedure.

Table 3: Adverse Event Relationship Criteria

Relationship	Criteria
Unrelated	The temporal sequence of the AE onset relative to treatment by the investigational device/SSOC is not reasonable. OR There is another obvious cause of the AE
Unlikely related	The relationship with the use of the device/SSOC can be reasonably explained by another cause, but additional information may be obtained.
Possibly related	The relationship with the use of the investigational device/SSOC is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent clinical condition or/and an effect of another device, or treatment
Probably related	The relationship with the use of the investigational device/SSOC seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Related	The AE can be explained only by the use of the investigational device/SSOC.
Uncertain	The relationship between the AE and the device is uncertain

12.7 Outcome

The clinical outcome of the AE or SAE will be characterized as follows:

Death - The SAE CRF must be completed for this outcome.

Recovered - The patient returned to baseline status.

Ongoing - Patient did not recover and symptoms continue.

Recovered with sequelae - The patient has recovered but with clinical sequelae from the event.

Unknown - The patient outcome is unknown.

12.8 Treatment or Action Taken

The treatment or action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment - Invasive intervention such as: surgery or intra-articular injection.

Non-surgical intervention - such as physical therapy

Medical Treatment - Medication initiated for event

None - No action is taken

12.9 SAE Reporting Requirements

12.9.1 Notification to the Sponsor: Initial and Follow-up

If the investigator identifies a SAE, a SAE report form must be completed and sent by fax or email to the Sponsor and CartiHeal within 24 hours of the investigator's knowledge of the event. Also fax copies of hospital case reports (i.e., hospital progress notes, results of applicable diagnostic tests, lab results and biopsy results) should be sent as soon as they become available. Autopsy reports and other documents, as applicable, should be sent upon request.

Reports should be made to the CartiHeal's Medical Director and the CRO's safety contact person:
Dror Robinson Tel: (972) 9 8810400 Fax: (972) 7 65104856 E-mail: dror@cartiheal.com; safety@cartiheal.com CRO TBD

The PI notification to the Sponsor should then be followed up by written notification within 5 days, using a designated Event form in the study file.

Any fatal or life-threatening event should be reported immediately. These preliminary reports will be followed as soon as reasonably possible by detailed descriptions that will include a completed SAE form, copies of hospital case reports, autopsy reports, and other documents, when requested and applicable.

In accordance with applicable regulations, all investigators will be notified of the occurrence of USADEs, if such events are related to the study device (i.e., if there is a reasonable possibility that the event may have been caused by the device and are thus deemed significant new adverse effects or risks with respect to the investigational device).

If applicable, the investigator should also inform the representative of the appropriate IRB/ Ethics Committee, as per the local requirements. A copy of the report cover letter should be filed within the study file.

12.9.2 Follow- Up of SAE/USADEs

Follow-up of SAEs/ USADEs that occur during the study will continue until their satisfactory resolution or stabilization.

If/when supplementary information is available, a follow-up SAE Report Form must be completed by the site and faxed within 24 hours to the Sponsor.

The contact information for follow up SAE reporting is the same as for initial SAE report (see above section).

Once faxed or e-mailed, the SAE form and accompanying documentation should be placed in the Safety section of the investigator's file. If supplementary information on a SAE has to be sent, the SAE form has to be used marked as 'follow-up report'.

All other SAE/AEs will be followed for new information/resolution as possible, or may be defined as 'ongoing without further follow-up' by the Investigator and Sponsor's decision.

12.10 Notification to Authorities

Events will be reviewed to determine any reporting obligations. Reporting will occur within the timelines described as per local regulations. In the event of a USADE, sponsor or designee will conduct and report the results of an evaluation to the appropriate authority and all participating investigators according to local regulations.

12.11 Anticipated Adverse Events Related to the Implant include:

- Transient or chronic pain and/or swelling and/or effusion of the operated joint
- Bone marrow edema
- Allergic or pseudo-allergic reaction and/or elevation of acute phase reactants
- Pseudo-septic reaction

- Reactive arthritis
- Bone cyst, bone fracture, bone deformities or bone aseptic necrosis
- Implant fracture, loosening or extrusion, with or without generation of particulate debris
- Abrasion of counter or nearby tissues
- Failure to induce tissue regeneration
- Tissue hypertrophy or intra-lesional bone formation
- Wound complications:
    - superficial or deep infections
    - septicaemia
    - wound dehiscence
    - hematoma or site drainage
- Intra-articular adhesions, hypertrophic tissue, hypertrophic synovitis, intra-articular adhesion, hypertrophic synovium or host reactions
- Inflammation of the joint and surrounding tissues
- Joint locking and limited range of motion, stiffness and arthrifibrosis
- Deep Vein Thrombosis
- Infection and related symptoms
- Elevation of the subchondral bone plate
- Degeneration of the surrounding cartilage
- Lack of cartilage integration
- Delamination
- Progression of degenerative changes and osteoarthritis
- Muscle atrophy

12.12 Anticipated Adverse Events – Related to tool-set include:

- Postoperative hematoma
- Deformity or fracture of the bone
- Insertion of the tool can lead to a damage of nerve or vascular elements
- Heat damage to bone might occur especially with worn out drill bits
- Metal fragments might chip of the tools and lead to foreign body reaction
- Tool fragments might get stuck in the bone
- Failure to create an appropriate recipient site

13 Statistical Considerations

13.1 Design Considerations (including Interim Analysis)

This is a two-arm, prospective, open-label, randomized, multi-center study in which subjects are assigned to treatment (Agili-C™) or control (SSOC) in a 2:1 ratio.

The subjects in the study will be randomized by site using variable block sizes.

The subjects in the study will be stratified by extent of osteoarthritis, defined dichotomously by the Kellgren–Lawrence grade:

- Strata I: 0 & 1
- Strata II: 2 & 3

13.2 Analysis Populations

13.2.1 Safety Set

The safety population will consist of all patients for whom treatment with either Agili-C™ or SSOC was performed.

13.2.2 Full Analysis Set

The full analysis set (FAS) will consist of all treated subjects in the Agili-C™ arm and treated subjects in the SSOC arm, for whom there is a valid overall KOOS score at baseline and at least one valid overall KOOS score post-baseline.

Consistent with ICH-E9, subjects with major entry violations will be excluded from FAS. "Major" is defined by having the potential to affect trial results and the decision of whether an entry violation is considered major will be performed by the Medical Director.

FAS will be used for the primary analysis.

Treatment of missing data:

1. KOOS Subscale Score:

   As per KOOS scale guideline, subscale scores will be computed based on observed items only if not more than 2 items are missing. Where more than two items are missing, the KOOS subscale score will be scored missing.

2. Overall KOOS Score:

   Overall KOOS Score will be defined as the average over the KOOS subscales, if not more than two subscales are missing. Where more than two KOOS subscales are missing, the Overall KOOS score will be scored missing.

13.3 Per Protocol Analysis Set (PP)

The PP analysis set is the subset of FAS Subject with no major protocol violations and with valid observations on the primary endpoint (Overall KOOS) at 12 months, at least.

Treatment of missing data: missing data in the PP population will be dealt with using the same procedures described for FAS; i.e. subscale data will be scored as per user manual

13.4 Treatment of Efficacy Data Following a "Failure"

For both Agili-C™ & SSOC groups, any secondary Invasive Intervention in the treated joint, regardless if related or unrelated to the original treatment, will be considered a Treatment Failure. Invasive Intervention incudes: open procedure, mini-open procedure, arthroscopic procedure and any intra articular injections, such as: HA, PRP, steroids and stem cells.

Subjects who are treatment failures with have their 24 month KOOS score imputed as their baseline KOOS score for analysis purposes.

For Agili-C™ group only:

- Failure to implant the device in indicated patients will be considered Treatment Failure. However failure to implant the device in contraindicated patient/condition will not be considered Treatment Failure. The latter subjects will not be included in the efficacy analyses.

13.5 Primary Analysis

The primary analysis will be conducted on the full analysis set. The primary goal of the trial is to demonstrate superiority of the Agili-C device relative to SSOC by testing the hypothesis:

$$H_0: \theta_1 = \theta_0 \qquad \text{vs.} \qquad H_A: \theta_1 > \theta_0.$$

where θ_d is the mean response for arm d ($d = 0$ for SSOC and $d = 1$ for Agili-C). To test this hypothesis, we calculate the posterior probability of superiority: Pr($\theta_1 > \theta_0$ | Data). The trial will be considered a success if the posterior probability exceeds 0.98 at the final analysis.

We model the individual subjects as

$$Y_i \sim N(\theta_{d_i}, \sigma^2)$$

The mean response is modeled independently for each arm using non-informative priors:

$$\theta_0 \sim N(0, 10000^2),$$

$$\theta_1 \sim N(0, 10000^2).$$

Thus, θ_d for each arm is estimated separately using only data from that arm.

The error variance is modeled as:

$$\sigma^2 \sim IG(0.5,264.5),$$

where $\mathrm{IG}(a, b)$ is the inverse gamma distribution defined by:

$$f(x|a, b) = \frac{b^a e^{-b/x}}{x^{a+1}\Gamma(a)}.$$

This prior on σ has an effective sample size of 1. The prior mean of the precision $(1/\sigma^2)$ is $1/23^2$. Thus this prior places a very small degree of weight towards values of σ close to 23, which is in line with prior data in this area. However, the prior is only very weakly informative compared to the $N = 250 - 500$ size of the trial.

Two classes of subjects have their 24 month KOOS scores imputed. First, treatment failures (defined in section 13.3) have their 24 month KOOS score imputed to the be their baseline KOOS value prior to the analysis. Second, dropout subjects are multiply imputed using a time course hierarchical model (see section 13.6 on longitudinal modeling).

Interim Analyses for Sample Size Selection

Interim analyses will occur when N=250, 300, 350, 400, and 450 subjects are enrolled (enrolled, not complete). At each interim analysis, an independent EAC, composing of at least three members, one orthopedic surgeon, one radiologist and one statistician, will review the data and will advise whether the trial should:

1) Stop enrollment for anticipated success – trial stops enrollment at that sample size and then all current patients are followed to their primary endpoint
2) Stop trial for futility

3) Continue

If the trial stops enrollment for anticipated success, the primary analysis occurs after follow-up is complete. If the trial does not stop enrollment at any time, the primary analysis occurs after the full sample size (N=500) has been enrolled and those subjects have completed follow-up. Regardless, the primary analysis occurs when all enrolled subjects have had an opportunity for full follow-up.

In this trial, we compute two predictive probabilities that are used in the selection of the sample size:

- $pp_{current}$: the predictive probability of eventual trial success once all currently enrolled subjects are followed to the final 24-month endpoint,
- pp_{max}: the predictive probability of eventual trial success once all future subjects ($N = 500$) have enrolled and all subjects are followed to the final 24-month endpoint.

At an interim, the trial will stop for futility if the predictive probability of eventual trial success at the maximum sample size is less than 0.05. That is, stop for futility if

$$pp_{max} < 0.05.$$

Accrual to the trial will stop for expected success at an interim if the predictive probability of eventual trial success with the current sample size exceeds 0.95. That is, stop accrual for expected success if

$$pp_{current} > 0.95.$$

13.6 Longitudinal Modeling (Multiple Imputation)

If at any analysis data is missing for reasons other than treatment failure (see section 13.3, in which case subjects final 24 month KOOS score is imputed as their baseline value), that missing data is handled through multiple imputation based on a time course hierarchical

model. This model has terms for a subject specific random effect, similar to an MMRM, and relates interim visits to the final endpoint.

At the interim analysis for sample size estimation, where many subjects will be incomplete, we utilize an informative prior based on prior pilot data.

At the primary (final) analysis, subjects will have had full follow up time and thus no subjects should be incomplete. However, some subjects may be dropouts. For the final analysis, missing data will also be handled through multiple imputation, however only weakly informative priors will be used.

See the attached adaptive design report for a full description of the model and prior distributions.

13.7 Randomization Procedure

Randomization is performed according to these 3 parameters: subject age, degree of OA and lesion size. Prior to arthroscopy 2 parameters will be available: subject age and degree of OA (as assessed off-site). Based on observation during the arthroscopy, lesion size is determined by the investigator and recorded in the randomization system. In case of successful enrollment, the subject will be randomized intra-operatively by a computerized system and will be allocated to Agili-C™ or SSOC. In case of randomization to SSOC, the computerized randomization system will determine the surgical treatment according to the surgical control algorithm (Figure 3).

13.8 Sample Size Considerations

The sample size selection procedure was selected to obtain approximately 80% power for 2:1 randomization with an alternative hypothesis corresponding to an 8 point improvement in 24 month KOOS augmented by a 15% treatment failure rate in each study arm (thus the 8

point difference is prior to baseline imputation). The standard deviation in each study arm was assumed to be 23.

Details of the operating characteristics of the model, including simulations justifying the type I error rate of 2.5%, can be found in the attached adaptive design report.

13.9 Procedure for Interim Analysis and Sample Size Selection

The interim analyses for sample size selection will be conducted by an independent statistician and will be reviewed by the EAC. The statistician conducting these analyses will not be involved in writing the study's statistical analysis plan (SAP)

13.10 Statistical Analyses

13.10.1 Overview

The data will be summarized in tables listing the mean, standard deviation or standard error, median, minimum, maximum, and number of subjects in a group for continuous data (e.g. age, weight) or in tables listing count and percentage for categorical data (e.g. gender, previous surgical treatment). Data will be presented by visit and treatment arm. Data listing by subject will be provided. The effects of noncompliance, dropouts, and covariates, and their interactions with treatment will be assessed to determine the impact on the general applicability of results from this study.

Primary and confirmatory secondary analyses will be conducted on the FAS. All efficacy endpoints will be tested on the PP analysis set as well. Safety analyses will be conducted on the safety analysis set composed of all treated subjects.

Deviations from the current statistical considerations, should there be any, will be described in an amendment to the protocol and/or the statistical analysis plan (SAP), which will be

completed prior to data freeze at interim analysis. Any such deviations will be justified and described in the final report as appropriate.

13.10.2 Subject Disposition

Subject disposition will be tabulated; the number of enrolled, treated, prematurely terminated, and completed subjects will be summarized separately according to treatment and by visit (where relevant). A list of dropouts will be prepared including treatment, reason for discontinuation and time of discontinuation.

13.11 Efficacy

13.11.1 Primary Endpoint Analysis

The Primary analysis is described above in section 13.5

13.11.2 Secondary Confirmatory Endpoint Analyses

This trial has 4 confirmatory secondary endpoints that will be tested hierarchically in the order presented below to preserve overall Type I Error = 0.05. The following three pairs of confirmatory hypotheses, relating to continuous endpoints, will be tested similarly to the primary endpoint as described in the preceding section:

Confirmatory I

H_0: Change in KOOS QOL (Agili-C^{TM}) at 24M ≤ Change in KOOS QOL (SSOC) at 24M

H_1: Change in KOOS QOL (Agili-C^{TM}) at 24M > Change in KOOS QOL (SSOC) at 24M

Confirmatory II

H_0: Change in KOOS Pain (Agili-C^{TM}) at 24M ≤ Change in KOOS Pain (SSOC) at 24M

H_1: Change in KOOS Pain (Agili-C^{TM}) at 24M > Change in KOOS Pain (SSOC) at 24M

Confirmatory III

H_0: Response Rate (Agili-C™) at 24M ≤ Response Rate (SSOC) at 24M

H_1: Response Rate (Agili-C™) at 24M > Response Rate (SSOC) at 24M

13.11.3 Definition of Overall KOOS Responder Rate

a. *Response = increase from baseline to 24 months of ≥ 30 points on overall KOOS*
b. *Non-response = otherwise.*

Type I error will be controlled hierarchically, such that testing will be done on each endpoint only if the null has been rejected for all preceding endpoints.

Confirmatory IV

H_0: Change in KOOS ADL (Agili-C™) at 24M ≤ Change in KOOS ADL (SSOC) at 24M

H_1: Change in KOOS ADL (Agili-C™) at 24M > Change in KOOS ADL (SSOC) at 24M

13.11.4 Secondary Endpoint Analysis

Secondary analysis will repeat the primary and confirmatory efficacy analyses in the PP population. Additional secondary endpoints will be tested in both FAS and PP.

- Percentage of Articular Defect Fill according to MRI at 12, and 24 months
- Change from baseline in average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) at 6, 12, and 18 Months
- Change from baseline in IKDC Subjective Knee Evaluation at 12, 18, and 24 Months
- Change from baseline in Tegner score at 12, 18, and 24 Months
- Change from baseline QOL as measured by SF-12 v2 at 6, 12, 18, and 24 Months
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with chondral lesions

- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with osteochondral lesions
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with single lesion
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with multiple lesions
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients without osteoarthritis (K/L 0-1)
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with osteoarthritis (K/L 2-3)
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with total lesion(s) size ≤3cm²
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with total lesion(s) size >3cm²
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with previous ligament reconstruction
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients without previous ligament reconstruction
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with intact meniscus
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with previous partial meniscectomy
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with concomitant partial meniscectomy
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in active patients

Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in non-active patients

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13.12 Safety

Safety analyses will be conducted on the safety analysis set. All AEs, including all SAEs and all USADEs will be summarized and tabulated. In addition, the following will be monitored:

- Unanticipated device effects
- Failure Rate

13.13 Covariate Analyses

Covariate analyses will be done on PP for the primary and secondary confirmatory endpoints by including each covariate of interest in the MMRM model, for both study groups, with one MMRM model per covariate listed below. Each covariate will appear in one MMRM. The covariates are

- Age
- Gender
- BMI
- Kellgren/Lawrence grade
- Lesion size
- ICRS grade

Note that the effect of interest is the Treatment x Covariate interaction term in the MMRM model. The tests will be conducted using a 0.15 significance level.
Additionally, descriptive statistics will be provided by covariate level.

13.14 Sensitivity Analyses

As noted, multiple imputation will be used to address missing data in the primary analysis. Several sensitivity analyses will also be provided.

- Tipping point. For each value X from the worst observed control subject to the best observed control subject, and for each value Y from the worse observed Agili-C subject to the best Agili-C subject, the primary analysis will be calculated imputing all missing Control subjects as X and all Agili-C subjects as Y, producing a grid over all plausible values for the control and Agili-C subjects. This grid includes a worst case scenario, where all control subjects are imputed with the best observed control value and all Agili-C patients imputed as the worst observed Agili-C patient. The grid also includes a best case scenario, imputing controls as the worst control patient and Agili-C patients as the best observed Agili-C patients. The tipping point curve can be observed looking in the grid for the required values of (X,Y) that result in primary analysis success.

13.15 Poolability analyses

Heterogeneity across sites and patients subgroups will be assessed with one way analyses of variance (one analysis for site, another for subgroup), using a size 0.15 test for each. If homogeneity is rejected, then an additional sensitivity analysis will be conducted based on a Bayesian hierarchical model (similar to a random effects model) with site and/or subgroup modeled as random effects, as appropriate. Regardless of the result of the poolability analyses, data will be summarized by site and by subgroup.

14 Compliance with IRB/EC Regulations

This study will be conducted in accordance with applicable regulations (U.S. 21 CFR for all centers and country specific regulations). The PI must obtain approval from a properly constituted IRB/EC prior to initiating the study and re-approval or review as required. The Sponsor is to be notified immediately if the responsible IRB/EC has been disqualified or if

proceedings leading to disqualification have begun. Copies of all IRB/EC correspondence with the PI should be provided to the Sponsor.

15 Compliance with Electronic Records; Electronic Signatures Regulations

This study will be conducted in compliance with the regulations on electronic records and electronic signature.

16 Changes to the Protocol

If it becomes necessary to amend the Clinical Investigation, the nature of the amendment will be agreed between the Sponsor and the Principal Investigator(s) and this will be recorded with a justification for the amendment. The appropriate IRB/EC and other applicable oversight committee as required will be informed of any amendments prior to implementation.

17 Subject Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities, but the subject's names will not be disclosed in these documents. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

18 Subject Privacy

Written authorization will be obtained from each subject prior to enrollment into the study in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for HIPAA) and any local national regulations.

19 Documentation

The PI will maintain a confidential Subject Contact List with the names and contact information for all subjects recruited for participation in the study, whether s/he enrolled, and reason(s) for those who do not enroll. Each subject will receive a unique Subject Number. The Subject Contact List will link the subject by name and Subject Number to this study. The PI will track the participation of enrolled subjects on a Study Visit Log, which identifies subjects by number and initials only.

20 Source Documents

Individual Subject records will be maintained in the PI's Source Documents (SDs). Source documentation is generally considered to be the document on which the information or data point was first recorded. SDs may include a subject's medical records, hospital charts, clinic charts, and the PI's study files as well as the results of diagnostic tests. Pertinent records related to the study, e.g., the subject's medical chart, will be made available to the Sponsor representative on request with due precaution to protect the privacy of the subject. Personal identifying information (except subject initials) will be removed from any photocopies of relevant medical records and replaced with the unique Subject Number before submission to the Sponsor. The PI will protect the confidentiality of all subjects' records within applicable laws.

20.1 Case Report Form (CRF) Completion

The PI is responsible for ensuring that data are properly recorded on each subject's CRFs and related documents. Source data must exist for all data entered in the CRF.

20.2 Retention of Documentation

Essential documents are any records that demonstrate the compliance of the subject, PI, Sponsor, and Monitor with the study protocol, with standards of GCP, and with all applicable regulatory requirements. Essential documents (including but not limited to study-related correspondence, subject records, subject privacy documentation, records of the distribution and use of all investigational devices, and copies of CRFs) should be retained and available for audit by the Sponsor's auditor and regulatory authorities According to applicable FDA and specific country regulation. These documents should be retained for a longer period, however, if mandated by the applicable regulatory requirements, by conditions imposed by the IRB/EC, or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the PI when these documents no longer need to be retained. The Sponsor requires that it be notified in writing if the PI chooses to store the records at a different physical address than the site address or if the PI wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

21 Monitoring Procedure

Appropriately trained representatives of the Sponsor will monitor the conduct of the trial at each investigational site, including visits to the site to review, audit, and retrieve copies of study-related documents. It is the responsibility of the PI to be present or available for consultation and to ensure that the Monitor has access to all study-related records during scheduled monitoring visits. The Monitor will review device accountability records and completed CRFs to ensure completeness and consistency with the source records and compliance with the protocol requirements. Study monitoring will be performed by a certified CRO, in compliance with recognized GCP, FDA's IDE guidance documents. On-site monitoring visits will ensure SDV and will include at least an initiation visit and any other visits that might be required during the study, and a final visit at the close of the study.

22 Regulatory and Health Authority Audits

The FDA, European Union authorities or local state health authorities (where applicable) may request access to all study records, including source documents for inspection. The PI and hospital staff are required to cooperate with these audits. The PI must notify the Sponsor of any health authority audit as soon as notification of such audit is made. A representative or designee of the Sponsor may also conduct similar audits and may be present during health authority audit.

23 Handling of Biological Specimens

Tissue biopsy(ies) might be obtained if clinically indicated. Biopsies can include: implants or parts of implants, synovial tissue, synovial fluid, cartilage, bone etc. Biopsies will be sent to an independent laboratory approved by the Sponsor, for analysis, as per the laboratory instructions. The specimens will be sent via an over-night delivery service. Routine biopsies are not recommended in this study. Biopsy samples for histological evaluation will be placed in formalin, securely sealed, and shipped to an independent laboratory for processing using established techniques and stains, such as hematoxylin and eosin (H&E), tri-chrome, or Safranin-O stain. A single board-certified pathologist who is experienced in histological evaluation of joint repair procedures will evaluate all slides from the study and will comment on the types and relative quantities of cells observed, the presence and status of the implant, the overall level of inflammation and any other interesting features. At the conclusion of the study, the laboratory and the pathologist will submit all tissue samples and slides to the Sponsor for retention with other essential study records (Section 12.3). The tissue samples and slides will not be used for any other purpose. Subject privacy concerns and biohazard handling precautions will be paramount. All evaluation shall be conducted according to GCP/GLP.

24 Publications

The Sponsor has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation among multiple investigators and sites and the Sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.

25 Appendixes

1. Appendix 1: MRI protocol
2. Appendix 2: MRI Defect Fill Assessment Method
3. Appendix 3: Weight bearing X-Ray Protocol
4. Appendix 4: Osteoarthritis Kellgren and Lawrence score
5. Appendix 5: Agili-C™ Surgical Technique
6. Appendix 6: Recommended Rehabilitation Protocol
7. Appendix 7: Study CRFs

26 Relevant publications

1. Dell'accio F, Vincent TL. Joint surface defects: clinical course and cellular response in spontaneous and experimental lesions. Eur Cell Mater. 2010 Sep 28;20:210-7.
2. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG (1997) Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy 13: 456-460.
3. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M (2002) Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy 18: 730-734.
4. Ding C, Cicuttini F, Jones G (2008) How important is MRI for detecting early osteoarthritis? Nat Clin Pract Rheumatol 4: 4-5.
5. Davies-Tuck M, Wluka AE, Wang Y, Teichtahl AJ, Jones G, Ding C, Cicuttini FM (2008) The natural history of cartilage defects in people with knee osteoarthritis. Osteoarthritis Cartilage 16: 337-342.
6. Wluka AE, Ding C, Jones G, Cicuttini FM (2005) The clinical correlates of articular cartilage defects in symptomatic knee osteoarthritis: a prospective study. Rheumatology (Oxford) 44: 1311-1316.
7. Demers C, Hamdy CR, Corsi K, Chellat F, Tabrizian M, Yahia L: Natural coral exoskeleton as a bone graft substitute: a review. Biomed Mater Eng 2002, 12: 15-35.
8. Le Graverand MP, Mazzuca,S, Lassere,M, Guermazi,A, Pickering,E, Brandt,K, Peterfy,C, Cline,G, Nevitt,M, Woodworth,T, Conaghan,P, and Vignon,E. Assessment of the radioanatomic positioning of the osteoarthritic knee in serial radiographs: comparison of three acquisition techniques. Osteoarthritis.Cartilage. 2006;14 Suppl A:A37-A43.
9. Botha-Scheepers S, Kloppenburg M, Kroon HM, Hellio Le Graverand MP, Breedveld FC, Ravaud P, Dougados M. Fixed-flexion knee radiography: the sensitivity to detect knee joint space narrowing in osteoarthritis. Osteoarthritis Cartilage. 2007 Mar;15(3):350-3.
10. Broglio KR, Connor JT, Berry SM. Not too big, not too small: a goldilocks approach to sample size selection. Journal of Biopharmaceutical Statistics. 2014;24(3):685-705.

Appendix 1: MRI protocol

Purpose: Optimal imaging of cartilage repair tissue of femoral condyles including the trochlea.

MR Imaging (general protocol for 1.5T):

For all scans: Field of view (FOV) 14cm; slice thickness 3-3.5mm; matrix 512 x 256(or 384); Receiver bandwidth: 80-120Hx/pixel

Coronal IW FSE no fatsat; TR ≥3000ms; TE = 30-40ms

Coronal PDW FSE with fatsat; TR ≥3000ms; TE = 10-20ms

Sagittal IW FSE no fatsat; TR ≥3000ms; TE = 30-40ms

Sagittal PDW FSE with fatsat; TR ≥3000ms; TE = 10-20ms

Axial IW FSE no fatsat; TR ≥3000ms; TE = 30-40ms

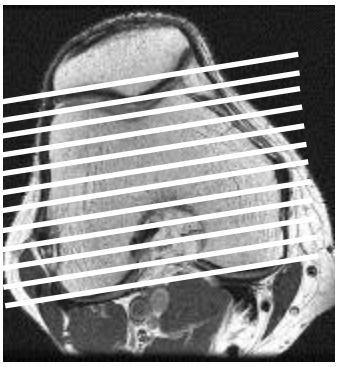
Axial T2W FSE with fatsat; TR ≥3000ms; TE = ≥70ms

Sagittal T1W no fatsat; TR = 600-800; TE = 10-20ms

Oblique PDW FSE with fatsat; TR ≥3000ms; TE = 10-20ms oriented orthogonal to scaffold.

Slice orientations:

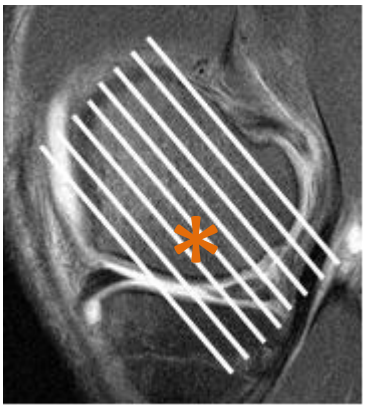
Coronal- parallel to a line drawn between the posterior femoral condyles on an axial image:



Sagittal- orthogonal to the line connecting the posterior condyles:

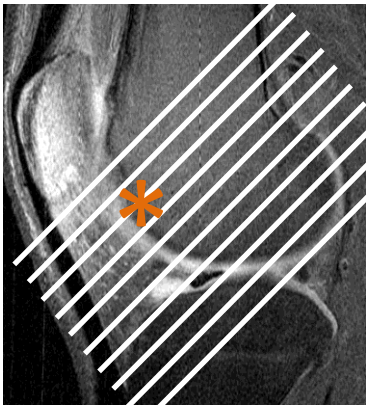
Oblique to scaffold- orthogonal to the articular surface at the repair site. Note, if there are 2 or more scaffolds, more angled images may be required (2 examples shown below): Only enough slices to cover the repair area are needed.

Repair Site*



posterior femoral condyle

Repair Site*



anterior femoral condyle

Appendix 2: MRI Defect Fill Assessment Method

Defect Fill Assessment Method

Defect Fill (in both groups) immediately following the procedure is defined as zero.

In the SSOC group, Defect Fill in each lesion will be measured and the patients Defect Fill score will be the averaged result.

In the Agili-C™ group, Defect Fill for each implantation site, will be measured and the patients Defect Fill score will be the averaged result.

Assessment Personnel

The MRI images will be assessed in a blinded fashion off-site. Two certified radiologists experienced in MRI evaluation of cartilage repair will assess each imaging study independently. The degree of cartilage defect volume fill will be semi-quantitatively assessed by each radiologist separately in increments of 25% fill (i.e 0-24% fill, 25-49% fill, 50-74% and 75-100%). When the radiologist's scores differ by only one increment, the two scores are averaged. When the radiologist's scores differ by two or more increments, a third blinded radiologist will assess the specific imaging study and then the scores will be averaged.

Assessment Score

On each MRI scan, 2-3 slices located within the implant on a sagittal scan and 2-3 slices located within the implant on a coronal scan will be assessed by each examiner.

Each slice will be scored in 25% increments (Figure 6). Results of these slices will be averaged. Thus, each score is a composite average of 4-6 slices in both sagittal and coronal orientation. In certain notch lesions and trochlear lesions axial cuts allow better evaluation of the defect and thus will be used. In addition to average defect fill, minimum and maximum defect fill scores will be recorded (Figure 6).

1. MRI date:

|__|__|__| |__|__| 20|__|__|*

Month *Day* *Year*

2. Time Point: ☐ 12M ☐ 24M ☐ Other _____

3. Location*:

☐ Lateral Femoral Condyle ☐ Medial Femoral Condyle

☐ Lateral Trochlea ☐ Medial Trochlea ☐ Central Trochlea

☐ Other _____

*** In case of multiple implants/lesions in the same area, specify the location of each lesion/implant**

4. Defect Fill: Degree of defect fill in comparison to adjacent cartilage**

**** In case of multiple implants/lesions, average the score of all implants/lesions**

Volume (excluding hypertrophy)

☐ 0-24%

☐ 25-49%

☐ 50-74 %

☐ 75-100 %

Performed by:	Signature	Date
_____	_____	_____ (MMM/DD/YY)

Figure 6: Example of Defect Fill Assessment Form

Appendix 3: Weight bearing X-Ray Protocol

The MTP method is used as it does not require fluoroscopic control.

The MTP protocol uses a horizontal X-ray beam and positions the first MTP joints beneath the front surface of the film cassette, the patellae in contact with the cassette and aligned vertically with the first MTP joints resulting in a knee angulation of approximately 7–10° flexion[8].

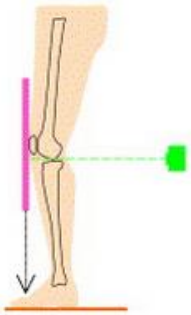


Figure 7: Metatarsophalangeal PA view

Standing semiflexed knee or MTP position (posteroanterior view). The x-ray tube is positioned so that the central ray of the x-ray beam is horizontal, parallel to the floor and perpendicular to the x-ray film. The radiographic technician identifies the position of the tibiofemoral joint space located midway between the inferior border stnof the patella and the superior margin of the tibial tuberosity. The line of the joint space is traced around to the side of the knee and the skin marked with a felt tip pen. This mark is used to help align the center of the x-ray beam with joint space. The patient stands with both knees facing the film cassette, the feet slightly externally rotated at about 15°, as recommended by Botha-Scheepers et al (2007)[9] in their assessment of the optimum foot position for knee radiography. The joint of the first MTP joint of each foot is positioned immediately below and in line with the front edge of the film cassette. The patient bends their knees so that the anterior surface of each knee touches the middle and front of the film cassette. The tube is positioned so that the X-ray beam is directed midway between the popliteal surface of the knees, and the tube's positioning light is aligned with the horizontal plane of the joint space (as described above). This plane lies above the horizontal skin crease of the popliteal fossa.

Appendix 4: Osteoarthritis Kellgren and Lawrence score

Source: http://radiopaedia.org/articles/kellgren-and-lawrence-system-for-classification-of-osteoarthritis-of-knee, visited on January 21st, 2016

By Dr Tim Luijkx and Dr Vivek Pai et al.

The Kellgren and Lawrence system is a method of classifying the severity OA using five grades:

K/L grade	Description
Grade 0	No radiographic features of OA are present
Grade 1	Doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2	Definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3	Multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4	Large osteophytes, marked JSN, severe sclerosis and definite bony deformity

1. X-Ray date:

|__|__|__| |__|__| 20|__|__|*

Month Day *Day* *Year*

Was AP x-ray available for analysis? ☐ Yes ☐ No
Was lateral x-ray available for analysis? ☐ Yes ☐ No

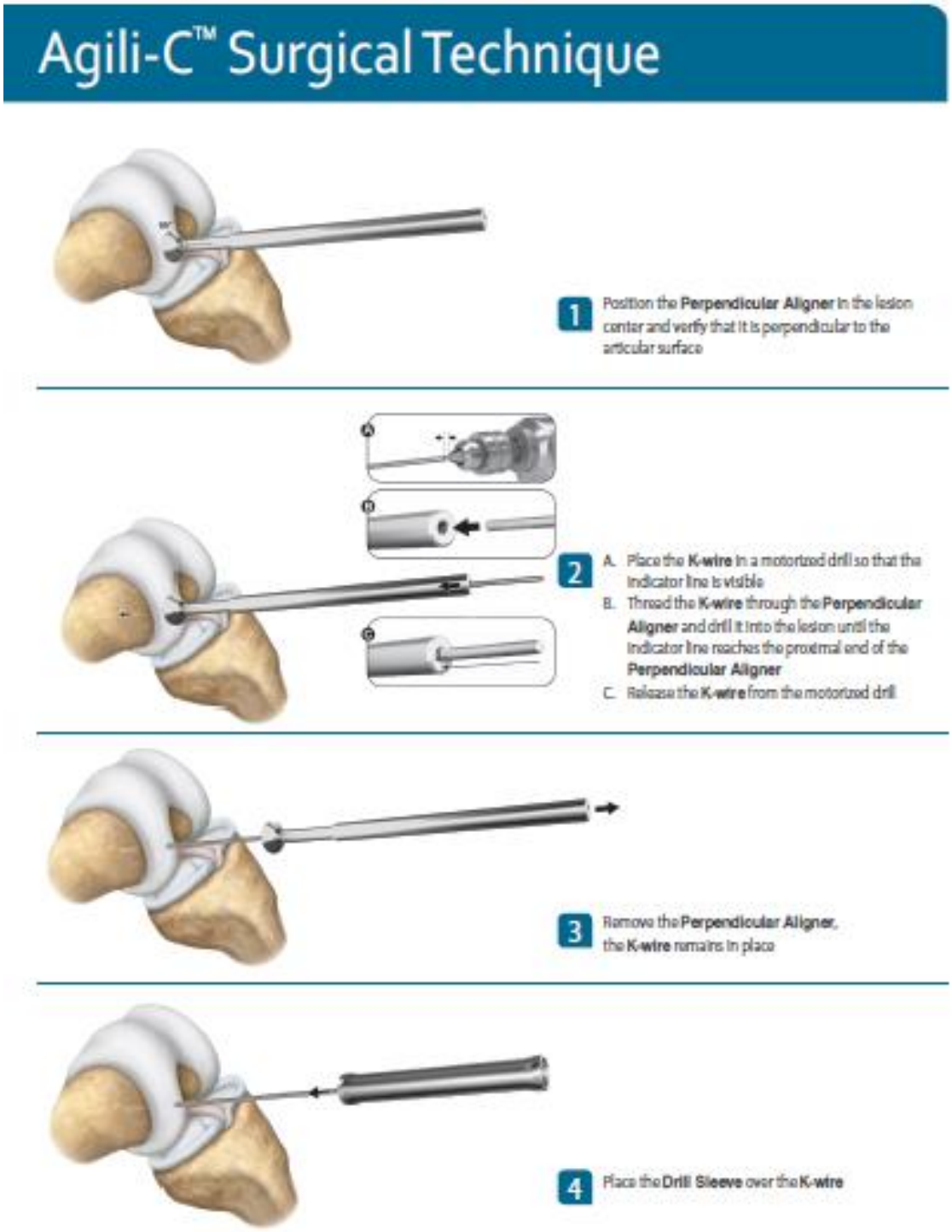
Kelgren Lawrence Grade: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Patient Stratification: ☐ NO OA (K/L grades 0-1)
☐ Mild to moderate OA (K/L grades 2-3)
☐ Severe OA (K/L grades 4) - Patient is excluded

_____ _____ M M M D D Y Y

Figure 8: X-ray Kellgren-Lawrence Evaluation at Screening

Appendix 5: Agili-C™ Surgical Technique



Agili-C™ Surgical Technique

5

A. Place the **Drill Bit** into a motorized drill
B. Hold the **Drill Sleeve** firmly against the articular surface
C. Thread the **Drill Bit** into the **Drill Sleeve** over the **K-wire** and drill until it reaches a stop

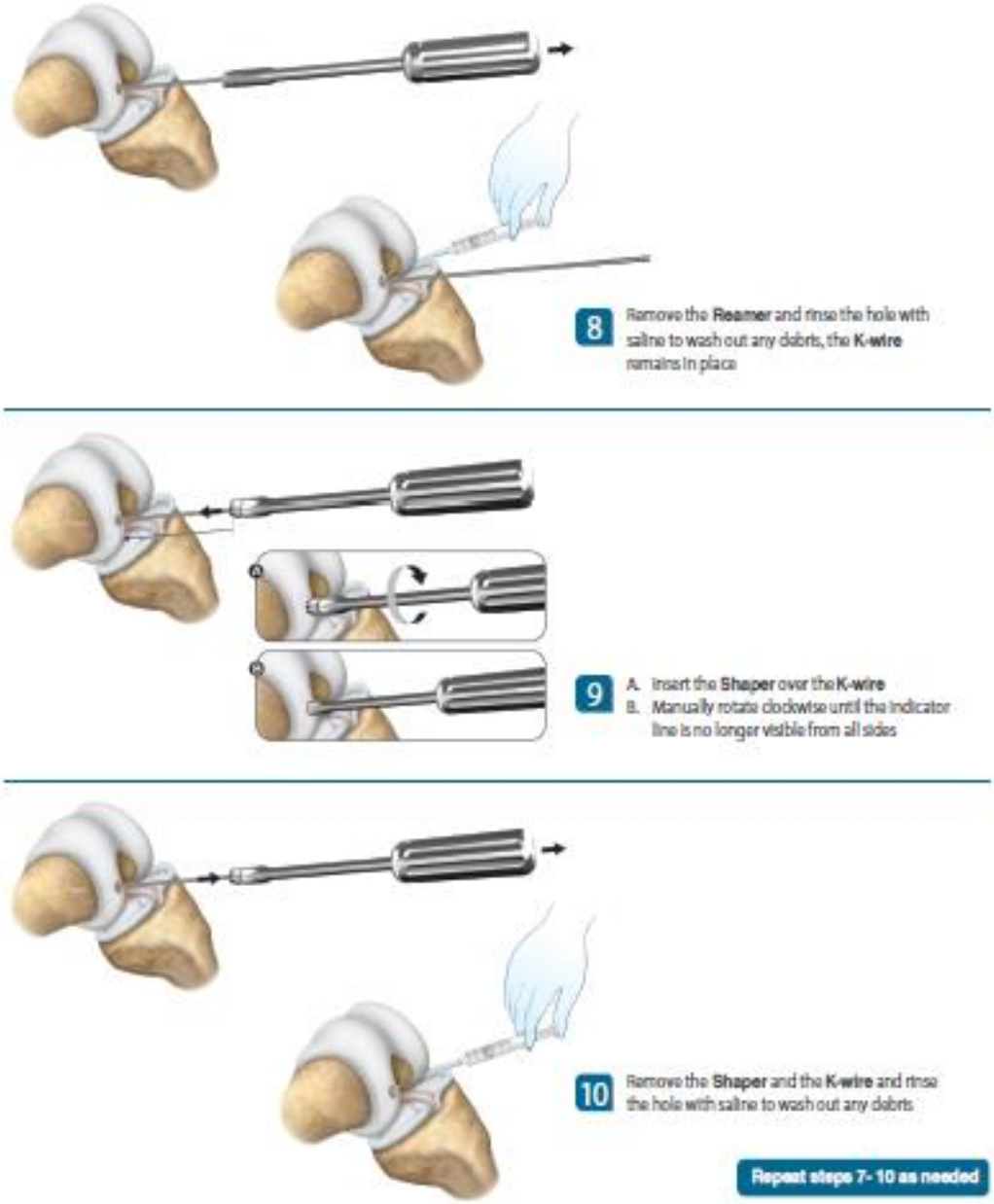
6

Remove the **Drill Bit** and **Drill Sleeve**, the **K-wire** remains in place

7

A. Insert the **Reamer** over the **K-wire**
B. Manually rotate the **Reamer** clockwise until the indicator line is no longer visible from all sides to ensure the correct depth of the hole

Central trochlear lesions
The indicator line should reach the articular surface level of the sulcus


8 Remove the Reamer and rinse the hole with saline to wash out any debris, the K-wire remains in place
9 A. Insert the Shaper over the K-wire
B. Manually rotate clockwise until the indicator line is no longer visible from all sides
10 Remove the Shaper and the K-wire and rinse the hole with saline to wash out any debris
Repeat steps 7- 10 as needed

11 Trim the peripheral cartilage using a scalpel to ensure smooth edges and to avoid invagination during Implant Insertion

12
A. **Agili-C™ Implant**
B. Manually insert the **Agili-C™ Implant** into the hole
C. Firmly push the implant using the thumb until it is flush with the articular cartilage
D. Implant flush with articular cartilage

13 Assemble the **Silicone Covers** over both ends of the **Tamper** according to the drawing

14 Gently impact the **Tamper** to insert the **Agili-C™ Implant** so its final position is 2mm below the surface of the articular cartilage

15 When multiple **Agili-C™ Implants** are used, it is important to keep a bone bridge of at least 5mm between the implants to avoid impingement

16 A. Apply Hyaluronic Acid (HA) to the top of the implant using the HA syringe supplied with the implant

B. Make sure to completely cover the top phase of the implant, at least to the level of the articular surface

* Do not apply more than 2ml of HA in a single joint

Precautions

1. During and post implantation visually inspect the **Agili-C™ Implant** to make sure that it is not fractured. If the **Agili-C™ Implant** is fractured, remove it and replace with a new implant

2. The **Agili-C™ Implant** must be recessed relative to the articular surface. Remove all implant protrusions with an orthopedic burr or shaver

DO NOT LEAVE ANY IMPLANT PROTRUSIONS

Appendix 6: Rehabilitation Recommendations (modified from Ebert et al. 2012)

Immediately after surgery:

- Exercise: Quadriceps isometric sets

Up to 48 hours:

- Physical treatment: Standard cryotherapy (ice packing)
- Ambulation: Flat Foot weight-bearing as tolerated (WBAT) with crutches

Up to 96 hours:

- Exercise: Continuous passive motion (CPM) from 48 hours after the procedure

From 96 hours to 2 weeks:

- Exercise: During physiotherapy Knee ROM: passive & active ROM as tolerated
- Exercise: isometric contractions & circulation exercises, CPM & cryotherapy

Week 3-6:

- Exercise: Knee ROM: active ROM from 0-90° (week 3) to 0-125° (week 6)
- Exercise: isometric/straight leg & passive/active knee flexion exercises, remedial massage, patella mobilization, CPM, cryotherapy & hydrotherapy
- Exercise: Stationary cycling is introduced, provided that the patient had reached knee flexion of 100 degrees
- Ambulation: Protected WBAT using crutches
- Ambulation: Progressive load increase to full weight-bearing

Week 7-12:

- Exercise: Knee ROM: full active ROM (week 7)
- Exercise: introduction of proprioceptive/balance activities, stationary cycling, walking, resistance & CKC activities

3-6 months:

- Exercise: Introduction of more demanding OKC (terminal leg extension) & CKC (inner range quadriceps and modified leg press)
- Exercise: Upright cycling, rowing ergometry & elliptical trainers

6-9 months:

- Exercise: Increase difficulty of proprioceptive/balance, OKC & CKC exercises (ie. step ups/downs, squats)
- Exercise: Introduce controlled mini trampoline

9-12 months:

- Exercise: Increase difficulty of CKC exercises (ie. lunge and squat activities on unstable surfaces)
- Exercise: Introduction of agility drills relevant to patient's sport
- Exercise: Jogging
- Return to competitive activity after 12 months

Appendix 7: Study CRFs