SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:
Implant, resorbable, for articular osteochondral repair

Device Trade Name: Agili-C™

Device Procode: QRU

Applicant's Name and Address:
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P210034

Date of FDA Notice of Approval: March 29, 2022

Breakthrough Device: Granted breakthrough device status on October 8, 2020, because the device and proposed indication for use met the criteria.

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

The Agili-C™ should not be implanted in subjects with the following conditions:

- Active or latent, bone or joint infection at the surgical site
- Active infection elsewhere in the body
- Neuropathic joint
- Hypersensitive, allergic, or intolerance of materials containing calcium carbonate or coral derivatives
- Critical limb ischemia
- Any known tumor of the knee area
- Severe osteoarthritis of the index knee, defined as grade 4 according to the Kellgren-Lawrence grading

- Uncontained lesion - lack of vital bone wall, at least 2mm thick, surrounding the implantation site
- Subchondral bone defect or bone cyst depth deeper than 8mm
- Inability to position the implant 2mm recessed relative to the articular surface
- Osteochondral or cystic lesions larger than what the implant can cover
- Implantation inside avascular necrosis

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Agili-C™ labeling.

V. DEVICE DESCRIPTION

The Agili-C™ is a cell-free, off-the-shelf implant for use in cartilage and osteochondral defects in traumatic and osteoarthritic joints. The implant is a porous, biocompatible, and biodegradable bi-phasic scaffold, consisting of interconnected natural inorganic calcium carbonate (aragonite) derived from purified, inorganic coral exoskeleton (**Figure 1**).

The Agili-C™ implant is implanted with the Agili-C™ Mini Disposable Toolset which is supplied sterile, for single use, and the Agili-C™ Reusable Toolset.

Figure 1: Agili-C™ Implant

Table 1. DEVICE SIZES

Diameter (mm)	Lengths (mm)
7.5	10
10	10
12.5	10
15	10

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of above knee-joint surface lesion(s), which may include non-operative and operative treatments.

Non-operative treatment options include the use of knee and leg braces, use of pain relievers and anti-inflammatory medicines, injections, hot/cold temperature baths, and limitation of activities.

Surgical treatment options for this indication include:

- Articular cartilage stimulation: drilling or micro-fracture of the subchondral bone. These are surgeries designed to disrupt the subchondral bone to stimulate new tissue formation.
- Debridement: a surgical procedure designed to clean out the joint and remove tissue that may be torn or detached.
- Osteochondral autograft transfer: a surgery that involves harvesting tissue from minimal weight-bearing areas of another joint in the patient's body and transplanting it to replace existing defects in weight-bearing areas of the knee.
- Osteochondral allograft transfer: involves harvesting grafts from external donors (e.g., cadavers).
- Autologous chondrocyte implantation: involves placement of patient's cultured chondrocytes in the articular cartilage defect. The procedure requires 2 surgeries: first for the biopsy and a second for implantation.
- Joint arthroplasty: either a total or partial replacement of the knee joint with metallic implants.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Agili-C™ has not been marketed in the United States. Agili-C™ received CE mark in 2011 and has not been recalled in any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Transient or chronic pain, including complex regional pain syndrome
- Transient or chronic swelling and/or effusion of the operated joint
- Transient or chronic synovitis
- Transient or chronic joint locking and/or limited range of motion, stiffness and arthrifibrosis
- Fever
- Bone marrow edema

- Allergic or pseudo-allergic reaction and/or elevation of acute phase reactants
- Pseudo septic reaction
- Reactive arthritis
- Aseptic arthritis
- Bone cyst
- Bone fracture
- Bone deformity
- Osteophyte formation
- Development or progression of osteoarthritis
- Formation of new cartilage or osteochondral defects, or worsening of current lesions
- Bone aseptic or avascular 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 formation deficiencies, lack of new tissue formation
- Partial ingrowth, overgrowth, fibrous tissue ingrowth or partial coverage of the implant
- Ligament laxity
- Damage to meniscus
- Joint deformation
- Tissue hypertrophy or inter-lesional bone formation or inter-lesional osteophytes
- Wound complications
- Superficial or deep infections
- Septicemia
- Wound dehiscence
- Intra-articular adhesions, hypertrophic tissue, hypertrophic synovitis or host reactions
- Inflammation of the joint and surrounding tissues
- Deep vein thrombosis
- Infection, including local and general complications
- Elevation of the subchondral bone plate
- Degeneration of the surrounding cartilage
- Lack of cartilage integration
- Delamination
- Muscle atrophy

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A variety of mechanical and other non-clinical tests were conducted to characterize the mechanical properties and performance of the Agili-C™, as outlined below. This testing included biocompatibility testing, mechanical fixation testing, and several animal studies to evaluate safety and performance.

A. Laboratory Studies

Table 2. Laboratory Studies

Test	Purpose	Acceptance Criteria	Results
Mechanical fixation testing	To evaluate fixation strength, push-out tests in artificial bone were performed on the device and bovine plugs representative of osteochondral autologous transfer system (OATS) plugs. The smallest and largest Agili-C™ implants were compared to bovine plugs of the same dimensions.	Device pushout load shall be not inferior to bovine plugs representative of OATS plugs.	Passed. Device pushout loads were superior to those of the comparison plugs.

B. Animal Studies

Table 3. Animal Studies

Study	Animals, Implantation sites, Duration	Evaluations	Results
PRC 0007 Report	14 goats: • 12 treated animals with 24 implants: 2 implants per joint, in the load bearing medial femoral condyle (MFC) and lateral femoral condyle (LFC); • 2 animals served as control with 4 empty defects. Duration: 6 months	Histology, macroscopic, X-ray	The design with hyaluronic acid (HA) added and drilled channels on the top showed the best results according to: modified Fortier scoring system, gross morphological evaluation, ICRS macroscopic evaluation, X-ray imaging, histology according to ICRS II and O'Driscoll grading, and immunohistochemistry.
PRC 0014 Report	20 goats: • 14 goats implanted with Agili-C™ • 6 goats with empty defects. Duration: 6 and 12 months	Histology, macroscopic, X-ray, Magnetic Resonance Imaging (MRI), Computed Tomography (CT)	Superior cartilage and subchondral bone formation at 6 and 12 months compared to control as confirmed by: histology, immunohistochemistry, ultrasound, X-ray, microCT, MRI, and macroscopic evaluations.
PRC 0019 Report	6 goats with 6 implants in the same joint: 2 in the load bearing MFC, 2 in the load bearing LFC,	Histology, macroscopic and	Macroscopic evaluation,

	and 2 in the Trochlea (total 36 implants) Duration: 1 month	radiographs	X-ray, MRI and histology confirmed better bone integration of implants with higher blood affinity.
PRC 0020 Report	6 goats 1 implant per joint, in the load bearing MFC Duration: 3 weeks	Radiographs	Radiographs showed better bone integration for implants with high blood affinity.
PRC 0026	25 goats, 1 implant per joint in the load bearing MFC.: • 14 animals – historical control (PRC0014): 7 animals with the 1st generation Agili-C™ followed for 6 months duration and 7 animals with the 1st generation Agili-C™ followed for 12 months duration • 11 animals: 5 animals with the 5th generation Agili-C™ followed for 6 months duration and 6 animals with the 5th generation Agili-C™ followed for 20 months duration.	Histology, macroscopic and radiographs	The comparison of the 4 groups showed equivalent results, with continuous improvement from 6 to 12 and 20 months. The results of the 2 methods for HA application, during implant production or *in-situ*, were similar and no difference in results was noted for any of the evaluation methods.
PRC 0030	8 animals, 1 implant per joint, in the load bearing MFC: • 6 goats with a large Agili-C™ oval implant; HA was applied to the top of the implant after final implant positioning, in situ, for lubrication. • 2 goats with a large Agili-C™ oval implant, without application of HA to the top of the implant after final implant positioning. Duration: 12 months	Histology, macroscopic and radiographs	In both groups the implant was fully degraded and replaced by cancellous bone. No local side effects were observed. The overall assessment of the defect healing indicated marked resurfacing with tissue formation. No difference was found between the 2 groups (with or without HA) at 12 months follow up.

C. Additional Studies

Biocompatibility of the device was evaluated according to International Organization for Standardization (ISO) 10993-1:2018 and FDA Guidance Document "Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process". The biocompatibility tests conducted included Cytotoxicity, Irritation, Sensitization, Implantation, Genotoxicity (Bacterial Gene Mutation Assay and In Vitro Mammalian Genotoxicity Assay),

Carcinogenicity, and Material Mediated Pyrogenicity. Results of testing in combination with toxicological risk evaluation demonstrated biocompatibility in line with the requirements of ISO 10993-1 for a permanent implant in contact with bone.

Table 4. Additional Studies

Test	Acceptance Criteria	Results	Analysis Type
Shelf-Life			
Packaging Testing	• Visual Inspection (ASTM F1886) – No abnormal changes for all tests articles • Dye Penetration (ASTM F1929) – no dye penetration • Peel strength (ASTM F88) - Not less than 1.2N/15mm • Burst Strength (ASTM F1140) - No less than 11.6 kPa (2 stdev lower than avg of time zero)	Passed - 5 Year Shelf Life	Accelerated and real-time aging validation.
Device Shelf-Life	• Visual inspection • Density • Porosity	Passed - 5 Year Shelf Life	Accelerated aging.
Sterilization			
Sterilization	Gamma Sterilization process is used. It is performed per ISO 11137:2015. Devices must have a sterility assurance of at least 10^{-6}.	Passed	Testing and Validation per ISO 11137:2015

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The Agili-C™ has been studied for use in knee joint surface lesions in 4 clinical trials, including 3 studies conducted outside of the US (OUS) and the pivotal study outlined below.

The 3 prior investigations were conducted post-CE mark during the development of Agili-C™ and included 1 first-in-human (FIH) pilot study ("Pilot CLN0002"), 1 follow-up to the pilot study ("CLN0002"), and 1 postmarket study ("CLN0019") that investigated later device generations:

1. Pilot CLN0002, First in Human (FIH) Study – "Evaluation of the Agili-C™ Bi-phasic Implant Performances in the Repair of Cartilage and Osteochondral Defects"

   In this Multi-Center, Prospective, Non-Randomized, Open-Label, Single Group Assignment trial, a pilot group of 12 patients was implanted with Agili-C™ implants ranging in size from 6mm to 10mm diameter using an off-the-shelf (Arthrex, OATS) surgical toolset, with 18 months follow-up.

2. CLN0002 – "Evaluation of the Agili-C™ Bi-phasic Implant Performances in the Repair of Cartilage and Osteochondral Defects"

   In this Multi-Center, Prospective, Non-Randomized, Open-Label, Single Group Assignment trial, 53 patients were implanted with the Agili-C™ implant at 7 European centers, with 24 months follow-up.

3. CLN0019 – "Agili-C™ Implant Performance Evaluation in the Repair of Cartilage and Osteochondral Defects"

   In this Multi-Center, Prospective, Non-Randomized, Open-Label, Single Group Assignment trial, 143 subjects were implanted with the Agili-C™ at 8 European centers, with 24 months follow-up.

Previous generation Agili-C™ devices were implanted in the 3 prior non-randomized clinical investigations above. These studies served to help improve the design of the device, including instrumentation. They also provided clinical experience with the device, which informed the design of the pivotal clinical trial. The current generation Agili-C™ device was evaluated in the pivotal trial described below. The primary data supporting this PMA are from the prospective, randomized controlled multi-center IDE trial performed to evaluate the safety and effectiveness of the Agili-C™ device compared to the surgical standard of care treatment of subjects with ICRS grade III or above knee-joint surface lesion(s). A summary of this pivotal clinical trial is presented below.

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of implantation with Agili-C™ for treatment of an ICRS grade III or above knee-joint surface lesion(s), with a total treatable area of 1-7cm^2, without severe osteoarthritis (Kellgren-Lawrence grade 0-3), in the US, Belgium, Italy, Israel, Hungary, Poland, Romania, and Serbia under IDE # G160205. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between 2017 and 2019. The database for this PMA reflected data collected through September 2021 and included 251 patients. There were 27 investigational sites, 11 in the US and 16 OUS.

The study was a prospective, multicenter, randomized, 2-arm controlled, open-label clinical study. The study enrolled subjects diagnosed with cartilage or osteochondral lesions of the knee (ICRS grade III or greater) with a total treatable area of 1-7cm^2 without severe osteoarthritis (no Kellgren-Lawrence grade 4). Patients between 21 and 75 years of age who had up to 3 lesions on the femoral condyles or trochlea were randomized in a 2:1 ratio to the Agili-C™ device versus the active control group consisting of surgical standard of care (SSOC). Subjects were assigned to their treatment arm using by site, block randomization with variable random block sizes of

3 and 6. Surgical standard of care consisted of treating each lesion with either debridement or microfracture. Debridement was used for lesion treatment in control patients older than 50 years of age if the lesion was larger than 3cm^2 or if the patient had arthritis grade greater than Kellgren-Lawrence 1. Debridement was used for lesion treatment in control patients less than or equal to 50 years of age if BOTH the lesion was larger than 3cm^2 AND the patient had arthritis grade greater than Kellgren-Lawrence grade 1. Microfracture was used for lesion treatment in control patients older than 50 years of age if BOTH the lesion was less than or equal to 3cm^2 AND the patient had earlier arthritis (Kellgren-Lawrence grade 0-1). Microfracture was used for lesion treatment in all lesions of control patients less than or equal to 50 years of age unless BOTH the lesion was greater than 3cm^2 AND the patient had more advanced arthritis (Kellgren-Lawrence grade 2-3). Up to 3 lesions could be treated in the index knee. In the device arm, up to 3 Agili-C™ devices could be used to treat each lesion in the index knee, with the objective of achieving >80% lesion coverage.

The adaptive trial design allowed a minimum of 250 subjects and up to a maximum number of 500 subjects to be randomized, with interim analyses that allowed for early stopping of the trial for futility, or for early stopping of enrollment, but continuing follow-up, for expected success. The interim analyses were conducted by an independent statistician and reviewed by an Endpoint Adjudication Committee.

The primary goal of the trial was to demonstrate superiority of the Agili-C™ device relative to SSOC using Bayesian analysis. The trial would be considered a success if the posterior probability exceeds 0.98 at the final analysis.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the study, 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, was limited to patients who met the following inclusion criteria:

   1. 21 – 75 years
   2. Up to 3 treatable joint surface lesion(s), International Cartilage Repair Society (ICRS) Grade III or above, on the femoral condyles and/or trochlea
   3. Symptomatic total treatable area 1-7 cm^2. Asymptomatic lesions were not 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

   Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

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

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

2. Follow-up Schedule

Post-procedure follow-up evaluated the patient's knee condition and clinical health. Follow-up visits were performed at 2 weeks, 3, 6, 12, 18 and 24 months (primary endpoint time point), and yearly thereafter until each patient reached 60 months follow-up. Anterior-Posterior and Lateral knee X-rays were taken at 2 weeks and 6, 12, 18, and 24-months post procedure. MRI was performed at 12 and 24 months. All complications and adverse events, device-related or not, were recorded at all visits and evaluated over the course of the study.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 5. Study Schedule

Procedures	Screen-ing Visit	Final Screening/ Procedure Visit	2 week Post-Procedure Visit (± 1.5 weeks)	3 ᵘ, 6^, 12 and 18 Months Post-Procedure Visit (± 16 weeks)	24 Month Post-Procedure Visit (± 16 weeks)	Annual Post-24 Month Visit Until 60 Months (± 16 weeks)	Un-scheduled Visit
Number of Visit	Visit 1	Visit 2	Visit 3	Visits 4-7	Visit 8	Visits 9-11	
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"	X***

Procedures	Screen-ing Visit	Final Screening/ Procedure Visit	2 week Post-Procedure Visit (± 1.5 weeks)	3 ᵘ, 6^, 12 and 18 Months Post-Procedure Visit (± 16 weeks)	24 Month Post-Procedure Visit (± 16 weeks)	Annual Post-24 Month Visit Until 60 Months (± 16 weeks)	Un-scheduled Visit
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	X***
IKDC Knee Examination form 2000 (Surgeon)	X			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	

Procedures	Screen-ing Visit	Final Screening/ Procedure Visit	2 week Post-Procedure Visit (± 1.5 weeks)	3 µ, 6^, 12 and 18 Months Post-Procedure Visit (± 16 weeks)	24 Month Post-Procedure Visit (± 16 weeks)	Annual Post-24 Month Visit Until 60 Months (± 16 weeks)	Un-scheduled Visit
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 - Implantation procedure		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. 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.

µ The 3 month visit may take place ±2 weeks.

^ The 6 month visit may take place ±12 weeks.

∞ Not applicable for the 3 months visit

“ Optional MRI

According to PI decision

3. Clinical Endpoints

Safety Endpoint

The safety endpoint was the rate of adverse events – including serious adverse events, reoperations and revisions – up to 24 months.

Primary Effectiveness Endpoint

The primary endpoint for this study was the change from baseline to 24 months in the average KOOS Overall Score, consisting of the average of the KOOS subscores: Pain, Other Symptoms, Quality of Life (QOL), Activities of Daily Living (ADL) and Sports.

Confirmatory Secondary Endpoints

The study had 4 confirmatory secondary endpoints for labeling purposes:

1. Change in KOOS Pain score from baseline to Month 24
2. Change in KOOS Quality of Life score from baseline to Month 24
3. Change in KOOS ADL score from baseline to Month 24
4. Response rate at Month 24, defined as an improvement in KOOS Overall Score $\geq$30

Additional Secondary Endpoints

Additional secondary endpoints included:

- Percentage of articular defect fill according to MRI at 12 and 24 months
- Change from baseline in average KOOS Overall 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 KOOS Overall score (Pain, Symptoms, QOL, ADL & Sports) in:
    a. patients with chondral lesions
    b. patients with osteochondral lesions
    c. patients with single lesion
    d. patients with multiple lesions
    e. patients without osteoarthritis (K/L 0-1)
    f. patients with osteoarthritis (K/L 2-3)
    g. patients with total lesion(s) size $\leq$3cm^2
    h. patients with total lesion(s) size >3cm^2
    i. patients without previous ligament reconstruction
    j. patients with intact meniscus
    k. patients with previous partial meniscectomy
    l. patients with concomitant partial meniscectomy
    m. active patients
    n. non-active patients

B. Accountability of PMA Cohort

At the time of database lock, of 251 patients enrolled in the PMA study, 95.6% (240) patients are available for analysis at the completion of the study, the 24 month post-operative visit (*final visit evaluated for safety and effectiveness as the basis for the PMA submission*).

Safety Analysis Set – 251 subjects: The safety analysis set includes N=167 subjects randomized and receiving Agili-C™ and N=84 subjects randomized and receiving SSOC.

Full Analysis Set (FAS) – 247 subjects: The FAS includes N=164 subjects randomized and receiving treatment with Agili-C™ and N=83 subjects randomized and receiving SSOC. 3 subjects were excluded in the Agili-C™ group and 1 in the SSOC group due to major entry violations.

Per Protocol (PP) Analysis Set – 246 subjects: There were no additional exclusions compared to the FAS due to a major protocol violation. There was 1 subject in the study, from the Agili-C™ arm, who withdrew consent prior to the 12 Month visit and did not perform the 12 Month visit. Therefore, the PP analysis set includes N=163 subjects randomized and receiving Agili-C™ and N=83 subjects randomized and receiving SSOC. Thus, all comparisons are nearly the same for the FAS and the PP analysis set.

Table 1: Subject Disposition

	All		**Agili-C™**		**SSOC**	
	N	**%**	**N**	**%**	**N**	**%**
Randomized and treated (438-187=251)[1]	**251**	**57.3%**	**167**	**---**	**84**	**---**
Analysis Sets[2]						
Safety	251		167	100.0%	84	100.0%
Full Analysis Set (FAS)	247		164	98.2%	83	98.8%
Per Protocol (PP)	246		163	97.6%	83	98.8%
Completed the Study[2]	240		163	97.6%	77	91.7%
Early Discontinuation[2]	11		4	2.4%	7	8.3%
Reasons for Early D/C Among Randomized[2]						
Subject withdrew consent	3		1	0.6%	2	2.4%
Lost To Follow-Up	8		3	1.8%	5	6.0%
With clinical data without BOCF in Safety Set[2, 3]						
Pre-Operative	251		167	100.0%	84	100.0%
Month 6	249		167	100.0%	82	97.6%
Month 12	248		166	99.4%	82	97.6%
Month 18	243		165	98.8%	78	92.9%
Month 24	240		163	97.6%	77	91.7%

	All		Agili-C™		SSOC	
	N	%	N	%	N	%

Notes:
[1] % is among screened.
[2] % is among randomized and treated within treatment group.
[3] Based on KOOS Overall Score

Table 2: Follow-Up Compliance (Full Analysis Set)

	Pre-Op		Month 6		Month 12		Month 18		Month 24	
	I	C	I	C	I	C	I	C	I	C
(1) Theoretical follow-up	164	83	164	83	164	83	164	83	164	83
(2) Cumulative Death			0	0	0	0	0	0	0	0
(3) Treatment Failures			2	3	8	10	10	16	11	18
(4) Not Yet Overdue (no data but still window)			0	0	0	0	0	2	0	0
(5) Expected Due [(5)=(1)-(2)-(4)]			164	83	164	83	164	81	164	83
Within Window Accounting (Actual)										
(8) Procedures with KOOS Overall Score in interval†	164	83	164	81	163	80	162	80	158	78
(9) Visit Compliance (%) = (8) / (5)			100%	98%	99%	96%	99%	99%	96%	94%
All Evaluated Accounting (Actual)										
(6) Procedures with KOOS Overall Score in interval[&]	164	83	164	81	163	81	162	80	160	79
(7) Visit Compliance (%) = (6) / (5)			**100%**	**98%**	**99%**	**98%**	**99%**	**99%**	**98%**	**95%**

Notes:
I = Agili-C™ (intervention), C = SSOC (control)
[&] Clinical values utilizing BOCF for treatment failures are assumed within window.
[†] Windows defined at exact anniversary +/- 16 weeks (+/- 112 days). Exact anniversaries were defined as 180 (6 mo.), 365 (12 mo.), 545 (18 mo.), and 730 (24 mo.).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a randomized controlled pivotal study performed in the US.

Table 8 to Table 12 summarize the 2treatment groups at baseline in the Safety Analysis Set. Specifically, these tables summarize the following information:

- Baseline and Demographic Continuous Variables (Table 8)
- Baseline and Demographic Categorical Variables (Table 9)
- Categorical Lesion Characteristics (Table 10)
- Continuous Lesion Variables (Table 11)
- History of and Concomitant Treatments (Table 12)

Table 3: Baseline and Demographic Continuous Variables (Safety Analysis Set)

	Agili-C™					SSOC					Agili-C™ - SSOC[1]		
Demographics - All	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age	167	42.0	11.2	21.2	71.8	84	46.2	11.2	22.7	70.2	-4.21	-7.15	-1.27
Height (cm)	167	174.9	9.0	155.0	198.0	84	173.9	10.5	143.0	193.0	0.95	-1.55	3.45
Weight (kg)	167	81.1	16.1	52.0	123.0	84	84.6	15.0	55.0	116.0	-3.51	-7.66	0.64
BMI (k/m^2)	167	26.4	4.2	18.0	34.9	84	27.9	3.8	20.1	34.8	-1.48	-2.55	-0.41
Baseline Functional Status	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**Diff**	**LB**	**UB**
KOOS-Symptoms Score	167	53.3	18.3	3.6	92.9	84	55.3	19.1	7.1	92.9	-1.96	-6.86	2.94
KOOS-Pain Score	167	46.9	11.6	22.2	63.9	84	48.4	10.9	22.2	63.9	-1.56	-4.55	1.44
KOOS-ADL Score	167	55.1	17.0	4.4	95.6	84	54.0	15.6	1.6	86.8	1.04	-3.32	5.40
KOOS-Sports Score	167	25.0	17.9	0.0	75.0	84	24.0	17.0	0.0	60.0	0.92	-3.72	5.56
KOOS-QOL Score	167	26.0	16.7	0.0	68.8	84	25.8	16.5	0.0	87.5	0.23	-4.15	4.61
KOOS-Overall Score	167	41.3	13.0	11.8	72.1	84	41.5	12.5	7.5	69.5	-0.26	-3.65	3.12
SF12-Physical Score	167	36.0	8.1	17.1	59.9	84	36.0	8.1	12.5	57.2	-0.02	-2.16	2.11
SF12-Mental Score	167	52.6	12.1	15.0	73.8	84	52.5	12.7	22.1	77.4	0.07	-3.17	3.31
IKDC Score	167	36.8	12.8	6.9	71.3	84	34.9	11.2	4.6	62.1	1.90	-1.34	5.14
Tegner Pre-Surgery	167	2.5	1.3	0.0	7.0	84	2.4	1.2	0.0	6.0	0.10	-0.25	0.44
Tegner Pre-Injury	167	6.1	1.9	1.0	10.0	84	6.0	2.0	2.0	10.0	0.02	-0.49	0.53

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.

Table 4: Baseline and Demographic Categorical Variables (Safety Analysis Set)

	Agili-C™		SSOC		Agili-C™ - SSOC[1]		
	n	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Number of subjects	167		84				
Males	107	64.1	51	60.7	3.4	-9.4	16.1
Females	60	35.9	33	39.3			

	Agili-C™		SSOC		Agili-C™ - SSOC[1]		
Ethnicity	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Hispanic or Latino	2	1.2	1	1.2	0.0	-2.9	2.9
Not Hispanic or Latino	164	98.8	82	98.8			
Race	**n**	**%**	**n**	**%**	**p[2]**		
White	159	95.2	81	97.6	0.736		
Black	6	3.6	2	2.4			
Asian	1	0.6	0	0.0			
Native	1	0.6	0	0.0			
BMI ≥ 30	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	37	22.2	27	32.1	-10.0	-21.8	1.8
No	130	77.8	57	67.9			
Tegner Activity (pre-injury)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Active (>4)	132	79.0	61	72.6	6.4	-4.9	17.8
Non-Active (≤4)	35	21.0	23	27.4			
Age Category							
≥50	40	24.0	34	40.5			
<50	127	76.0	50	59.5			
Age Group	**n**	**%**	**n**	**%**	**p[2]**		
21-<45 (Young adulthood)	94	56.3	41	48.8	0.533		
45-<65 (Middle adulthood)	68	40.7	40	47.6			
≥65 (Elderly)	5	3.0	3	3.6			
Site Location	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
US	33	19.8	18	21.4	-1.7	-12.3	9.0
OUS	134	80.2	66	78.6			
Smoking History	**n**	**%**	**n**	**%**	**p[2]**		
Current[3]	37	22.2	22	26.2	0.191		
Past	22	13.2	17	20.2			
Never	108	64.7	45	53.6			

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.
[2] P-value for Chi-Square test.
[3] Includes 2 Agili-C™ subjects and 1 SSOC subject who quit smoking within 6 months of index procedure.

Table 5: Categorical Lesion Characteristics (Safety Analysis Set)

	Agili-C™		SSOC		Agili-C™ - SSOC[1]		
Kellgren-Lawrence Grade	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
None	91	54.5	30	35.7	18.8	6.0	31.5
Mild/Moderate	76	45.5	54	64.3			
Lesion Size >3 cm²	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	98	58.7	41	48.8	9.9	-3.2	22.9
No	69	41.3	43	51.2			
Single vs Multiple Lesions	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Single	109	65.3	58	69.0	-3.8	-16.0	8.5
Multiple	58	34.7	26	31.0			

	Agili-C™		SSOC		Agili-C™ - SSOC[1]		
ICRS Grade (worst across lesions)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Osteochondral lesions (ICRS 4b)	63	37.7	16	19.0	18.7	7.5	29.8
Chondral lesions (ICRS 3 & 4a)	104	62.3	68	81.0	.	.	.

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences

Table 6: Continuous Lesion Variables (Safety Analysis Set)

	Agili-C™					SSOC					Agili-C™ - SSOC[1]		
	N	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**Diff**	**LB**	**UB**
Sum of lesion areas (1, 2 + 3)	167	3.9	2.0	1.0	7.0	84	3.4	1.9	1.0	7.0	0.53	0.01	1.05
Lesion Area 1	167	2.9	1.6	1.0	7.0	84	2.6	1.6	0.1	7.0	0.27	-0.15	0.70
Lesion Area 2	58	2.7	1.5	0.5	6.0	26	2.1	1.1	0.8	4.5	0.64	-0.03	1.30
Lesion Area 3	6	2.7	1.2	1.5	5.0	5	2.3	1.3	1.0	4.0	0.39	-1.29	2.08

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.

Table 7: History of and Concomitant Treatments (Safety Analysis Set)

	Agili-C™		SSOC		Agili-C™ - SSOC[1]		
Hx of ACL Repair (Intra/Extra articular)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	13	7.8	7	8.3	-0.5	-7.7	6.6
No	154	92.2	77	91.7	.	.	.
Hx of meniscectomy (medial/lateral)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	36	21.6	22	26.2	-4.6	-15.9	6.6
No	131	78.4	62	73.8	.	.	.
Concomitant meniscectomy (medial/lateral)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	50	29.9	19	22.6	7.3	-4.0	18.6
No	117	70.1	65	77.4	.	.	.
Meniscus Status	**n**	**%**	**n**	**%**	**p-value[2]**		
Intact	94	56.3	44	52.4	0.072		
History (partial)	23	13.8	21	25.0	.		
Concomitant	50	29.9	19	22.6	.		

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.
[2] P-value for Chi-Square test

D. Safety and Effectiveness Results

1. Safety Results

Agili-C™ demonstrated a favorable safety profile in the pivotal study compared to the SSOC. Importantly, among the pre-specified adverse events summarized below

in Table 14 occurred in 23.4% of Agili-C™ patients in the pivotal study, compared to 50.0% of SSOC patients. Moreover, the rates of any AE, serious AE, and treatment failure were lower in Agili-C™ compared to SSOC.

The analysis of safety was based on the safety cohort of 251 total subjects treated (167 randomized and treated Agili-C™ subjects, and 84 SSOC subjects) . Adverse effects are reported in Tables 13 to 16. Treatment failures are presented below in Tables 17 to 18.

Adverse effects that occurred in the PMA clinical study

The overall adverse event ("AE") rate was lower for the Agili-C™ group (58.7%) compared to the SSOC group (77.4%). At least 1 Severe AE was present in 9.6% of the Agili-C™ subjects compared to 20.2% in SSOC subjects, and at least 1Serious AE was present in 15.6% of the Agili-C™ subjects compared to 20.2% of SSOC subjects. Overall, adverse event (AE) rates were lower for Agili-C™ subjects compared to SSOC subjects.

Table 8: Summary of AEs By Treatment Group (Safety Analysis Set)

	Agili-C™ N= 167		**SSOC N= 84**		**Comparison**		
Number (%) of Patients	**n**	**%**	**n**	**%**	**Diff.**	**95% LB**	**95% UB**
With no AEs	68	40.7%	19	22.6%	18.1	6.5	29.7
With one or more AE§	99	59.3%	65	77.4%	-18.1	-29.7	-6.5
With one or more Serious AEs	27	16.2%	17	20.2%	-4.1	-14.3	6.2
- With one or more serious device/toolset-related AEs	3	1.8%	--	--	--	--	--
- With one or more serious procedure-related AEs	4	2.4%	5	6.0%	-3.6	-9.1	2.0
With one or more device/toolset OR procedure-related* AEs	28	16.8%	23	27.4%	-10.6	-21.7	0.5
- With one or more device/toolset-related* AEs	5	3.0%	--	--	--	--	--
- With one or more procedure-related* AEs	23	13.8%	23	27.4%	-13.6	-24.5	-2.7
With one or more severe AEs	17	10.2%	17	20.2%	-10.1	-19.8	-0.3
With one or more moderate or severe AEs	79	47.3%	52	61.9%	-14.6	-27.5	--1.7
AE with outcome of death	0	0.0%	0	0.0%			
AE with outcome of device/toolset-related death	0	0.0%	--	--	--	--	--

	Agili-C™ N= 167		SSOC N= 84		Comparison		
Number (%) of Patients	**n**	**%**	**n**	**%**	**Diff.**	**95% LB**	**95% UB**
Treatment Failure (Surgery or Injection)	12	7.2%	18	21.4%	-14.2	-23.9	-4.6

Notes:
§ AEs included with onset date on or before the Month 24 visit date (if missing, end-of-study date) or Day 730, whichever is later.
*Related is defined as definitely or probably related.

Table 9: Incidence Rates (%) and Event Counts of AEs by System Organ Class and Preferred Term (Safety Analysis Set)

AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
PRE-SPECIFIED	39	23.4%	42	42	50.0%	48	-26.6	-39.1	-14.2
Decreased range of motion compared to baseline	2	1.2%	2	1	1.2%	1	0.0		
Deep vein thrombosis (DVT) and related complications				1	1.2%	1			
Increased swelling (or effusion) in the operated joint, compared to baseline	9	5.4%	9	4	4.8%	4	0.6	-5.1	6.3
Increased transient or chronic pain in the operated joint, compared to baseline	25	15.0%	25	33	39.3%	37	-24.3	-36.1	-12.6
Infection (including septicemia or deep infections in the operated joint) and related symptoms, such as fever and/or pus	1	0.6%	1						
Joint locking	1	0.6%	1						
Muscle atrophy compared to baseline	2	1.2%	2						
Progression of osteoarthritis (degeneration of surrounding bone and cartilage or delamination) compared to baseline				4	4.8%	4			
Wound complications (wound dehiscence, hematoma, site drainage or superficial infection)	2	1.2%	2	1	1.2%	1	0.0		
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	0.6%	1						
Foetal hypokinesia	1	0.6%	1						
CARDIAC DISORDERS				1	1.2%	1			
Coronary artery disease				1	1.2%	1			
CONGENITAL, FAMILIAL AND GENETIC DISORDERS				1	1.2%	1			
Arteriovenous malformation				1	1.2%	1			

AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
EAR AND LABYRINTH DISORDER	1	0.6%	1						
Conductive deafness	1	0.6%	1						
ENDOCRINE DISORDERS	1	0.6%	1						
Hypothyroidism	1	0.6%	1						
EYE DISORDERS	3	1.8%	3						
Eye irritation	1	0.6%	1						
Retinal vein occlusion	1	0.6%	1						
Vision blurred	1	0.6%	1						
GASTROINTESTINAL DISORDERS	6	3.6%	6	2	2.4%	2	1.2		
Abdominal pain upper	1	0.6%	1						
Anal fistula				1	1.2%	1			
Colitis ulcerative	1	0.6%	1						
Constipation	1	0.6%	1						
Crohn's disease				1	1.2%	1			
Gastroesophageal reflux disease	1	0.6%	1						
Inguinal hernia	1	0.6%	1						
Umbilical hernia	1	0.6%	1						
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2	1.2%	2	2	2.4%	2	-1.2		
Adverse drug reaction				1	1.2%	1			
Asthenia	1	0.6%	1						
Chest pain				1	1.2%	1			
Thermal burn	1	0.6%	1						
IMMUNE SYSTEM DISORDERS	4	2.4%	4	1	1.2%	1	1.2		
Allergy to metals	1	0.6%	1						
Drug hypersensitivity	3	1.8%	3	1	1.2%	1	0.6		
INFECTIONS AND INFESTATIONS	17	10.2%	18	8	9.5%	8	0.7	-7.1	8.4
Covid-19	6	3.6%	6	2	2.4%	2	1.2		
Coxsackie viral infection				1	1.2%	1			
Diverticulitis	1	0.6%	1						
Ear infection fungal	1	0.6%	1						
Gastroenteritis	1	0.6%	1						
Influenza	1	0.6%	1						
Nasopharyngitis	1	0.6%	1						
Orchitis	1	0.6%	1						
Otitis media	1	0.6%	1	1	1.2%	1	-0.6		
Pharyngitis streptococcal	1	0.6%	1	1	1.2%	1	-0.6		
Pneumonia	1	0.6%	1	1	1.2%	1	-0.6		
Stitch abscess	1	0.6%	1						
Tooth abscess	1	0.6%	1						
Tooth infection				1	1.2%	1			
Upper respiratory tract infection	1	0.6%	1	1	1.2%	1	-0.6		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	23	13.8%	25	12	14.3%	15	-0.5	-9.6	8.6

AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
Animal bite	1	0.6%	1						
Cartilage injury				1	1.2%	1			
Chemical burns of eye				1	1.2%	1			
Contusion	5	3.0%	5	3	3.6%	3	-0.6	-5.3	4.2
Facial bones fracture	1	0.6%	1						
Hand fracture	1	0.6%	1						
Head injury	1	0.6%	1						
Iatrogenic injury	1	0.6%	1						
Iliotibial band syndrome	2	1.2%	2	1	1.2%	1	0.0		
Inadequate osteointegration	1	0.6%	1						
Injury	1	0.6%	1						
Ligament sprain	1	0.6%	1						
Limb injury				1	1.2%	1			
Meniscus injury				1	1.2%	1			
Muscle rupture	1	0.6%	1						
Muscle strain	1	0.6%	1						
Nerve injury				1	1.2%	1			
Post procedural haematoma	1	0.6%	1						
Post-traumatic neck syndrome	1	0.6%	1	1	1.2%	1	-0.6		
Procedural pain	1	0.6%	1						
Repetitive strain injury	1	0.6%	1						
Rib fracture				1	1.2%	1			
Road traffic accident				2	2.4%	2			
Sciatic nerve injury				1	1.2%	1			
Tendon rupture	1	0.6%	1	1	1.2%	1	-0.6		
Tooth fracture	1	0.6%	1						
Traumatic arthropathy	1	0.6%	1						
Wrist fracture	1	0.6%	1						
METABOLISM AND NUTRITION DISORDERS	3	1.8%	3						
Hyperlipidaemia	1	0.6%	1						
Obesity	1	0.6%	1						
Type 2 diabetes mellitus	1	0.6%	1						
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	35	21.0%	43	20	23.8%	22	-2.9	-13.9	8.2
Arthralgia	15	9.0%	16	10	11.9%	11	-2.9	-11.1	5.2
Back pain	2	1.2%	2	2	2.4%	2	-1.2		
Bursitis	1	0.6%	1						
Chondropathy	1	0.6%	1						
Foot deformity	1	0.6%	1						
Haemarthrosis	3	1.8%	3	1	1.2%	1	0.6		
Intervertebral disc degeneration				2	2.4%	2			
Intervertebral disc disorder				1	1.2%	1			
Joint effusion	1	0.6%	1						
Joint instability	1	0.6%	1						

AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
Joint swelling	1	0.6%	1						
Musculoskeletal stiffness	1	0.6%	1						
Osteoarthritis	3	1.8%	3	1	1.2%	1	0.6		
Osteochondrosis	1	0.6%	1	1	1.2%	1	-0.6		
Pain in extremity	2	1.2%	2						
Plantar fasciitis	1	0.6%	1						
Rotator cuff syndrome	1	0.6%	1						
Spinal osteoarthritis				1	1.2%	1			
Spinal synovial cyst				1	1.2%	1			
Spondylolisthesis	1	0.6%	1						
Temporomandibular joint syndrome	1	0.6%	1						
Tendon disorder	3	1.8%	3						
Tendonitis	2	1.2%	2	1	1.2%	1	0.0		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	0.6%	1	2	2.4%	2	-1.8		
Choroid neoplasm				1	1.2%	1			
Colon adenoma				1	1.2%	1			
Neuroma	1	0.6%	1						
NERVOUS SYSTEM DISORDERS	15	9.0%	15	5	6.0%	5	3.0	-3.6	9.7
Cervical radiculopathy	2	1.2%	2						
Migraine without aura				1	1.2%	1			
Post-traumatic headache				1	1.2%	1			
Sciatica	11	6.6%	11	3	3.6%	3	3.0	-2.5	8.5
Syncope	1	0.6%	1						
Thoracic outlet syndrome	1	0.6%	1						
PRODUCT ISSUES	1	0.6%	1						
Breast implant rupture	1	0.6%	1						
PSYCHIATRIC DISORDERS	1	0.6%	1	2	2.4%	2	-1.8		
Anxiety				1	1.2%	1			
Claustrophobia				1	1.2%	1			
Depression	1	0.6%	1						
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5	3.0%	5	1	1.2%	1	1.8		
Menometrorrhagia	1	0.6%	1	1	1.2%	1	-0.6		
Menopausal symptoms	1	0.6%	1						
Penile discharge	1	0.6%	1						
Prostatism	1	0.6%	1						
Vaginal haemorrhage	1	0.6%	1						
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3	1.8%	3	2	2.4%	2	-0.6		
Acute respiratory failure	1	0.6%	1						
Bronchiectasis				1	1.2%	1			
Dyspnoea	1	0.6%	1						
Pulmonary fibrosis				1	1.2%	1			

AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
Sinusitis	1	0.6%	1						
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	1.8%	3						
Dermatitis contact	1	0.6%	1						
Rash	1	0.6%	1						
Urticaria	1	0.6%	1						
SURGICAL AND MEDICAL PROCEDURES	1	0.6%	1	1	1.2%	1	-0.6		
Ligament operation	1	0.6%	1	1	1.2%	1	-0.6		
VASCULAR DISORDERS	4	2.4%	4						
Lymphoedema	1	0.6%	1						
Thrombophlebitis	1	0.6%	1						
Thrombosis	1	0.6%	1						
Varicose vein	1	0.6%	1						

Notes:
‡95% confidence intervals are provided when at least 3 subjects in both groups experienced the event. 95% confidence intervals that include 0.0 indicate that the observed treatment difference is consistent with chance variation.
§AEs included with onset date on or before the Month 24 visit date (if missing, end-of-study date) or Day 730, whichever is later.

Table 15 presents the incidence rates and events counts of severe AEs. Across all categories, group differences were in favor of Agili-C™.

Table 10: Incidence Rates (%) and Event Counts of Severe AEs by System Organ Class and Pre-specified or Preferred Term (Safety Analysis Set)

Severe AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
PRE-SPECIFIED	1	0.6%	1	10	11.9%	10	-11.3		
Deep vein thrombosis (DVT) and related complications				1	1.2%	1			
Increased transient or chronic pain in the operated joint, compared to baseline	1	0.6%	1	7	8.3%	7	-7.7		
Progression of osteoarthritis (degeneration of surrounding bone and cartilage or delamination) compared to baseline				2	2.4%	2			
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	0.6%	1						
Foetal hypokinesia	1	0.6%	1						
CARDIAC DISORDERS				1	1.2%	1			
Coronary artery disease				1	1.2%	1			

Severe AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
IMMUNE SYSTEM DISORDERS	1	0.6%	1						
Allergy to metals	1	0.6%	1						
INFECTIONS AND INFESTATIONS	3	1.8%	3	1	1.2%	1	0.6		
Covid-19	3	1.8%	3	1	1.2%	1	0.6		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3	1.8%	3	3	3.6%	3	-1.8	-6.2	2.7
Injury	1	0.6%	1						
Meniscus injury				1	1.2%	1			
Nerve injury				1	1.2%	1			
Post procedural haematoma	1	0.6%	1						
Tendon rupture	1	0.6%	1	1	1.2%	1	-0.6		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5	3.0%	5	3	3.6%	3	-0.6	-5.3	4.2
Arthralgia	1	0.6%	1	1	1.2%	1	-0.6		
Haemarthrosis	1	0.6%	1						
Intervertebral disc degeneration				1	1.2%	1			
Osteoarthritis	1	0.6%	1						
Osteochondrosis	1	0.6%	1						
Rotator cuff syndrome	1	0.6%	1						
Spinal synovial cyst				1	1.2%	1			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				1	1.2%	1			
Choroid neoplasm				1	1.2%	1			
NERVOUS SYSTEM DISORDERS	1	0.6%	1						
Sciatica	1	0.6%	1						
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	0.6%	1	1	1.2%	1	-		
Menometrorrhagia				1	1.2%	1			
Vaginal haemorrhage	1	0.6%	1						
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	1.2%	2						
Acute respiratory failure	1	0.6%	1						
Dyspnoea	1	0.6%	1						
SURGICAL AND MEDICAL PROCEDURES	1	0.6%	1	1	1.2%	1	-0.6		
Ligament operation	1	0.6%	1	1	1.2%	1	-0.6		

Notes:
‡95% confidence intervals are provided when at least 3 subjects in both groups experienced the event. 95% confidence intervals that include 0.0 indicate that the observed treatment difference is consistent with chance variation.
§AEs included with onset date on or before the Month 24 visit date (if missing, end-of-study date) or Day 730, whichever is later.

Table 16 presents the incidence rates and event counts of serious AEs. Group differences were negative (favoring Agili-C™) or similar between groups. The most common serious AEs in the Agili-C™ group were COVID-19 (n=4, 2.4%), contusion (n=3, 1.8%), "increased transient or chronic pain in the operated joint, compared to baseline" (n=2, 1.2%), and arthralgia (n=2, 1.2%). The rate of "increased transient or chronic pain in the operated joint, compared to baseline" was substantially lower in the Agili-C™ arm compared to the SSOC group (n=7, 8.3%).

There were no unanticipated serious adverse device effects (USADEs).

Table 11: Incidence Rates (%) and Event Counts of Serious AEs by System Organ Class and Pre-specified or Preferred Term (Safety Analysis Set)

Serious AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
PRE-SPECIFIED	4	2.4%	4	10	11.9%	10	-9.5	-16.8	-2.2
Decreased range of motion compared to baseline	1	0.6%	1						
Deep vein thrombosis (DVT) and related complications				1	1.2%	1			
Increased transient or chronic pain in the operated joint, compared to baseline	2	1.2%	2	7	8.3%	7	-7.1		
Infection (including septicemia or deep infections in the operated joint) and related symptoms, such as fever and/or pus	1	0.6%	1						
Progression of osteoarthritis (degeneration of surrounding bone and cartilage or delamination) compared to baseline				2	2.4%	2			
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	0.6%	1						
Foetal hypokinesia	1	0.6%	1						
CARDIAC DISORDERS				1	1.2%	1			
Coronary artery disease				1	1.2%	1			
EAR AND LABYRINTH DISORDER	1	0.6%	1						
Conductive deafness	1	0.6%	1						
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	0.6%	1						
Asthenia	1	0.6%	1						
IMMUNE SYSTEM DISORDERS	1	0.6%	1						
Allergy to metals	1	0.6%	1						
INFECTIONS AND INFESTATIONS	4	2.4%	4	1	1.2%	1	1.2		
Covid-19	4	2.4%	4	1	1.2%	1	1.2		

Serious AEs	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7	4.2%	7	4	4.8%	4	-0.6	-6.0	4.9
Cartilage Injury				1	1.2%	1			
Contusion	3	1.8%	3						
Injury	1	0.6%	1						
Meniscus Injury				1	1.2%	1			
Nerve Injury				1	1.2%	1			
Post Procedural Haematoma	1	0.6%	1						
Tendon Rupture	1	0.6%	1	1	1.2%	1	-0.6		
Traumatic Arthropathy	1	0.6%	1						
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5	3.0%	5	2	2.4%	2	0.6		
Arthralgia	2	1.2%	2						
Intervertebral Disc Degeneration				1	1.2%	1			
Osteoarthritis	1	0.6%	1						
Osteochondrosis	1	0.6%	1						
Rotator Cuff Syndrome	1	0.6%	1						
Spinal Synovial Cyst				1	1.2%	1			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				1	1.2%	1			
Choroid neoplasm				1	1.2%	1			
NERVOUS SYSTEM DISORDERS	1	0.6%	1						
Sciatica	1	0.6%	1						
PRODUCT ISSUES	1	0.6%	1						
Breast implant rupture	1	0.6%	1						
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	0.6%	1	1	1.2%	1	-0.6		
Menometrorrhagia				1	1.2%	1			
Vaginal haemorrhage	1	0.6%	1						
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0.6%	1						
Acute respiratory failure	1	0.6%	1						
SURGICAL AND MEDICAL PROCEDURES	1	0.6%	1	1	1.2%	1	-0.6		
Ligament operation	1	0.6%	1	1	1.2%	1	-0.6		
VASCULAR DISORDERS	1	0.6%	1						
Thrombophlebitis	1	0.6%	1						

Notes:
‡95% confidence intervals are provided when at least 3 subjects in both groups experienced the event. 95% confidence intervals that include 0.0 indicate that the observed treatment difference is consistent with chance variation.
§AEs included with onset date on or before the Month 24 visit date (if missing, end-of-study date) or Day 730, whichever is later.

Treatment Failures

Treatment failures, including relatedness to the device or procedure, are summarized below in Tables 17 and 18. In the safety analysis set, 12 of 167 (7.2%) Agili-C™ subjects and 18 of 84 (21.4%) SSOC subjects experienced a treatment failure based on the prespecified definition of treatment failure (for both treatment groups: any secondary invasive intervention in the treated joint, regardless if related or unrelated to the original treatment; for Agili-C™ group only: failure to implant the device, unless patient was contraindicated) in the study protocol. The treatment group difference was statistically significant according to an unadjusted chi-square test (p=0.002). 4of the treatment failures in the Agili-C™ group were due to knee trauma (zero in the SSOC group), while four of the treatment failures in the SSOC group were due to knee replacements and osteotomies (zero in the Agili-C™ group).

Among subjects with mild to moderate osteoarthritis (OA), 27.8% of the subjects in the SSOC group were treatment failures compared to 5.3% in the Agili-C™ group. A similarly high failure rate was noted in SSOC subjects with large lesions (22.0% of the subjects), compared to 5.1% in the Agili-C™ group.

Table 12: Main AE Term: Summary of Treatment Failures by Treatment Group (Safety Analysis Set)

	All N= 251		Agili-C™ N= 167		SSOC N= 84		p-values‡
	N	%	N	%	N	%	
Treatment Failures	30	12.0%	12	7.2%	18	21.4%	0.002
Main AE term:							
- Increased transient or chronic pain (pre-specified)	19	7.6%	4	2.4%	15	17.9%	<0.001
- Progression of osteoarthritis (pre-specified)	2	0.8%	0	0.0%	2	2.4%	0.111
- Activity related knee pain (Other)	1	0.4%	0	0.0%	1	1.2%	0.335
- Knee trauma (Other)	4	1.6%	4	2.4%	0	0.0%	0.304
- ACL graft complications (Other)	2	0.8%	2	1.2%	0	0.0%	0.553
- New osteochondral lesion (Other)	1	0.4%	1	0.6%	0	0.0%	1.000
- Infection (pre-specified)	1	0.4%	1	0.6%	0	0.0%	1.000

Notes:
‡ Fisher's Exact tests

Table 13: AE Relatedness: Summary of Treatment Failures by Treatment Group (Safety Analysis Set)

	All N= 251		Agili-C™ N= 167		SSOC N= 84		p-values‡
	N	%	N	%	N	%	
Treatment Failures	30	12.0%	12	7.2%	18	21.4%	0.002
AE Relatedness:							
- Related	6	2.4%	1	0.6%	5	6.0%	0.017
- Related to device and/or toolset	1	0.4%	1	0.6%	--	--	--
- Related to procedure	5	2.0%	0	0.0%	5	6.0%	0.004
- Probably related	8	3.2%	5	3.0%	3	3.6%	1.000
- Probably related to device and/or toolset	2	0.8%	2	1.2%	--	--	--
- Probably related to procedure	6	2.4%	3	1.8%	3	3.6%	0.405
- Possibly related	14	5.6%	4	2.4%	10	11.9%	0.006
- Possibly related to device and/or toolset	2	0.8%	2	1.2%	--	--	--
- Possibly related to procedure	12	4.8%	2	1.2%	10	11.9%	<0.001
- Unrelated	2	0.8%	2	1.2%	0	0.0%	0.553

Notes:
‡ Fisher's Exact tests

Device Removals

The rate of treatment failures was 21.4% (n=18) in the SSOC arm and 7.2% (n=12) in the Agili-C™ arm. Among the 12 treatment failures in the Agili-C™ arm, 8cases included a device removal (4.8%, 8/167). Of the 8 implant removal cases, five removals (representing 3% of the subjects in the study group) occurred due to knee trauma or subjects overdoing exercise early in the post-implantation period.

2. Effectiveness Results

The analysis of effectiveness was based on the 237 evaluable patients at the 24-month time point. Key effectiveness outcomes are presented in Tables 19 to 28.

The Bayesian analysis results for KOOS Overall (primary endpoint) and the KOOS subscales (confirmatory secondary endpoints and secondary endpoints) at 24 Months are summarized below in Table 19. Agili-C™'s performance was both statistically significant and clinically meaningful across all KOOS endpoints. As discussed in more detail below, results across the other secondary analyses, as well as sensitivity and covariate analyses, were similarly favorable. Thus, study success was established by meeting the primary endpoint and all secondary confirmatory endpoints, and was confirmed to be robust across several secondary analyses.

Primary Endpoint Results

The primary endpoint was assessed as the change from baseline to 24 months in the average KOOS Overall Score in the Full Analysis Set (FAS) to evaluate the superiority of the Agili-C™ compared to the SSOC. The mean of the posterior distribution for changes from baseline to Month 24 in the KOOS Overall Score for subjects randomized to Agili-C™ was 42.65 (39.55, 45.54). For subjects randomized to SSOC, the mean of the posterior distribution was 21.39 (17.35, 25.71). The mean (95% credible interval) of the posterior distribution for the group difference (Agili-C™ minus SSOC) in change from baseline to Month 24 in the KOOS Overall Score was 21.27 (16.17, 26.60) (Table 19).

Based on these results, the posterior probability of superiority was determined to be 1.000. Since 1.000 > 0.98, the null hypothesis is rejected, and these results demonstrate that the Agili-C™ is superior to SSOC in terms of improvements from baseline to Month 24 in KOOS Overall Score.

Table 14: Bayesian Posterior Probability of Month 24 Superior of Agili-C™ Relative to SSOC (FAS)

Parameter	Mean of Posterior Distribution	SD of Posterior Distribution	LB of 95% HPD Interval	UB of 95% HPD Interval	Posterior Probability of Superiority[2]
Agili-C™	42.65	1.54	39.55	45.54	.
SSOC	21.39	2.14	17.35	25.71	.
Agili-C™ - SSOC	21.27	2.67	16.17	26.60	**1.000**

Notes:
[1]Baseline observation carried forward after treatment failure for 11 Agili-C™ and 18 SSOCs.
[2]Posterior probability that the mean improvement is larger for Agili-C™ compared to SSOC.
Setting for the Markov chain Monte Carlo simulations: N=5000

A Mixed Model for Repeated Measures (MMRM) was applied to changes in KOOS Overall Score over time for both the Agili-C™ and SSOC groups. The mean changes for each group and the group difference in mean changes (Agili-C™ minus SSOC) separately at every follow-up time period are provided in Table 20. The estimated group difference (95% CI) in mean changes from baseline to Month 24 is 21.35 (16.24, 26.47) and the treatment-by-visit interaction was statistically significant (p<0.0001), demonstrating the increasingly larger group differences in mean improvements over time.

Table 15: Mixed Model for Repeated Measures (MMRM) for Changes in KOOS Overall Score (FAS)

Agili-C™				
Visit	**LS Mean Change**	**LB of 2-sided 95% CI**	**UB of 2-sided 95% CI**	**p-value[2]**
Month 6	27.46	24.85	30.07	<.0001

Month 12	33.93	31.07	36.78	<.0001
Month 18	39.20	36.34	42.07	<.0001
Month 24	42.67	39.71	45.63	<.0001
Test for Trend[3]				<.0001
Surgical Standard of Care (SSOC)				
Visit	**LS Mean Change**	**LB of 2-sided 95% CI**	**UB of 2-sided 95% CI**	**p-value[2]**
Month 6	19.93	16.23	23.62	<.0001
Month 12	21.75	17.73	25.77	<.0001
Month 18	21.49	17.46	25.52	<.0001
Month 24	21.32	17.15	25.49	<.0001
Test for Trend[3]				0.568
Agili-C™ minus SSOC				
Visit	**LS Group Difference in Mean Change**	**LB of 2-sided 95% CI**	**UB of 2-sided 95% CI**	**p-value[2]**
Month 6	7.54	3.01	12.06	0.0012
Month 12	12.18	7.24	17.11	<.0001
Month 18	17.71	12.76	22.65	<.0001
Month 24	21.35	16.24	26.47	<.0001
Visit by Group Interaction[4]				<.0001

Notes:
[1] Baseline observation carried forward after treatment failure for 11 Agili-C™ and 18 SSOC.
[2] p-value for within treatment group mean changes.
[3] F-test for linear trend. The null hypothesis is that mean changes are constant over time.
[4] The visit by group interaction tests whether the group difference in mean changes varies over time.

Confirmatory Secondary Endpoint Results

The 4 pre-specified confirmatory secondary endpoints were:

- Change in KOOS Pain score from baseline to Month 24.
- Change in KOOS Quality of Life score from baseline to Month 24.
- Change in KOOS ADL score from baseline to Month 24.
- Response rate at Month 24 defined as an improvement in KOOS Overall Score ≥ 30.

The 4 pre-specified confirmatory secondary endpoints (Table 21) were to be tested in a hierarchical manner in order to control the type 1 error rate. Each of these secondary endpoints required a Bayesian posterior probability greater than 0.975 for declaring superiority. As shown in the summary table below, Agili-C™ demonstrated superiority on each of the confirmatory secondary endpoints.

The KOOS Overall responder rate, percentage of patients who had at least a 30 point gain at 24 months, showed the mean posterior distribution (95% credible interval) for the group difference was 0.443 (0.320, 0.557), corresponding to a 77.8% response rate for Agili-C™ compared to 33.6% for SSOC.

Table 16: Summary of Confirmatory Secondary Endpoint Results at Month 24

Parameter	Mean of Difference in Posterior Distribution	SD of Difference in Posterior Distribution	LB of 95% HPD Interval	UB of 95% HPD Interval	Posterior Probability of Superiority
KOOS Pain:					
Agili-C™	41.52	1.43	38.51	44.09	
SSOC	21.20	2.00	17.26	25.11	
Difference	20.33	2.50	15.37	25.05	**1.000**
KOOS QoL:					
Agili-C™	47.29	1.98	43.50	51.24	
SSOC	23.49	2.76	18.05	28.80	
Difference	23.79	3.44	17.01	30.44	**1.000**
KOOS ADL:					
Agili-C™	37.59	1.37	34.94	40.29	
SSOC	18.35	1.92	14.62	22.12	
Difference	19.25	2.39	14.60	23.84	**1.000**
KOOS Overall ≥ 30:					
Agili-C™	0.778	0.032	0.712	0.838	
SSOC	0.336	0.051	0.240	0.440	
Difference	0.443	0.061	0.320	0.557	**1.000**

The results of the first confirmatory secondary endpoint, change in KOOS Pain score, from baseline to Month 24, are shown in Table 21. The mean posterior distribution (95% credible interval) for the group difference in KOOS Pain score change was 20.33 (15.37, 25.05). The posterior probability of superiority was 1.000, which is larger than the pre-specified 0.975. Therefore, the Agili-C™ is superior to SSOC from baseline to Month 24 in KOOS Pain score.

Additional Secondary Endpoint Results

Table 22 summarizes the percentages of defect fill, with MRI analyses performed at Month 12 and at Month 24. In order to preserve the ordinal nature of the categories, group comparisons were performed using a Wilcoxon rank sum test at each time point.

Table 22: Summary of MR Defect Fill at 12 and 24 Months (FAS)

	Agili-C™		SSOC		
Month 12 MRI Defect Fill (%)	**n**	**%**	**n**	**%**	**p-value[1]**
0-24	2	1.3	24	31.2	<0.0001
25-49	2	1.3	13	16.9	
50-74	16	10.1	14	18.2	
75-99	107	67.7	17	22.1	

100	31	19.6	9	11.7	
Month 24 MRI Defect Fill (%)					
0-24	0	0.0	22	32.4	<0.0001
25-49	2	1.3	12	17.6	
50-74	16	10.3	13	19.1	
75-99	95	60.9	14	20.6	
100	43	27.6	7	10.3	
Notes: [1] P-value for Wilcoxon rank sum test					

The results of the MRI defect fill demonstrated statistically significant (<0.0001) differences between treatment groups. At 24 months, 88.5% of subjects treated with Agili-C™ had at least 75% defect fill compared to 30.9% among subjects treated with SSOC. Moreover, only 1.3% of the Agili-C™ subjects had less than 50% defect fill at 24 Months, compared to 50% in the SSOC group.

The change from baseline in the International Knee Documentation Committee ("IKDC") score was evaluated at 12, 18, and 24 months, as shown in Table 23. The group differences (95% CI) in mean change values increased from 12.0 (6.5, 17.5) at Month 12, to 16.3 (10.7, 21.9) at Month 18, and to 22.7 (16.8, 28.6) at Month 24.

Table 23: IKDC Knee Examination Change from Baseline (FAS)

	Agili-C™					SSOC					Agili-C™ - SSOC[1]		
Month	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**Diff**	**LB**	**UB**
6	164	24.0	18.8	-25.3	67.8	81	17.6	18.6	-29.9	60.9	6.4	1.4	11.4
12	163	32.5	20.6	-17.2	80.5	80	20.5	20.3	-23.0	80.5	12.0	6.5	17.5
18	162	38.1	20.8	-18.4	82.8	81	21.8	21.4	-20.7	86.2	16.3	10.7	21.9
24	160	43.0	21.2	-13.8	82.8	79	20.3	23.0	-17.2	86.2	22.7	16.8	28.6
Notes: [1] Device group differences and 95% confidence intervals (CI) for group differences.													

As shown in the table above, the IKDC change from baseline in the Agili-C™ group was 24.0±18.8 at 6 months, 32.5±20.6 at 12 months, 38.1±20.8 at 18 months, and 43.0±21.2 at 24 months. These results show that the IKDC scores are substantially higher than a mimimal clinically important difference (MCID) of 16.7 at each timepoint, demonstrating that these patients reported clinically significant improvements in symptoms and function in daily living activities. These results are consistent with the improvement in KOOS assessed as the primary endpoint.

The change from baseline in the Tegner Score was evaluated at 12, 18, and 24 months, as shown in Table 24. The Tegner Score is a patient reported outcome that provides a standardized method for determining the patient's level of activity before and after a knee injury. The group differences (95% CI) in mean change values

increased from 0.6 (0.1, 1.0) at Month 12, to 0.8 (0.4, 1.3) at Month 18, and to 1.5 (1.0, 1.9) at Month 24.

Table 17: Tegner Score Change from Baseline (FAS)

	Agili-C™					SSOC					Agili-C™ - SSOC[1]		
Month	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**Diff**	**LB**	**UB**
6	164	1.0	1.5	-3.0	5.0	81	0.8	1.5	-2.0	4.0	0.3	-0.1	0.7
12	163	1.7	1.6	-2.0	8.0	81	1.1	1.7	-3.0	8.0	0.6	0.1	1.0
18	161	2.0	1.8	-1.0	8.0	81	1.2	1.8	-3.0	8.0	0.8	0.4	1.3
24	160	2.5	1.7	0.0	8.0	79	1.0	1.6	-2.0	8.0	1.5	1.0	1.9

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.

The change from baseline to Month 24 in KOOS Sports score was evaluated as shown in Table 25. The mean posterior distribution for the group difference in KOOS Sports score was 27.84 (20.69, 34.89). The posterior probability of superiority was 1.000, which is larger than the pre-specified 0.975. Therefore, the Agili-C™ is superior to SSOC from baseline to Month 24 in KOOS Sports score.

Table 18: Bayesian Posterior Probability of Month 24 Superiority Agili-C™ Relative to SSOC for Change from Baseline to Month 24 in KOOS Sports Score (FAS)

Parameter	Mean of Posterior Distribution	SD of Posterior Distribution	LB of 95% HPD Interval	UB of 95% HPD Interval	Posterior Probability of Superiority[2]
Agili-C™	53.65	2.09	49.51	57.64	.
SSOC	25.81	2.93	20.16	31.60	.
Agili-C™ - SSOC	27.84	3.64	20.69	34.89	**1.000**

Notes:
[1]Baseline observation carried forward after treatment failure for 11 Agili-C™ and 18 SSOCs.
[2]Posterior probability that the mean improvement is larger for Agili-C™ compared to SSOC.
Setting for the Markov chain Monte Carlo simulations: N=5000

The change from baseline to Month 24 in KOOS Symptoms score was evaluated as shown in Table 26. The mean posterior distribution for the group difference in KOOS Symptoms score was 15.15 (10.23, 19.87). The posterior probability of superiority was 1.000, which is larger than the pre-specified 0.975. Therefore, the Agili-C™ is superior to SSOC from baseline to Month 24 in KOOS Symptoms score.

Table 26: Bayesian Posterior Probability of Month 24 Superiority Agili-C™ Relative to SSOC for Change from Baseline to Month 24 in KOOS Other Symptoms Score (FAS)

Parameter	Mean of Posterior Distribution	SD of Posterior Distribution	LB of 95% HPD Interval	UB of 95% HPD Interval	Posterior Probability of Superiority[2]
Agili-C™	33.30	1.43	30.59	36.15	.
SSOC	18.15	2.00	14.21	22.06	.
Agili-C™ - SSOC	15.15	2.49	10.23	19.87	**1.000**

Notes:
[1]Baseline observation carried forward after treatment failure for 11 Agili-C™ and 18 SSOCs.
[2]Posterior probability that the mean improvement is larger for Agili-C™ compared to SSOC.
Setting for the Markov chain Monte Carlo simulations: N=5000

The change from baseline in the SF-12 Physical Health Component was evaluated at 6, 12, 18, and 24 months, as shown in Table 27. The group differences (95% CI) in mean change values of SF-12 Physical component were 2.8 (0.0, 5.6) at Month 6, 4.6 (1.8, 7.5) at Month 12, 6.9 (3.9, 9.8) at Month 18, and 7.8 (4.8, 10.8) at Month 24. These results demonstrate that the Agili-C™ patients reported clinically significant greater improvements, compared to the control patients, in physical quality of life measurements, including general health, bodily pain, usual physical role activities, and physical functioning.

Table 19: Change from Baseline for the 12-item Short Form Survey (SF-12) Physical Health Component Score (FAS)

	Agili-C™					SSOC					Agili-C™ - SSOC[1]		
Month	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	Diff	LB	UB
6	164	10.2	10.3	-19.4	37.9	81	7.4	10.8	-13.0	33.5	2.8	0.0	5.6
12	163	12.8	10.1	-10.2	39.1	81	8.2	11.7	-14.0	40.8	4.6	1.8	7.5
18	162	14.9	10.5	-14.2	40.9	80	8.0	11.5	-20.6	40.8	6.9	3.9	9.8
24	160	16.0	10.5	-14.3	37.3	79	8.2	12.0	-28.8	45.1	7.8	4.8	10.8

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.

The change from baseline in the SF-12 Mental Health Component was evaluated at 6, 12, 18, and 24 months, as shown in Table 28. The group differences (95% CI) in mean change values were 2.8 (-0.3, 6.0) at Month 12, 2.7 (-0.7, 6.1) at Month 18, and 5.1 (1.8, 8.4) at Month 24 for the Mental Health Component score. There were no significant differences in the Mental Health Component score between the Agili-C™ and SSOC treatment groups.

Table 28: Change from Baseline for the 12-item Short Form Survey (SF-12) Mental Health Component Score (FAS)

	Agili-C™					SSOC					Agili-C™ - SSOC[1]		
Month	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**Diff**	**LB**	**UB**
6	164	3.0	12.1	-34.9	37.1	81	1.0	12.9	-30.7	39.8	2.0	-1.3	5.3
12	163	4.3	11.9	-30.5	41.5	81	1.5	11.6	-20.0	40.3	2.8	-0.3	6.0
18	162	4.3	13.1	-41.7	36.2	80	1.6	11.9	-20.3	40.3	2.7	-0.7	6.1
24	160	5.5	12.5	-30.1	36.9	79	0.5	11.1	-26.8	37.3	5.1	1.8	8.4

Notes:
[1] Device group differences and 95% confidence intervals (CI) for group differences.

3. Subgroup Analyses

   Preoperative demographic and clinical characteristics that could impact outcomes were evaluated using both subgroup analysis and covariate analysis. Subgroup analyses included variables such as lesion type, number of lesions, level of osteoarthritis, lesion location, lesion size, previous ligament reconstruction, meniscus status, activity status, and US vs. OUS (outside US). Agili-C™'s superiority in effectiveness relative to standard of care was confirmed across all subgroups. Factors such as subjects' activity level, status of anterior cruciate ligament (ACL) and meniscus, type of lesion, size of lesion, or number of lesions, which may be expected to negatively impact treatment outcomes due to challenging conditions, did not negatively impact the Agili-C™ superiority over the current SSOC.

   In addition, covariate analysis was performed using covariates of age, sex, BMI, lesion type, number of lesions, level of OA, lesion size, ACL status, meniscus status, pre-injury activity status, smoking history, and lesion location. Consistent with the subgroup analysis, the covariate analysis demonstrated that factors that could be expected to negatively impact treatment outcomes due to more challenging conditions, such as a subject's activity level, BMI, status of ACL and meniscus, age, smoking history, and type, size, number, or location of lesions, did not negatively impact the Agili-C™ performance. The robustness of the data across many difficult-to-treat subgroups with consistent advantage for Agili-C™ over SSOC provides additional evidence of benefit and of the ability to use the device in a wide range of patients.

4. Pediatric Extrapolation

   In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any

clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 30 principal investigators and 79 sub-investigators of which none were full-time or part-time employees of the sponsor and two (2) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The Agili-C™ demonstrated superiority in the Primary Endpoint KOOS Overall Score at 24 months relative to SSOC: the Posterior Probability of Superiority = 1.000, which is greater than the criterion > 0.98 that was predetermined in the Statistical Analysis Plan. Thus, the clinical study met the primary effectiveness endpoint.

The Agili-C™ demonstrated superiority over the SSOC control on all secondary confirmatory endpoints:

- Change in KOOS Pain score from baseline to Month 24 (difference of 20.41 points favoring the Agili-C™ group, $p<0.0001$)
- Change in KOOS Quality of Life score from baseline to Month 24 (difference of 23.90 points favoring the Agili-C™ group, $p<0.0001$)
- Change in KOOS ADL score from baseline to Month 24 (difference of 19.32 points favoring the Agili-C™ group, $p<0.0001$)
- Response rate at Month 24 defined as an improvement in KOOS Overall Score ≥30 was 77.8% in the Agili-C™ arm compared to 33.6% in the SSOC.

Defect fill at 24 months favored the Agili-C™ group with 88.5% of subjects reporting 75-100% defect fill as compared to 30.9% of SSOC subjects. The IKDC score change from baseline to Month 24 in the Agili-C™ group was 43.0±21.2 as compared to 20.3±23.0 in the SSOC control. The Tegner score change from baseline to Month 24 in the Agili-C™ group was 2.5±1.7 points as compared to 1.0±1.6 points in the SSOC control group. The effectiveness results were demonstrated to be robust across subgroup and covariate analyses.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

The overall adverse event ("AE") rate was lower for the Agili-C™ group (58.7%) compared to the SSOC group (77.4%). At least 1 Severe AE was present in 9.6% of the Agili-C™ subjects compared to 20.2% in SSOC subjects, and at least 1 Serious AE was present in 15.6% of the Agili-C™ subjects compared to 20.2% of SSOC subjects.

Implantation of the Agili-C™ implant is performed in an arthrotomy procedure which involve knee opening, osteochondral drilling to create a designated implantation site and implants placement. In contrast SSOC procedures are conducted through mini-invasive arthroscopy procedures. Nevertheless, there is no evidence of any increase in adverse events, serious adverse events, or device-related/procedure-related events for Agili-C™ compared to the SSOC control. The only adverse events that occurred in more than 5% of Agili-C™ patients were increased transient or chronic pain in the operated joint, compared to baseline (15.0% Agili-C™ vs. 39.3% SSOC), arthralgia (9.0% Agili-C™ vs. 11.9% SSOC), sciatica (6.6% Agili-C™ vs. 3.6% SSOC), and increased swelling (or effusion) in the operated joint, compared to baseline (5.4% Agili-C™ vs. 4.8% SSOC). The only serious adverse event that occurred in more than 2% of Agili-C™ patients was COVID-19 (2.4%). No severe adverse events occurred in more than 2% of Agili-C™ patients.

The data supports the safety of the Agili-C™ for the proposed indications.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits include significant improvements in pain and function as measured by KOOS Overall score and KOOS subscores, as well as defect fill with 88.5% of Agili-C™ subjects having at least 75% defect fill at 24 months compared to 30.9% of SSOC subjects showing the same level of defect fill ($p<0.0001$).

Agili-C™'s superiority in effectiveness relative to standard of care was confirmed across all subgroups defined by pre-specified covariates. Factors such as subjects' activity level, BMI, status of ACL and meniscus, age, type of lesion, size of lesion or number of lesions – which could be expected to negatively impact treatment outcomes due to challenging conditions – did not negatively impact the Agili-C™ superiority over the surgical standard of care, microfracture and debridement. Additionally, subgroup analysis confirmed the poolability of the data across sites, geographic regions (US versus OUS), race (within the US only), and several other subgroups including Agili-C™ with HA vs Agili-C™ alone, unilateral vs bilateral symptomatic knees, site visit window (within original window vs within extended COVID window), and onsite vs offsite evaluations.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Pre-specified adverse events were determined given their potential relatedness to Agili-C™ or the Agili-C™ implantation procedure. Pre-specified adverse events occurred in 23.4% of Agili-C™ patients in the pivotal study, compared to 50.0% of SSOC patients. The most common pre-specified adverse event was increased transient or chronic pain in the operated joint (compared to baseline), which occurred in 15% of Agili-C™ subjects and 39.3% of SSOC subjects. This was followed by increased swelling/effusion in the operated joint, which occurred in 5.4% of Agili-C™ subjects and 4.8% of SSOC subjects. The remaining pre-specified adverse events occurred in the Agili-C™ group in only 1.2% of subjects or less. Only 2.4% of Agili-C™ patients experienced a serious pre-specified adverse event, compared to 11.9% of SSOC patients.

Additional factors considered in determining probable risks and benefits for the Agili-C™ device included uncertainties related to the heterogeneity of subgroups, unbalanced arms (Agili-C™ vs. SSOC), and study site poolability, including geographic poolability.

1. Patient Perspective
   Patient perspectives considered during the review included patient-reported outcomes as measured by the ICRS Cartilage Injury Standard Evaluation Form 2000 at baseline, plus the following questionnaires at 6, 12, 18, and 24 months:
   - KOOS subscales Questionnaire (KOOS Pain, KOOS ADL, KOOS QOL, KOOS Symptoms and KOOS Sports)
   - Tegner activity score form
   - SF-12 Health Survey (v2)
   - 2000 IKDC Subjective Knee Evaluation Form

   The pivotal study primary endpoint was a patient-perspective metric, the change from baseline to 24 months in the average KOOS Overall Score, which was defined as the average over the KOOS subscales, if not more than 2 subscales were missing (Pain, ADL, QOL, Other Symptoms, and Sports). The confirmatory secondary endpoints were also patient-perspective metrics, consisting of the KOOS Pain, QoL, and ADL scores, as well as response rate $\geq$ 30% in overall

KOOS score. Additional secondary endpoints that were patient-perspective metrics included:

- Change from baseline in overall KOOS score at 6, 12, and 18 months
- Change from baseline in Tegner activity 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 in various subgroups

In conclusion, given the available information above, the data support that for the treatment of an ICRS grade III or above knee-joint surface lesion(s), with a total treatable area of 1-7cm^2, without severe osteoarthritis (Kellgren-Lawrence grade 0-3), the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Given the available information summarized above, the data support that for the Agili-C™, which is intended for use in the treatment of ICRS grade III or above knee-joint surface lesion(s) with a total treatable area of 1-7cm^2, without severe osteoarthritis (Kellgren-Lawrence grade 0-3), the probable benefits outweigh the probable risks.

XIII. CDRH DECISION

CDRH issued an approval order on March 29, 2022. The final clinical conditions of approval cited in the approval order are described below.

As a condition of approval, the applicant agreed to conduct the Post-Approval Study (PAS) as described below:

"A Post Approval 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" will be conducted in accordance with protocol CLN0021-US Rev 8 dated Jan 25, 2022. The study will consist of all living subjects who were enrolled in the IDE study, "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". Subject follow-up will continue for all cohorts based on the timelines and assessments stipulated in the IDE protocol. The objective of this PAS is to characterize the clinical outcomes annually through 5 years post-procedure. Data will be collected per the study protocol, including, but not limited to, the following key safety and effectiveness endpoints: Adverse events, including serious adverse events, reoperations and revisions, up to 60 months – safety endpoints; Change from baseline to 60 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) – primary endpoint; Change from baseline to 60 months in KOOS Pain subscore, KOOS QOL subscore, KOOS ADL subscore, KOOS Symptoms

subscore, KOOS Sports subscore, and Overall KOOS responder rate (defined as an increase from baseline to 60 months of ≥ 30 points on overall KOOS) – confirmatory secondary endpoints; Change from baseline at 36, 48 and 60 Months in IKDC Subjective Knee Evaluation, Tegner score, SF-12 v2 Physical Component Summary (PCS) score and Mental Health Component Summary (MCS), and analyses of various subgroups – additional secondary endpoints. The statistical analyses will be conducted using the same statistical models that were used in the analyses in the pivotal trial. Interim analyses will be submitted in interim reports in October 2022 and annually thereafter until study completion, with a final report in Quarter 2, 2025.

The applicant's manufacturing facilities have been determined, through prior on-site inspection and (due to constraints posed by the COVID-19 pandemic) by a review of relevant manufacturing site documentation and compliance history, to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

None