CartiHeal

Agili-C

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STERILE	R

CAUTION

Federal (United States) law restricts this device to sale by or on the order of a physician.

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 using the Mini Disposable Toolset which is supplied sterile, for single use, and the Reusable Toolset.

Figure 1. Agili-C™ Implant

DEVICE SIZES

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

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).

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

⚠ WARNINGS

The safety and effectiveness of the Agili-C™ has not been established in patients with the following conditions:

- Morbid obesity (BMI >35)
- Known insulin dependent diabetes mellitus
- Immunocompromised patients, including patients receiving a previous intra-articular steroid injection within the last 1 month
- Systemic conditions affecting wound healing
- Systemic bone disorder, such as but not limited to, osteoporosis and osteogenesis imperfecta
    - The implant has not been tested in patients with osteoporosis.
    - Osteoporosis may impact a patient's ability to integrate the implant and to biodegrade it while forming a new bone.
    - Exercise caution in use in patients with osteoporosis.
- Chemotherapy during the past 12 months
- Ligamentous instability
- Significant malalignment
- Total or subtotal meniscectomy or lack of functional meniscus
- The implant is not indicated for treatment in patients with inflammatory arthropathy or crystal-deposition arthropathy

- Skeletally immature – do not implant the device through the epiphyseal plate (growth-plate)
- Inability to refrain from contact sports or other high-impact activities for the recommended recovery period
- Noncompliance due to major psychiatric disorder, alcohol or drug abuse
- Skin conditions within the field of surgery, such as psoriasis

ADDITIONAL WARNINGS

- The implant should not be implanted through arthroscopic approach. The Agili-C™ should be implanted through arthrotomy or mini-arthrotomy approach.
- The implant is not indicated for treatment in Patellar cartilage and osteochondral defects or for use in other joints.
- Use the device according to the provided instructions.
- The contents of this package are for single use only.
- Do not re-sterilize.
- Do not use the device after the expiration date.
- Do not use if package is damaged.
- Open the package carefully to prevent implant damage.
- Inspect the implant prior to use and not to use the implant if broken.
- This device can only be used by a qualified orthopedic surgeon. It is the surgeon's responsibility to be familiar with the appropriate surgical technique prior to using this device.
- Agili-C™ should be exclusively implanted using its designated surgical tool set. Using any other implantation system may lead to improper device positioning and may cause implant breakage and/or malfunction.
- 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.
- The surgeon must take into consideration the joint geometry especially close to the condyle notch, lateral lesions, 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 implant must be inserted into the defect in a press fit manner. Non-press fit positioning may lead to failure due to lack of implant integration.
- In case of multiple implants, do not place the devices in an overlapping manner; it is important to keep a bone bridge of at least 5 mm between any two proximal implants to ensure the entire circumference of each implant is in direct contact with the bone, and that the implants are not impinging on each other.
- It is not advisable to apply the device by means of mosaicplasty technique (i.e., kissing implants)
- The implant should be positioned 2mm recessed relative to the articular surface; Protruding implants may lead to procedure failure.
- 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 of the implant above the articular surface, may lead to implant breakage and/or injury of nearby tissue. It is required that all implant sharp edges be removed.
- Implant fragments or particulate debris may cause an inflammatory response.
- In case of a need of intra-operative revision, remove an implant, and use a new implant of the same size or larger. Do not re-implant the removed implant.
- Avoid entrapment of soft tissue between the implant and the bone which may lead to penetration of synovial fluid, formation of cyst around the implant and lack of integration.
- In case of implant breakage or cracks, remove the implant and use a new one. Do not leave a cracked, fragmented or broken implant in the joint.
- In case of implant removal, carefully remove all remnants and wash the joint intensively. Implant particles, if left in the joint, can cause synovitis and may lead to damage.
- The device is composed of a porous brittle material, applying excess mechanical pressure during insertion may lead to implant breakage and particles generation.
- Do not use excess force during implant insertion; Do not use hammer or any other mechanical instruments for implant insertion, besides the designed Tamper provided in the surgical toolset.

PRECAUTIONS

- The Agili-C™ implant is a biphasic scaffold. The implant surface with the drilled channels is the implant top and faces the articular surface. The tapered side, without the drilled channels, is the implant bottom and faces the bone. Before implanting the device, pay attention to the side to be placed in contact with the bone. Incorrect orientation of implant positioning may lead to improper healing.
- Incorrect use of the surgical toolset can lead to bone breakage, damage to neurovascular structures, bone cyst formation, implant breakage or improper implantation site creation.
- 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.
- High impact or extreme shear forces on the implantation site during recuperation period, as results of trauma or sports activities, can lead to implant breakage and revision.
- Post-surgical ambulation should follow the physician recommended rehabilitation regime in order to avoid extreme forces during the recuperation period.

ADVERSE REACTIONS

Possible adverse reactions during the post-operative phase include, but are not limited to:

- 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 (AEs) that occurred in the clinical study of the Agili-C™ device, see the Safety Results in the CLINICAL STUDIES section below.

CLINICAL STUDIES

CartiHeal conducted a prospective, multicenter, open-label, randomized, controlled pivotal study. Subjects were randomized in a 2:1 ratio to Agili-C™ or the control treatment, surgical standard of care (SSOC), with twice as many subjects allocated to the investigational device.

The objective of the study was to evaluate the superiority of the Agili-C™ device versus the current most common SSOC, which consisted of either debridement (for older patients with lager lesions and with OA) or microfracture (for younger patient with smaller lesions and without OA). The primary endpoint for this study was the change from baseline to 24 months in the average Knee Injury and Osteoarthritis Outcome Score ("KOOS") (Pain, Symptoms, Quality of Life ("QOL"), Activities of Daily Living ("ADL"), & Sports).

Subjects were enrolled according to the inclusion/exclusion criteria outlined below. Subjects were required to meet all of the inclusion and none of the exclusion criteria.

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

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 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 microfracture, 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 two 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 2 mm 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

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, 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, 24, 36, 48- and 60-months post procedure. MRI was performed at 12 and 24 months. All complications and adverse events, device-related or not, were evaluated over the course of the study.

Table 1: 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 (± 16 weeks)	24 Months Post-Procedure Visit (± 16 weeks)	Annual Post-24 Months Visit Until 60 Months (± 16 weeks)	Unscheduled 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	Screening 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 Months Post-Procedure Visit (± 16 weeks)	Annual Post-24 Months Visit Until 60 Months (± 16 weeks)	Unscheduled 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	
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

CLINICAL ENDPOINTS

Primary Endpoint

The primary endpoint for this study was the change from baseline to 24 months in the average KOOS Overall Score (Pain, Other Symptoms, QOL, ADL and Sports).

Safety Endpoint

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

Confirmatory Secondary Endpoints

The study had four confirmatory secondary endpoints for labeling purposes:

- 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

Secondary Endpoint

Additional secondary endpoints included:

- 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[1] at 12, 18, and 24 Months
- Change from baseline QOL as measured by SF-12 v2[2] 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:
    - patients with chondral lesions
    - patients with osteochondral lesions
    - patients with single lesion
    - patients with multiple lesions
    - patients without osteoarthritis (K/L 0-1)
    - patients with osteoarthritis (K/L 2-3)
    - patients with total lesion(s) size ≤3cm²
    - patients with total lesion(s) size >3cm²
    - patients without previous ligament reconstruction
    - patients with intact meniscus
    - patients with previous partial meniscectomy

[1] Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;198:43–9.

[2] Ware J.E., Kosinski M., & Keller S.D., SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. 3rd ed. QualityMetric, Lincoln, RI 1998.

- patients with concomitant partial meniscectomy
- active patients
- non-active patients

ACCOUNTABILITY OF PMA COHORT

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

Full Analysis Set (FAS) – 247 subjects: The FAS included 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 one 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 2. 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-op	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%

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

Table 3. Subject Accountability

	Pre-Op		Month 6		Month 12		Month 18		Month 24	
	Agili-C™	SSOC	Agili-C™	SSOC	Agili-C™	SSOC	Agili-C™	SSOC	Agili-C™	SSOC
(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

	Pre-Op		Month 6		Month 12		Month 18		Month 24	
	Agili-C™	SSOC	Agili-C™	SSOC	Agili-C™	SSOC	Agili-C™	SSOC	Agili-C™	SSOC
(5) Expected Due [(5)=(1)-(2)-(4)]			164	83	164	83	164	81	164	83
Within Window Accounting (Actual[A])										
(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[B])										
(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:
& 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.).

STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

Table 4 to **Table 8** summarize the two treatment groups at baseline in the Safety Analysis Set. Specifically, these tables summarize the following information:

- Baseline and Demographic Continuous Variables (**Table 4**)
- Baseline and Demographic Categorical Variables (**Table 5**)
- Categorical Lesion Characteristics (**Table 6**)
- Continuous Lesion Variables (**Table 7**)
- History of and Concomitant Treatments (**Table 8**)

Table 4. Baseline and Demographic Continuous Variables – Safety Analysis Set

	Agili-C™						SSOC						Agili-C™ - SSOC[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age	167	42.0	11.2	42.9	21.2	71.8	84	46.2	11.2	46.1	22.7	70.2	-4.21	-7.15	-1.27
Height (cm)	167	174.9	9.0	175.2	155.0	198.0	84	173.9	10.5	175.0	143.0	193.0	0.95	-1.55	3.45
Weight (kg)	167	81.1	16.1	80.0	52.0	123.0	84	84.6	15.0	86.1	55.0	116.0	-3.51	-7.66	0.64
BMI (k/m2)	167	26.4	4.2	26.0	18.0	34.9	84	27.9	3.8	27.6	20.1	34.8	-1.48	-2.55	-0.41
Baseline Functional Status	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
KOOS-Symptoms Score	167	53.3	18.3	53.6	3.6	92.9	84	55.3	19.1	57.1	7.1	92.9	-1.96	-6.86	2.94
KOOS-Pain Score	167	46.9	11.6	47.2	22.2	63.9	84	48.4	10.9	50.0	22.2	63.9	-1.56	-4.55	1.44
KOOS-ADL Score	167	55.1	17.0	54.4	4.4	95.6	84	54.0	15.6	54.4	1.6	86.8	1.04	-3.32	5.40
KOOS-Sports Score	167	25.0	17.9	25.0	0.0	75.0	84	24.0	17.0	25.0	0.0	60.0	0.92	-3.72	5.56
KOOS-QOL Score	167	26.0	16.7	25.0	0.0	68.8	84	25.8	16.5	25.0	0.0	87.5	0.23	-4.15	4.61
KOOS-Overall Score	167	41.3	13.0	43.0	11.8	72.1	84	41.5	12.5	42.8	7.5	69.5	-0.26	-3.65	3.12
SF12-Physical Score	167	36.0	8.1	35.3	17.1	59.9	84	36.0	8.1	36.8	12.5	57.2	-0.02	-2.16	2.11
SF12-Mental Score	167	52.6	12.1	53.8	15.0	73.8	84	52.5	12.7	52.0	22.1	77.4	0.07	-3.17	3.31
IKDC Score	167	36.8	12.8	37.9	6.9	71.3	84	34.9	11.2	37.4	4.6	62.1	1.90	-1.34	5.14
Tegner Pre-Surgery	167	2.5	1.3	2.0	0.0	7.0	84	2.4	1.2	2.0	0.0	6.0	0.10	-0.25	0.44
Tegner Pre-Injury	167	6.1	1.9	6.0	1.0	10.0	84	6.0	2.0	6.0	2.0	10.0	0.02	-0.49	0.53

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

Table 5. 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			
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.

The treatment groups had similar lesion characteristics (see **Table 6** and **Table 7**) with only minor differences that would not have biased the study in favor of the Agili-C™ group. The percentage of subjects with large lesions (defined as total lesion area > 3 cm^2) was larger in subjects randomized to Agili-C™ compared to SSOC (58.7% vs 48.8%). This was also reflected in the total lesion size (**Table 7**), where the total lesion size was larger in subjects randomized to Agili-C™ compared to SSOC (3.9cm^2 vs 3.4cm^2). Similarly, the percentage of subjects with osteochondral lesions (ICRS grade 4B) was higher in subjects randomized to Agili-C™ compared to SSOC (37.7% vs 19.0%). Additionally, the percentage of subjects with multiple lesions was higher in subjects randomized to Agili-C™ compared to SSOC (34.7% vs 31.0%). In contrast the percentage of subjects with mild/moderate osteoarthritis (K/L grades 2-3) was smaller in

subjects randomized to Agili-C™ compared to SSOC (45.5% vs 64.3%). Overall, while there were some differences between groups, the degree of overall severity was similar. Subgroup analyses for lesion size, lesion type, and level of osteoarthritis demonstrate that these minor differences in lesion characteristics did not affect the study results.

Table 6. 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			
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 7. Continuous Lesion Variables – Safety Analysis Set

	Agili-C™						SSOC						Agili-C™ - SSOC[1]		
	N	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Sum of lesion areas (1, 2 + 3)	167	3.9	2.0	3.8	1.0	7.0	84	3.4	1.9	3.0	1.0	7.0	0.53	0.01	1.05
Lesion Area 1	167	2.9	1.6	2.3	1.0	7.0	84	2.6	1.6	2.2	0.1	7.0	0.27	-0.15	0.70
Lesion Area 2	58	2.7	1.5	3.0	0.5	6.0	26	2.1	1.1	1.9	0.8	4.5	0.64	-0.03	1.30
Lesion Area 3	6	2.7	1.2	2.3	1.5	5.0	5	2.3	1.3	2.5	1.0	4.0	0.39	-1.29	2.08

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

Table 8. 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

SAFETY AND EFFECTIVENESS RESULTS

SAFETY SUMMARY

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 10** occurred in 23.4% of Agili-C™ patients in the pivotal study, compared to 50.0% of SSOC patients. Moreover, as shown in **Figure 2**, the rates of any AE, serious AE, and treatment failure were lower in Agili-C™ compared to SSOC.

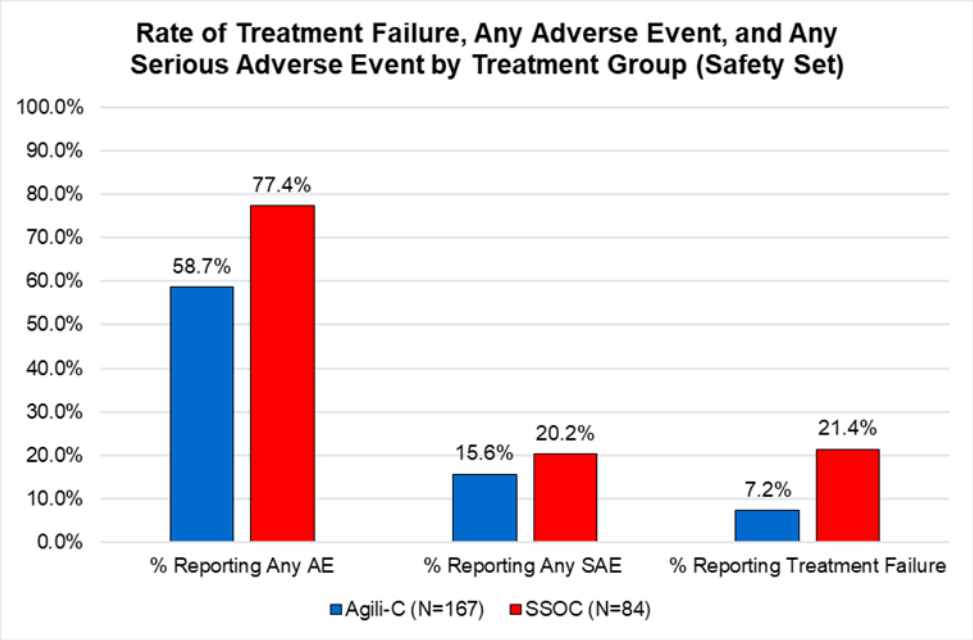

Figure 2: Rate of Any Adverse Event, Any Serious Adverse Event, and Treatment Failure by Treatment Group (Safety Set)

SAFETY RESULTS

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).

The overall adverse event rate was less for the Agili-C™ Group (58.7%) compared to the SSOC group (77.4%).

At least one Severe AE was present in 9.6% of the Agili-C™ subjects compared to 20.2% in SSOC subject, and at least one Serious AE was present in 15.6% of the Agili-C™ subjects compared to 20.2% in SSOC subjects. Overall, AE rates were lower for Agili-C™ subjects compared to SSOC subjects, supporting a very favorable safety profile for Agili-C™.

CartiHeal

Table 9. Summary of Adverse Events (AEs) By Treatment Group As Treated (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%	--	--	--	--	--
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 10. Incidence Rates (%) and Event Counts of AEs by System Organ Class and Preferred Term, Safety Analysis Set

	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			
EAR AND LABYRINTH DISORDER	1	0.6%	1						
Conductive deafness	1	0.6%	1						

	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
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
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						

	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
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						
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			

	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
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	1.2		
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			
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 11 presents the incidence rates and events counts of severe AEs. Across all categories, group differences were in favor of Agili-C™, further supporting the device's safety profile.

Table 11. Incidence Rates (%) and Events Counts of Severe AEs by System Organ Class and Pre-specified or Preferred Term, Safety Analysis Set

	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		

	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
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			
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 12 presents the incidence rates and event counts of serious AEs. Importantly, all group differences were negative (favoring Agili-C™) or similar between groups, further supporting the favorable safety profile of Agili-C™.

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

	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		
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		
Athralgia	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						

	Agili-C™ N= 167			SSOC N= 84			Comparison‡		
With one or more AE§	**n**	**%**	**Count**	**n**	**%**	**Count**	**Diff.**	**95% LB**	**95% UB**
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

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 as defined in the protocol. The treatment group difference was statistically significant according to an unadjusted chi-square test (p=0.002). As indicated in **Table 13**, 4 of the treatment failures in Agili-C™ were due to knee trauma (0 in the SSOC), while 4 of the treatment failures in the SSOC were due to knee replacements and osteotomies (0 in the Agili-C™).

Among subjects with mild to moderate OA, 27.8% of the subjects in the SSOC group were treatment failures compared to 5.3% in the Agili-C™ arm. 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™ arm.

Table 13. 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‡
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 14. AE Relatedness: Summary of Treatment Failures by Treatment Group, Safety Analysis Set

	All N= 251		Agili-C N= 167		SSOC N= 84		p-values‡
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 only 7.2% (n=12) in the Agili-C™ arm. Among the 12 treatment failures in the Agili-C™ arm, 8 cases included a device removal (4.8%, 8/167). Of the 8 implant removal cases, 5 removals (representing 3% of the subjects in the study arm) occurred due to knee trauma or subjects overdoing exercise early in the post-implantation period.

EFFECTIVENESS SUMMARY

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 **Figure 3**. 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.

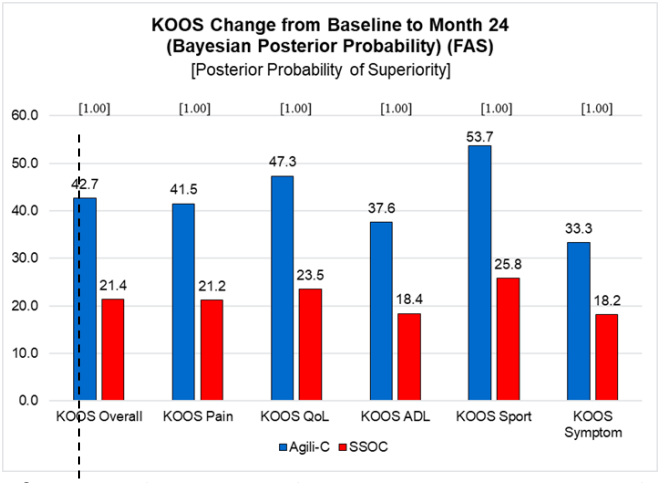

Figure 3: KOOS Change from Baseline to Month 24, Bayesian Posterior Probability (FAS) [Posterior Probability of Superiority]

EFFECTIVENESS 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™ is 42.65 (39.55, 45.54). For subjects randomized to SSOC, the mean of the posterior distribution is 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 is 21.27 (16.17, 26.60) (**Table 15**).

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 15. Bayesian Posterior Probability of Month 24 Superior of Agili-C™ Relative to SSOC (FAS)

Parameter	N	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™	5000	42.65	1.54	39.55	45.54	.
SSOC	5000	21.39	2.14	17.35	25.71	.
Agili-C™ - SSOC	5000	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.

An MMRM model 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 16**. 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 is statistically significant (p<0.0001) demonstrating the increasingly larger group differences in mean improvements over time.

Table 16. Mixed Model for Repeated Measures (MMRM) for Changes in Overall KOOS 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.

The four 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 $\geqslant$ 30.

The four confirmatory secondary endpoints were to be tested in a hierarchical manner in order to control the type 1 error rate. Each of these secondary endpoints requires 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.

Table 17. Summary of Confirmatory Secondary Endpoint Results

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
Pain	20.33	2.50	15.37	25.05	**1.000**
QoL	23.79	3.44	17.01	30.44	**1.000**
ADL	19.25	2.39	14.60	23.84	**1.000**
KOOS Overall ≥ 30	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 18**. 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.

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

Parameter	N	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™	5000	41.52	1.43	38.51	44.09	.
SSOC	5000	21.20	2.00	17.26	25.11	.
Agili-C™ - SSOC	5000	20.33	2.50	15.37	25.05	**1.000**

Parameter	N	Mean of Posterior Distribution	SD of Posterior Distribution	LB of 95% HPD Interval	UB of 95% HPD Interval	Posterior Probability of Superiority[2]
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.						

In general, the minimal clinically important difference (MCID), i.e., the smallest change score needed for the effect to be clinically relevant, for the KOOS Pain score is between 8-10.[3] The KOOS Pain score MCID has also been reported for cartilage restoration procedures (16.7)[4] high tibial osteotomy (15.4)[5] and total knee arthroplasty (13.5).[6] The KOOS Pain score change from baseline in the Agili-C™ group was 31.4±16.2 at 6 months, 36.0±17.2 at 12 months, 40.3±17.4 at 18 months, and 42.1±18.1 at 24 months. As the change in KOOS Pain score was substantially greater than the reported MCID values (approximately 4X the MCID by 24 months), these results demonstrate that patients receiving the Agili-C™ treatment experienced a substantial and clinically meaningful improvement in pain at each time point.

The mean posterior distribution group difference in KOOS QOL score change was 23.79 (17.01, 30.44). 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 QOL score.

Table 19. Bayesian Posterior Probability of Month 24 Superiority Agili-C™ Relative to SSOC for Change from Baseline to Month 24 in KOOS QOL Score (FAS)

Parameter	N	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™	5000	47.29	1.98	43.50	51.24	.
SSOC	5000	23.49	2.76	18.05	28.80	.
Agili-C™ - SSOC	5000	23.79	3.44	17.01	30.44	**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.						

The MCID for the KOOS QOL score in general is between 8-10.[7] The KOOS QOL score MCID has also been reported for high tibial osteotomy (16.5)[8] and total knee arthroplasty (5.5).[9] The KOOS QOL score change from baseline in the Agili-C™ group was 26.4±25.3 at 6 months, 36.0±26.5 at 12 months, 42.4±27.2 at 18

3 http://www.koos.nu/koosfaq.html
4 Ogura T, Ackermann J, et al., The Minimal Clinically Important Difference and Substantial Clinical Benefit in the Patient-Reported Outcome Measures of Patients Undergoing Osteochondral Allograft Transplantation in the Knee, Cartilage. 2021 Jan;12(1):42-50.
5 Jacquet C, Pioger C, et al., Evaluation of the "Minimal Clinically Important Difference" (MCID) of the KOOS, KSS and SF-12 scores after open-wedge high tibial osteotomy, Knee Surg Sports Traumatol Arthrosc. 2021 Mar;29(3):820-826.
6 Eckhard L, Munir S, et al., Minimal important change and minimum clinically important difference values of the KOOS-12 after total knee arthroplasty, Knee. 2021 Mar;29:541-546.
7 http://www.koos.nu/koosfaq.html
8 Jacquet C, Pioger C, et al., Evaluation of the "Minimal Clinically Important Difference" (MCID) of the KOOS, KSS and SF-12 scores after open-wedge high tibial osteotomy, Knee Surg Sports Traumatol Arthrosc. 2021 Mar;29(3):820-826.
9 Eckhard L, Munir S, et al., Minimal important change and minimum clinically important difference values of the KOOS-12 after total knee arthroplasty, Knee. 2021 Mar;29:541-546.

months, and 47.5±27.1 at 24 months. As the change in KOOS QOL score was greater than the reported MCID, these results demonstrate that patients receiving the Agili-C™ treatment experienced a substantial, clinically meaningful improvement in quality of life at each time point.

The mean posterior distribution (95% credible interval) for the group difference in KOOS ADL score change was 19.25 (14.50, 23.84). 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 ADL score.

Table 20. Bayesian Posterior Probability of Month 24 Superiority Agili-C™ Relative to SSOC for Change from Baseline to Month 24 in KOOS ADL Score (FAS)

Parameter	N	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™	5000	37.59	1.37	34.94	40.29	.
SSOC	5000	18.35	1.92	14.62	22.12	.
Agili-C™ - SSOC	5000	19.25	2.39	14.60	23.84	**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.

The MCID for the KOOS ADL score in general is between 8-10.[10] Furthermore, the KOOS ADL score MCID has been reported for high tibial osteotomy (17)[11] and total knee arthroplasty (13.7).[12] The KOOS ADL score change from baseline in the Agili-C™ group was 28.0±18.4 at 6 months, 31.6±19.9 at 12 months, 35.8±18.8 at 18 months, and 37.7±19.5 at 24 months. As the change in KOOS ADL score was greater than the MCID, these results demonstrate that patients receiving the Agili-C™ treatment experienced a substantial, clinically meaningful improvement in function during activities of daily living at each time point.

The mean posterior for the group difference in response rate was 0.443 (0.320, 0.557) (corresponding to a 77.8% response rate for Agili-C™ compared to only 33.6% for SSOC). These results demonstrate that patients treated with the Agili-C™ responded to treatment at significantly higher rate compared to SSOC indicating that the Further, 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 with regard to the overall KOOS responder rate.

Table 21. Bayesian Posterior Probability of Month 24 Superiority Agili-C™ Relative to SSOC for Increase from Baseline to Month 24 of ≥ 30 points on KOOS Overall Score (FAS)

Parameter[2]	N1[3]	N2[4]	Mean of Posterior Distribution	SD of Posterior Distribution	LB of Non-Parametric 95% CI	UB of Non-Parametric 95% CI	Posterior Probability of Superiority[5]

10 http://www.koos.nu/koosfaq.html
11 Jacquet C, Pioger C, et al., Evaluation of the "Minimal Clinically Important Difference" (MCID) of the KOOS, KSS and SF-12 scores after open-wedge high tibial osteotomy, Knee Surg Sports Traumatol Arthrosc. 2021 Mar;29(3):820-826.
12 Eckhard L, Munir S, et al., Minimal important change and minimum clinically important difference values of the KOOS-12 after total knee arthroplasty, Knee. 2021 Mar;29:541-546.

Agili-C™	20	5000	0.778	0.032	0.712	0.838	.
SSOC	20	5000	0.336	0.051	0.240	0.440	.
Agili-C™ - SSOC	20	5000	0.443	0.061	0.320	0.557	**1.000**

Notes:
[1]Baseline observation carried forward after treatment failure for 11 Agili-C™ and 18 SSOCs.
[2]Statistics describing posterior distribution and posterior probability of superiority presented as mean across multiple imputations
[3]Number of Bayesian multiple imputations
[4]Number of random draws from posterior distribution for determining statistics under each multiple imputation
[5]Posterior probability that the mean improvement is larger for Agili-C™ compared to SSOC.

Additional secondary endpoints included:

- 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[13] at 12, 18, and 24 Months
- Change from baseline in Tegner score[14] at 12, 18, and 24 Months
- Change from baseline QOL as measured by SF-12 v2[15] 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
    - patients with osteochondral lesions
    - patients with single lesion
    - patients with multiple lesions
    - patients without osteoarthritis (K/L 0-1)
    - patients with osteoarthritis (K/L 2-3)
    - patients with total lesion(s) size ≤3cm²
    - patients with total lesion(s) size >3cm²
    - patients without previous ligament reconstruction
    - patients with intact meniscus
    - patients with previous partial meniscectomy
    - patients with concomitant partial meniscectomy
    - active patients
    - non-active patients

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.

13 The FDA guidance document, *Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage* (Dec. 2011), lists the IKDC Subjective Knee Evaluation Form 2000 as a measure that may be used to assess efficacy in clinical studies of products intended to repair or replace knee cartilage.

14 Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;198:43–9.

15 Ware J.E., Kosinski M., & Keller S.D., SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. 3rd ed. QualityMetric, Lincoln, RI 1998.

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 only 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) 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]		
	N	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Month 6	164	24.0	18.8	24.7	-25.3	67.8	81	17.6	18.6	18.4	-29.9	60.9	6.4	1.4	11.4
Month 12	163	32.5	20.6	34.5	-17.2	80.5	80	20.5	20.3	21.3	-23.0	80.5	12.0	6.5	17.5
Month 18	162	38.1	20.8	41.4	-18.4	82.8	81	21.8	21.4	20.7	-20.7	86.2	16.3	10.7	21.9
Month 24	160	43.0	21.2	46.0	-13.8	82.8	79	20.3	23.0	19.5	-17.2	86.2	22.7	16.8	28.6

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

The MCID for IKDC has been reported to be 16.7 at 12 months after articular cartilage repair surgeries.[16] 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 the MCID at each timepoint, demonstrating that these patients reported clinically significant improvements in symptoms and function in daily living activities.[17] These results are consistent with the improvement in KOOS assessed as the primary endpoint.

16 Roos EM, Engelhart L, et al., Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects, Cartilage. 2011 Apr; 2(2): 122–136.
17 Higgins LD, Taylor MK, et al., Reliability and validity of the International Knee Documentation Committee (IKDC) Subjective Knee Form, Joint Bone Spine. 2007 Dec; 74(6): 594-9.

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.[18] 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 24. Tegner Score Change from Baseline (FAS)

	Agili-C™						SSOC						Agili-C™ - SSOC[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Month 6	164	1.0	1.5	1.0	-3.0	5.0	81	0.8	1.5	0.0	-2.0	4.0	0.3	-0.1	0.7
Month 12	163	1.7	1.6	2.0	-2.0	8.0	81	1.1	1.7	1.0	-3.0	8.0	0.6	0.1	1.0
Month 18	161	2.0	1.8	2d.0	-1.0	8.0	81	1.2	1.8	1.0	-3.0	8.0	0.8	0.4	1.3
Month 24	160	2.5	1.7	2.0	0.0	8.0	79	1.0	1.6	1.0	-2.0	8.0	1.5	1.0	1.9

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

These results are clinically meaningfully as each 1-unit increment of the Tegner scale represents a distinct class of functionality and activity level. For instance, both treatment arms began the study with a mean Tegner score of approximately 2.5, which correlates the ability to perform light work (e.g., walking on uneven ground, etc.). By Month 24 the Agili-C™ group improved by 2.5 points on average to a score of 5 on the Tegner scale. This indicates that Agili-C™ subjects, on average, could perform heavy labor and participate in competitive sports (e.g., soccer). By contrast, the SSOC control group improved by 1 point on average to a mean score of 3.5 on the Tegner scale. This indicates that control subjects, on average, were able to engage in moderately heavy labor (e.g., truck driving), but would not have improved to the point where they could participate in competitive sports or recreational sports (e.g., jogging). A return to recreational and competitive sports, as well as the option to engage in heavy labor, is a clinically relevant difference between the treatment groups in favor of the Agili-C.

The change from baseline to Month 24 in KOOS Sports score was also 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 25. 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	N	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™	5000	53.65	2.09	49.51	57.64	.
SSOC	5000	25.81	2.93	20.16	31.60	.
Agili-C™ - SSOC	5000	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.

18 https://www.apta.org/patient-care/evidence-based-practice-resources/test-measures/tegner-activity-scale

The MCID for the KOOS Sports score in general is between 8-10.[19] The KOOS Sports score MCID has also been reported for high tibial osteotomy (11.2)[20] and for cartilage restoration procedures (25).[21] As the change in KOOS Sports score was greater than the reported MCID at each time point, these results demonstrate that patients receiving the Agili-C™ treatment experienced a substantial, clinically meaningful improvement in physical function when active.

The change from baseline to Month 24 in KOOS Symptoms score was also 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	N	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™	5000	33.30	1.43	30.59	36.15	.
SSOC	5000	18.15	2.00	14.21	22.06	.
Agili-C™ - SSOC	5000	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.

The MCID for the KOOS Symptoms score in general is between 8-10.[22] The KOOS Symptoms score MCID has also been reported for high tibial osteotomy (15.1)[23] and for total knee arthroplasty (7).[24] As the change in KOOS Symptoms score was greater than the reported MCID at each time point, these results demonstrate that patients receiving the Agili-C™ treatment experienced a substantial, clinically meaningful improvement knee symptoms, including swelling, bending and straightening, and movement of the knee.

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. The MCID for the SF-12 physical component has been reported as 1.8-4.3 after total knee arthroplasty procedures

19 http://www.koos.nu/koosfaq.html
20 Jacquet C, Pioger C, et al., Evaluation of the "Minimal Clinically Important Difference" (MCID) of the KOOS, KSS and SF-12 scores after open-wedge high tibial osteotomy, Knee Surg Sports Traumatol Arthrosc. 2021 Mar;29(3):820-826.
21 Ogura T, Ackermann J, et al., The Minimal Clinically Important Difference and Substantial Clinical Benefit in the Patient-Reported Outcome Measures of Patients Undergoing Osteochondral Allograft Transplantation in the Knee, Cartilage. 2021 Jan;12(1):42-50.
22 http://www.koos.nu/koosfaq.html
23 Jacquet C, Pioger C, et al., Evaluation of the "Minimal Clinically Important Difference" (MCID) of the KOOS, KSS and SF-12 scores after open-wedge high tibial osteotomy, Knee Surg Sports Traumatol Arthrosc. 2021 Mar;29(3):820-826.
24 Haydel A, Guilbeau S, et al., Achieving Validated Thresholds for Clinically Meaningful Change on the Knee Injury and Osteoarthritis Outcome Score After Total Knee Arthroplasty: Findings From a University-based Orthopaedic Tertiary Care Safety Net Practice, J Am Acad Orthop Surg Glob Res Rev. 2019 Nov 4;3(11):e00142.

at 12 months and 6.2-8.2 after autologous chondrocyte implantation procedures at 24 months[25]. These results show that the SF-12 physical component scores are higher than the control group by a MCID from 12 months and on, demonstrating that these patients reported clinically significant improvements in physical quality of life measurements, including general health, bodily pain, usual physical role activities, and physical functioning[26].

Table 27. Change from Baseline for the 12-item Short Form Survey (SF-12) Physical Component Score (FAS)

	Agili-C						SSOC						Agili-C™ - SSOC[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Month 6	164	10.2	10.3	8.6	-19.4	37.9	81	7.4	10.8	6.1	-13.0	33.5	2.8	0.0	5.6
Month 12	163	12.8	10.1	12.2	-10.2	39.1	81	8.2	11.7	5.0	-14.0	40.8	4.6	1.8	7.5
Month 18	162	14.9	10.5	16.0	-14.2	40.9	80	8.0	11.5	5.1	-20.6	40.8	6.9	3.9	9.8
Month 24	160	16.0	10.5	16.5	-14.3	37.3	79	8.2	12.0	7.5	-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 also 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. As expected, there are 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]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Month 6	164	3.0	12.1	1.2	-34.9	37.1	81	1.0	12.9	-0.4	-30.7	39.8	2.0	-1.3	5.3
Month 12	163	4.3	11.9	1.8	-30.5	41.5	81	1.5	11.6	0.0	-20.0	40.3	2.8	-0.3	6.0
Month 18	162	4.3	13.1	2.3	-41.7	36.2	80	1.6	11.9	0.0	-20.3	40.3	2.7	-0.7	6.1
Month 24	160	5.5	12.5	2.5	-30.1	36.9	79	0.5	11.1	0.0	-26.8	37.3	5.1	1.8	8.4

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

SUBGROUP AND COVARIATE 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,

25 Clement ND, Weir D, et al., Meaningful changes in the Short Form 12 physical and mental summary scores after total knee arthroplasty, Knee. 2019 Aug;26(4):861-868. doi: 10.1016/j.knee.2019.04.018; Clement ND, MacDonald D, et al., The minimal clinically important difference in the Oxford knee score and Short Form 12 score after total knee arthroplasty, Knee Surg Sports Traumatol Arthrosc. 2014 Aug;22(8):1933-9. doi: 10.1007/s00167-013-2776-5; Ogura T, Ackermann J, et al., Minimal Clinically Important Differences and Substantial Clinical Benefit in Patient-Reported Outcome Measures after Autologous Chondrocyte Implantation, Cartilage. 2020 Oct;11(4):412-422. doi: 10.1177/1947603518799839.

26 Ware J, Kosinski M, Keller S. SF-12: How to score the SF-12 Physical and Mental Summary Scales. 2nd ed. Boston, MA: The Health Institute, New England Medical Center; 1995.

number of lesions, level of osteoarthritis, lesion location, lesion size, previous ligament reconstruction, meniscus status, and activity status. Agili-C™'s superiority in effectiveness relative to standard of care was confirmed across all subgroups. Factors, such as subjects' activity level, status of 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.

BENEFIT/RISK CONCLUSIONS

The risks presented by Agili-C™ are similar to or lower than those presented by existing surgical standard of care options (microfracture and debridement) for the same population. In the pivotal study, 58.7% of patients in the Agili-C™ arm experienced at least one adverse event (AE), compared to 77.4% of the subjects in the surgical standard of care (SSOC) group. The most common AE was increased transient chronic knee pain, which was present in 15.0% of the subjects in the Agili-C™ arm compared to 39.3% of the SSOC subjects. 9.6% of Agili-C™ subjects experienced at least one severe AE compared to 20.2% of SSOC subjects, and 15.6% of Agili-C™ subjects experienced at least one serious AE compared to 20.2% of SSOC subjects. Overall, AE rates were lower for Agili-C™ subjects compared to SSOC subjects, supporting a very favorable safety profile for Agili-C™. In the Safety Analysis Set of the pivotal study, a significantly higher rate of treatment failures was observed in the SSOC arm (21.4%) compared to the Agili-C™ arm (7.2%) (p=0.001).

Notably, none of these procedure-related risks were seen in the pivotal study. For the Agili-C™ group, there were 25 procedure-related adverse events (AEs), 4 of which were considered serious. This was similar to the SSOC group, which experienced 23 procedure-related AEs, 5 of which were serious.

Furthermore, although the SSOC procedures are conducted through minimally invasive arthroscopy procedures, the safety results from the pivotal study show that group differences are all negative, reflecting a favorable safety profile for the Agili-C™ implant and its related procedure. In several cases, the upper bound of the 95% confidence intervals are less than zero, suggesting a superior safety profile. Thus, as shown by the pivotal study, risks related to the Agili-C™ implantation procedure can be significantly mitigated by appropriate physician training and clear instructions for use (IFU).

Agili-C™ presents several benefits over current SSOC. In the pivotal study, the estimated mean improvement in KOOS Overall score was clinically and statistically significantly larger for Agili-C™

compared to SSOC starting at Month 6. The magnitude of the mean improvement increased over time for Agili-C™, but not for SSOC. At Month 24, the posterior mean for the treatment group improvement from baseline in the Agili-C™ arm was 42.7 compared to only 21.4 for the SSOC arm. The posterior mean of the difference in mean improvements was 21.3 (95% credible interval 16.2 to 26.6). A similar superiority margin was observed among subjects in the FAS with mild-moderate OA (Kellgren-Lawrence Grades of 2 or 3). The superiority margin increased to 27.3 with 95% credible interval of 20.5 to 33.9 for subjects with large lesions (total lesion areas larger than 3 cm^2). Results were very similar in the Per Protocol analysis set, which was identical to the FAS analysis set apart from excluding 1 participant randomized to Agili-C™.

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 current surgical standard of care, microfracture and debridement.

Therefore, the benefits of Agili-C™ outweigh the risks.

CONCLUSIONS DRAWN FROM THE STUDY DATA

The clinical data demonstrate the safety and effectiveness of Agili-C™ when used in accordance with the indications for use. All primary endpoints of the study were satisfied at 24 month follow-up intervals. Based on the clinical study results, the clinical benefits of the use of Agili-C™ outweigh the risks associated with the device and surgical procedure.

INSTRUCTIONS FOR USE

Please see the Surgical Technique Quick Guide for the complete set of instructions.

- Select suitable implant/s corresponding to the lesion dimensions.
- Select the correct tool size from the designated surgical tool set to match the desired implant dimensions.
- Check implant size, specifications and expiry date.
- Open the implant package carefully.
- Insert the implant gently and perpendicular into the implantation site in a pressed fit manner. Pay attention to the direction of the implant - the implant top has drilled channels. **The implant must be placed at least 2mm below the surface of the articular cartilage on all sides and fully surrounded by vital bone.**
- Multiple implants must not overlap. When multiple implants are used it is important to keep a bone bridge of at least **5 mm** between them to ensure the entire circumference of each implant is in direct contact with the bone.

PACKAGING

The Agili-C™ implant pre-packaged and sterile. It is intended for single use only. The implant is sterilized by gamma radiation using a minimum dose of 22.5kGy.

STORAGE CONDITIONS

Store the device in its sterile packaging at Room Temperature.

MRI SAFETY INFORMATION

The Agili-C™ is MR Safe.

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Definition	Symbol
Lot/batch number:	
Catalogue number	REF
Use by/ Expiration date:	
See Instruction for use	
Single use only	
Do not re-sterilize	
By prescription only	
Do not use if package is damaged	
Manufacturer