Five-Year Follow-up of a Multicenter Randomized Controlled Trial Comparing an Aragonite-Based Scaffold With Microfracture and Debridement for Chondral and Osteochondral Knee Lesions

Nir Altschuler,* MSc, Kenneth R. Zaslav,† MD, Berardo Di Matteo,‡§‖ MD, PhD, Seth L. Sherman,¶ MD, Andreas H. Gomoll,# MD, Scott A. Hacker,** MD, MS, Peter Verdonk,†† MD, PhD, Oliver Dulic,‡‡§§ MD, PhD, Jenel M. Patrascu,‖‖ MD, PhD, Andrew S. Levy,¶¶ MD, Dror Robinson,## MD, PhD, and Elizaveta Kon,§‖ MD
Investigation performed at Humanitas University, Milan, Italy

Background: Chondral/osteochondral knee lesions are commonly encountered and often associated with progression of osteoarthritis (OA). Nevertheless, knee repair trials have traditionally excluded patients with concurrent mild to moderate OA.

Purpose: To compare the clinical and safety outcomes of knee repair with an aragonite-based osteochondral implant with outcomes of surgical standard of care (SSOC) in patients with chondral/osteochondral knee lesions, including those with mild to moderate OA.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Investigators at 26 centers across 8 countries enrolled adult patients (21-75 years of age) with $\leq$3 cartilage defects of International Cartilage Regeneration & Joint Preservation Society grade $\geq$3a located on the femoral condyles and/or trochlea, total treatable area 1 to 7 cm^2, bony defect depth $\leq$8 mm, and Kellgren-Lawrence knee OA score of 0 to 3. Patients were randomized 2:1 to receive an aragonite-based implant or SSOC (arthroscopic debridement or microfracture) and followed for 5 years. The primary endpoint was improvement in overall Knee injury and Osteoarthritis Outcome Score (KOOS). Secondary endpoints included percentage of responders (minimum overall KOOS improvement $\geq$ 30 points), patient-reported outcomes (KOOS subscale values and International Knee Documentation Committee subjective score), treatment failure (ie, need for any secondary treatment), and treatment-emergent adverse events. A covariate analysis compared primary/secondary outcomes between patients with no to minimal and mild to moderate OA.

Results: In total, 167 patients underwent knee repair with the study implant and 84 with SSOC, with follow-up compliance rates of 88.4% and 83.1%, respectively, at 5 years. The mean baseline overall KOOS values were comparable between the implant (41.2 $\pm$ 13.1) and SSOC (41.7 $\pm$ 12.4) groups. By the final follow-up, improvement was significantly greater for the implant group (81.0 $\pm$ 23.0 vs 59.1 $\pm$ 25.2; 22.6-point difference; 95% CI, 16.6-28.7). The overall KOOS responder rate was 74.7% in the implant group and 29.6% in the SSOC group. The implant group experienced significantly superior outcomes between baseline and the final follow-up for all secondary patient-reported outcome measures. Treatment failure rate was significantly higher with SSOC than the implant (35.7% vs 15.0%; $P < .001$). Among patients with mild to moderate OA, the implant group exhibited a higher overall KOOS responder rate (74.6% vs 36.2%) and lower failure rate (13.2% vs 40.7%; $P < .001$) than the SSOC group.

Conclusion: The results confirmed that the aragonite-based scaffold is both safe and superior to SSOC in improving clinical outcomes at up to 5 years' evaluation, as well as in patients with mild to moderate OA.

Keywords: osteoarthritis; aragonite; scaffold; cartilage regeneration; osteochondral; microfracture

Chondral and osteochondral lesions of the knee are common, with a reported prevalence of approximately 60% to 70%.[4,10,33] Untreated focal cartilage lesions are vulnerable to progressive joint damage, deterioration of the collagen network, and tissue swelling.[14]

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Chondral defects rarely present in isolation and are frequently accompanied by signs of broader joint degeneration. In an analysis of 25,124 knee arthroscopies, 70% of lesions were nonisolated and 29% had accompanying osteoarthritis (OA).[33] Even in the absence of OA at the time of diagnosis, these lesions can lead to joint degeneration given the avascular nature of cartilage and its limited healing capacity.[28]

The first-line surgical standard of care (SSOC) for chondral and osteochondral lesions includes arthroscopic debridement, wherein unstable cartilage fragments are removed, and microfracture, wherein the subchondral bone is penetrated to stimulate bone marrow cellular components to repair the joint surface. Although both interventions can lead to short-term improvements in pain and function, they do not address the underlying mechanical and biological contributors to disease progression.[25,29] Debridement does not repair the underlying cartilage, and microfracture generates fibrocartilage, which lacks the durability of native hyaline cartilage and deteriorates over time.[25] Postoperative clinical improvements after microfracture have been shown to plateau at 1 year and then gradually worsen,[15] with treatment failure anticipated beyond 5 years postoperatively.[12] Clinical outcomes after microfracture are notably inferior in patients with more extensive cartilage pathologies (eg, lesions >2 cm^2, multiple lesions, and degenerative defects) and previous knee surgeries.[31] Yet patients with these common comorbidities have historically been excluded from knee repair trials, leaving a knowledge gap in how to offer effective, evidence-based treatment options to these populations.[23]

A novel, aragonite-based, biphasic, acellular scaffold (Agili-C; Smith & Nephew, formerly CartiHeal) was developed as an off-the-shelf solution for treating chondral and osteochondral defects of the knee in traumatic and osteoarthritic joints. Aragonite is a naturally occurring form of calcium carbonate, derived from a purified coral exoskeleton, with a 3-dimensional microarchitecture that closely mimics human cancellous bone. This structure is designed to support articular cartilage regeneration by supporting differentiation of bone marrow–derived stem cells into chondrocytes in the channels, and migration of chondrocytes from the periphery of the implant. The scaffold also promotes repair of the subchondral bone; preclinical studies have demonstrated the scaffold's osteoinductive, osteoconductive, and osteotransductive properties.[1,8,19-21,24,27] The scaffold enables a single-stage implantation procedure and has shown encouraging safety and efficacy, with case series reporting sustained improvements in patient-reported outcomes and radiographic defect fill lasting $\leq$5 years.[3,11,17,22,30]

A randomized, multicenter, open-label pivotal trial was conducted to evaluate the superiority of this aragonite-based scaffold over SSOC for the treatment of chondral and osteochondral lesions of the knee. This trial prospectively enrolled patients with mild to moderate knee OA (Kellgren-Lawrence [K/L] score 2 or 3) and additional clinical complications (eg, prior meniscectomy and multiple

‡Address correspondence to Berardo Di Matteo, MD, PhD, Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 4, 20072 Pieve Emanuele, Milan, Italy (email: berardo.dimatteo@gmail.com).
*Altschuler Consulting, LLC, Kfar Saba, Israel.
†Lennox Hill Hospital–Northwell Health Orthopedic Institute, New York, New York, USA.
§IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.
‖Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.
¶Department of Orthopaedic Surgery, Stanford University, Stanford, California, USA.
#Hospital for Special Surgery–Orthopedic Surgery and Sports Medicine, New York, New York, USA.
**Grossmont Orthopedic Medical Group, San Diego, California, USA.
††Orthoca, Antwerp, Belgium.
‡‡University of Novi Sad, Novi Sad, Serbia.
§§University Clinical Center of Vojvodina, Novi Sad, Serbia.
‖‖Victor Babeş Timisoara University of Medicine and Pharmacy, Timisoara, Romania.
¶¶Center for Advanced Sports Medicine, Knee and Shoulder, Millburn, New Jersey, USA.
##Robinson Clinic, Bat Yam, Israel.
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lesions), who have historically been excluded from cartilage repair trials, thereby improving the clinical relevance of the findings to routine practice.[23]

In 2023, 2-year results from this trial were published.[2] These indicated that the implant outperformed SSOC in meeting the primary outcome of superiority in mean improvement of the overall Knee injury and Osteoarthritis Outcome Score (KOOS), which was twice that of the control arm. Patients receiving the implant experienced statistically superior results in all secondary outcomes, including achieving ≥75% defect fill on magnetic resonance imaging (MRI; 88.5% vs 30.9%; $P < .0001$) and a lower failure rate (7.2% vs 21.4%; $P = .002$). The results were used to support the US Food and Drug Administration (FDA) premarket approval, the first product of its kind to obtain this status for cartilage lesions in patients with focal defects as well as mild to moderate OA. Subsequently published subgroup analyses further confirmed the implant's superiority at later follow-up points across different lesion locations and between genders.[9,16]

The current publication presents outcomes at the 5-year follow-up, aiming to confirm the long-term durability of these effects. It was hypothesized that the implant would continue to demonstrate superiority over SSOC in the primary outcome of improvement in the overall KOOS, as well as in all secondary measures.

METHODS

Study Design

The design of this prospective, multicenter, open-label, randomized controlled trial has previously been described in detail.[2] Patients were enrolled at 26 centers in 8 countries (Belgium, Israel, Hungary, Italy, Poland, Romania, Serbia, and United States).

Adult patients aged 21 to 75 years were eligible for inclusion if they met the following criteria: (1) ≤3 treatable lesions on the femoral condyles or trochlea assessed as International Cartilage Regeneration & Joint Preservation Society (ICRS) grade ≥3a, (2) symptomatic total treatable area of 1 to 7 cm^2, (3) willingness and ability to comply with the postoperative rehabilitation protocol and scheduled study visits, and (4) nonresponsive to physical therapy for at least 3 to 4 weeks.

Conversely, patients were excluded if they met at least one of the following criteria: (1) baseline KOOS Pain subscale value <20 or >65 (maximum pain = 0; pain-free = 100); (2) bony defect depth >8 mm, as determined on baseline MRI, radiographic imaging, or arthroscopy; (3) cartilage lesions in the tibia or patella, ICRS grade ≥4a; (4) OA of the index knee, K/L score 4; (5) instability of the index knee according to International Knee Documentation Committee (IKDC) Knee Examination Form 2000, grade C (abnormal) or D (severely abnormal); (6) malalignment >8° varus or 8° valgus; (7) lack of functional remaining meniscus, ≥5-mm rim at the end of the procedure; (8) any known history of intra-articular or osseous infection of the index knee; (9) uncontained lesion—lack of vital bone wall ≥2 mm thick completely surrounding the lesion; (10) inability to position the implant 2 mm recessed relative to the articular surface; and (11) body mass index (BMI) >35 kg/m^2.

The protocol was approved by the FDA and the ethics committees/institutional review boards of all sites. All patients signed an informed consent before study inclusion.

Randomization Process

Patients underwent arthroscopy to confirm eligibility. Screening data, including arthroscopic findings, were recorded into the randomization application on a dedicated tablet provided to the sites. Once confirmed, patients were enrolled and randomized intraoperatively to receive either the study scaffold or SSOC in a 2:1 ratio. This allowed surgeons to proceed in real time with the selected treatment. Secured, sealed envelopes were available as a backup randomization method. Site personnel did not have access to the allocation sequence details.

Randomization to SSOC included 1 of 2 procedures, microfracture or debridement, which are typically used for different patient profiles. For example, microfracture is often limited to smaller lesions, whereas debridement is typically used for lesions regardless of size. Patient age and level of OA may also affect which of these 2 procedures is recommended as SSOC.[31] Given these considerations, the specific SSOC procedure was determined depending on a prespecified algorithm (Figure 1), as discussed with regulatory authorities during presubmission interactions.

Outcomes

Patient-reported outcomes were obtained by site staff at baseline and postoperatively at 6, 12, 18, 24, 36, 48, and 60 months.

The primary endpoint was the change from baseline to 60 months in the mean overall KOOS. Confirmatory secondary endpoints included the change from baseline to 60 months in the KOOS subscales of Pain, Quality of Life (QOL), Activities of Daily Living (ADL), Symptoms, and Sports, as well as the overall KOOS responder rate, defined as achieving an increase of ≥30 points in the overall KOOS. Additionally, patients were evaluated with the IKDC Subjective Knee Evaluation Form 2000, Tegner Activity Scale, and 12-item Short Form Survey (SF-12) for both the Mental Component Score (MCS) and Physical Component Score.

Safety analysis included the systematic recording of all device/procedure-related treatment-emergent adverse events (TEAEs); treatments, defined as any secondary invasive intervention in the treated joint (eg, open, mini-open, or arthroscopic surgical procedures, as well as any intra-articular injection) and determined for relatedness to index procedure; all-cause reoperations; and secondary surgeries related to index procedures.

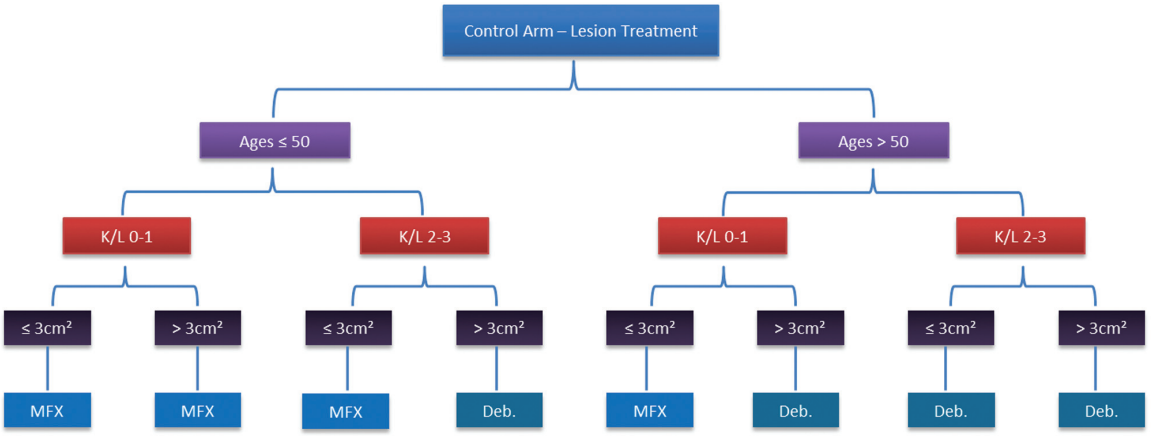

Figure 1. Treatment algorithm used to determine surgical standard of care. Deb, debridement; K/L, Kellgren-Lawrence score; MFX, microfracture.

Study Treatments

The surgical technique for implanting the aragonite-based biphasic implant has been described in previous studies.[2,17,18]

All patients followed the recommended rehabilitation program described in the 2-year follow-up publication.[2]

Statistical Analysis

Sample Size Calculation. The trial had a flexible sample size determined adaptively using a "Goldilocks" strategy,[6] which incorporated interim analyses to determine the appropriate sample size. The initial sample size was set to 250 patients. The selection procedure was designed to obtain approximately 80% power for a 2:1 randomization with an alternative hypothesis corresponding to an 8-point improvement in the overall KOOS at 24 months and assuming a 15% treatment failure rate in each study arm.

For the extension of this study to a 5-year duration, it was assumed that the sample sizes would be 75% as large as originally required (120 and 59 patients in the implant and SSOC groups, respectively). Statistical power was determined to be adequate for confirming month 60 superiority, given the results from the 24-month interim analysis and reasonable conservative assumptions.

Outcome Analysis. The primary analysis was conducted on the full analysis set. The trial's primary goal was to demonstrate superiority of the implant as relative to SSOC at 60 months using the following hypothesis: H_0: $\theta_1 = \theta_0$ vs H_A: $\theta_1 > \theta_0$, where θ_d is the mean response for arm d ($d = 0$ for SSOC and $d = 1$ for implant) in KOOS overall score change from baseline to 60 months postprocedure. To test this hypothesis, the posterior probability of superiority was calculated: $Pr(\theta_1 > \theta_0 | \text{Data})$. The trial was considered a success if the posterior probability exceeded 0.975 at the final analysis.

The previously described 6 confirmatory secondary endpoints (change from baseline to month 60 in the KOOS Pain, QOL, ADL, Symptoms, and Sports subscales, as well as the overall KOOS responder rate) were prespecified to be tested in a hierarchical manner to control the type 1 error rate if primary superiority was demonstrated. Each secondary endpoint required a Bayesian posterior probability of 0.975 for declaring superiority.

Baseline observation carried forward was applied to primary and secondary endpoints when a case was defined as a treatment failure (ie, change from baseline assumed to be zero).

Follow-up compliance does not incorporate imputed values. Follow-up compliance was calculated based on the safety analysis set and defined as the number of patients with observed (non-missing; see Missing Data below) overall KOOS score divided by the number of patients expected to contribute overall KOOS score at that time point. Therefore, the denominator could be smaller than the number of patients in the safety analysis set because it excluded the patients who were not expected to complete the overall KOOS questionnaire at that visit.

Covariate Analysis. Analysis of the primary and secondary endpoints was performed for prespecified covariates related to patient characteristics (age, sex, BMI category, and geographic location [US vs outside US]), lesion characteristics (lesion type [chondral vs osteochondral], grade, size, location, and number of lesions), and comorbidities/clinical characteristics (previous ligament reconstruction, meniscal status, preinjury activity status, smoking history, and presence of OA).

For the current analysis, it was decided to restrict the reporting to 1 covariate: presence of OA (no to minimal OA [K/L score 0 or 1] vs mild to moderate OA [K/L score 2 or 3]). The primary and secondary confirmatory endpoints were analyzed for this covariate in a mixed model for repeated measures (MMRM).[32] An interaction P value $<.15$ was considered evidence for supporting the presence of heterogeneity of treatment effects.

Missing Data. KOOS subscale values were calculated when ≤ 2 observed items were missing. Otherwise,

subscale scores were left as missing. The overall KOOS was calculated when ≤2 subscale scores were missing. When >2 subscale scores were missing, the overall KOOS was left as missing. For all primary and secondary confirmatory analyses, patients with treatment failure had postfailure outcomes replaced with baseline values in a baseline observation carried forward method. Patients missing data due to dropout had missing data handled through multiple imputation. However, only weakly informative priors were used for final analysis.

RESULTS

Patient enrollment began September 25, 2017, and ended November 7, 2019. When the minimum enrollment of 250 patients was met, an interim analysis was conducted by an external endpoint adjudication committee on November 22, 2019. The committee determined to cease enrollment due to anticipated success. One additional patient was enrolled to the SSOC arm after the interim analysis, resulting in a total enrollment of 167 patients in the implant group and 84 patients in the SSOC group, with comparable demographics and baseline scores between the groups (Table 1). Three patients in the implant group and 1 in the SSOC group were later excluded from the full analysis set owing to detection of major entry violation exclusion criteria (Figure 2). Follow-up was completed on November 12, 2024. Follow-up compliance rates for the implant and SSOC groups at 2 years were 97.6% (160/164) and 95.2% (79/83), respectively. Compliance remained robust through 5 years (88.4% (129/146) and 83.1% (59/71), respectively).

Primary Endpoint

Change from baseline to 60-month follow-up in the mean overall KOOS was significantly greater for the implant group compared to the SSOC group, with a 22.6-point difference (95% CI, 16.6-28.7) in favor of the implant group at final analysis. The implant group had significantly higher overall KOOS values at all postoperative follow-up points (Table 2). The Bayesian posterior probability of superiority was >0.999, thereby confirming superiority of the implant to SSOC.

Secondary Endpoints

The Bayesian posterior probability of superiority was >0.999 for all outcomes assessed, reinforcing the conclusion that the implant was superior to SSOC. The overall KOOS responder rate at 60 months was 74.7% (109/146 patients) in the implant group compared with 29.6% (21/71 patients) in the SSOC group ($P < .001$). The Bayesian posterior probability of superiority for the responder rate in the implant group versus the SSOC group was >0.999.

The implant group demonstrated significantly larger improvement between baseline and 60-month follow-up for all patient-reported outcome measures assessed except SF-12 MCS (Appendix Table A1, available in the online version of this article).

Safety

TEAEs occurred in 71.9% (120/167 patients) of the implant group and 81.0% (68/84 patients) of the SSOC group. The most common TEAE was transient/chronic knee pain, reported in 22.2% (37/167 patients) of the implant group and 48.8% (41/84 patients) of the SSOC group. Severe TEAEs occurred in 21.0% (35/167 patients) of the implant group and 32.1% (27/84 patients) of the SSOC group, and serious TEAEs in 29.3% (49/167 patients) of the implant group and 29.8% (25/84 patients) in the SSOC group. Four patients in the SSOC group were diagnosed with OA progression from baseline, versus none in the implant group. No unanticipated serious TEAEs occurred in either group.

Procedure-related TEAEs were less frequent in the implant group than in the SSOC group (8.4% [14/167 patients] vs 21.4% [18/84 patients], respectively). Serious procedure-related TEAEs occurred in 4 patients in the implant group (decreased range of motion, metal allergy, injury, and hematoma) and 6 patients in the SSOC group.

Treatment failure (surgery and/or injection) occurred in 15.0% (25/167 patients) of the implant group and 35.7% (30/84 patients) of the SSOC group, a statistically significant difference ($P < .001$). Of the 25 treatment failures in the implant group, 14 were at least possibly related to the device and/or toolset. By contrast, all treatment failures in the SSOC arm were considered at least possibly procedure related.

Failure rates among patients with mild to moderate OA were significantly higher in the SSOC group than in the implant group (40.7% vs 13.2%; $P < .001$). Failure rates were higher among those with no to minimal OA in the SSOC group compared with the implant group, although the difference was not statistically significant (26.7% vs 16.5%; $P = .282$).

Intra-articular injection was required by significantly more patients in the SSOC group than the implant group (27.4% [23/84 patients] vs 6.6% [11/167 patients]; $P < .001$). Rates of subsequent knee surgeries were comparable between the SSOC and implant groups (14.3% [12/84 patients] vs 11.4% [19/167 patients], respectively; $P = .545$). Of the 19 secondary surgeries in the implant group, 6 were categorized as "unlikely related" or "unrelated" to the study device, toolset, and/or procedure; the remaining 13 secondary surgeries were classified as "related," "possibly related," or "probably related" to the device, toolset, and/or procedure. In the SSOC group, however, all 12 secondary surgeries were classified as "related," "possibly related," or "probably related" to the procedure. Significantly more patients in the SSOC group required a knee replacement or osteotomy than patients in the implant group (9.5% [8/84 patients] vs 1.8% [3/167 patients]; $P = .008$)

TABLE 1
Baseline Characteristics of Implant and SSOC Treatment Groups[a]

	Agili-C	SSOC
Sex		
Female	60 (35.9)	33 (39.3)
Male	107 (64.1)	51 (60.7)
Age, y (SD)	42.0 (11.2)	46.2 (11.2)
Age category, y		
Age <50	127 (76.0)	50 (59.5)
Age ≥50	40 (24.0)	34 (40.5)
Age group, y		
Age 21 to <45, young adulthood	94 (56.3)	41 (48.8)
Age 45 to <65, middle adulthood	68 (40.7)	40 (47.6)
Age ≥65, older adulthood	5 (3.0)	3 (3.6)
BMI (SD)	26.4 (4.2)	27.9 (3.8)
BMI category		
BMI <30	130 (77.8)	57 (67.9)
BMI ≥30	37 (22.2)	27 (32.1)
Tegner activity before onset of knee cartilage lesion		
Active (>4)	132 (79.0)	61 (72.6)
Inactive (≤4)	35 (21.0)	23 (27.4)
Smoking history		
Current	37 (22.2)	22 (26.2)
Never	108 (64.7)	45 (53.6)
Past	22 (13.2)	17 (20.2)
Kellgren-Lawrence OA score		
Mild/moderate: 2 or 3	76 (45.5)	54 (64.3)
None: 0 or 1	91 (54.5)	30 (35.7)
Lesion size >3 cm^2		
No	69 (41.3)	43 (51.2)
Yes	98 (58.7)	41 (48.8)
Single vs multiple lesions		
Multiple	58 (34.7)	26 (31.0)
Single	109 (65.3)	58 (69.0)
ICRS grade		
Chondral lesions: ICRS grades 3 and 4a	104 (62.3)	68 (81.0)
Osteochondral lesions: ICRS grade 4b	63 (37.7)	16 (19.0)
History of previous ACL reconstruction		
No	154 (92.2)	77 (91.7)
Yes	13 (7.8)	7 (8.3)
History of meniscectomy (medial/lateral)		
No	131 (78.4)	62 (73.8)
Yes	36 (21.6)	22 (26.2)
Concomitant meniscectomy (medial/lateral)		
No	117 (70.1)	65 (77.4)
Yes	50 (29.9)	19 (22.6)
Meniscal status		
Concomitant surgery on meniscus	50 (29.9)	19 (22.6)
History of partial meniscectomy	23 (13.8)	21 (25.0)
Intact at the moment of surgery	94 (56.3)	44 (52.4)

[a]Data are presented as n (%) or mean (SD). ACL, anterior cruciate ligament; Agili-C, aragonite-based scaffold; BMI, body mass index; ICRS, International Cartilage Regeneration & Joint Preservation Society; OA, osteoarthritis; SSOC, surgical standard of care.

Covariate Analysis: Effect of the Presence of OA

A covariate analysis was conducted on patients in the implant and SSOC groups with no to minimal OA (90 and 30 patients, respectively) and mild to moderate OA (74 and 53 patients, respectively).

The implant group had superior mean overall KOOS values to the SSOC group at each time point. The mean change in the overall KOOS from baseline to 60 months for those with no to minimal OA was 39.4 points in the implant group and 14.3 points in the SSOC group. Among those with mild to moderate OA, the mean change was 39.8 points in the implant group and 18.2 points in the SSOC group. The Bayesian posterior probability of superiority for changes in the overall KOOS from baseline to 60 months was >0.999 in favor of the implant group versus the SSOC

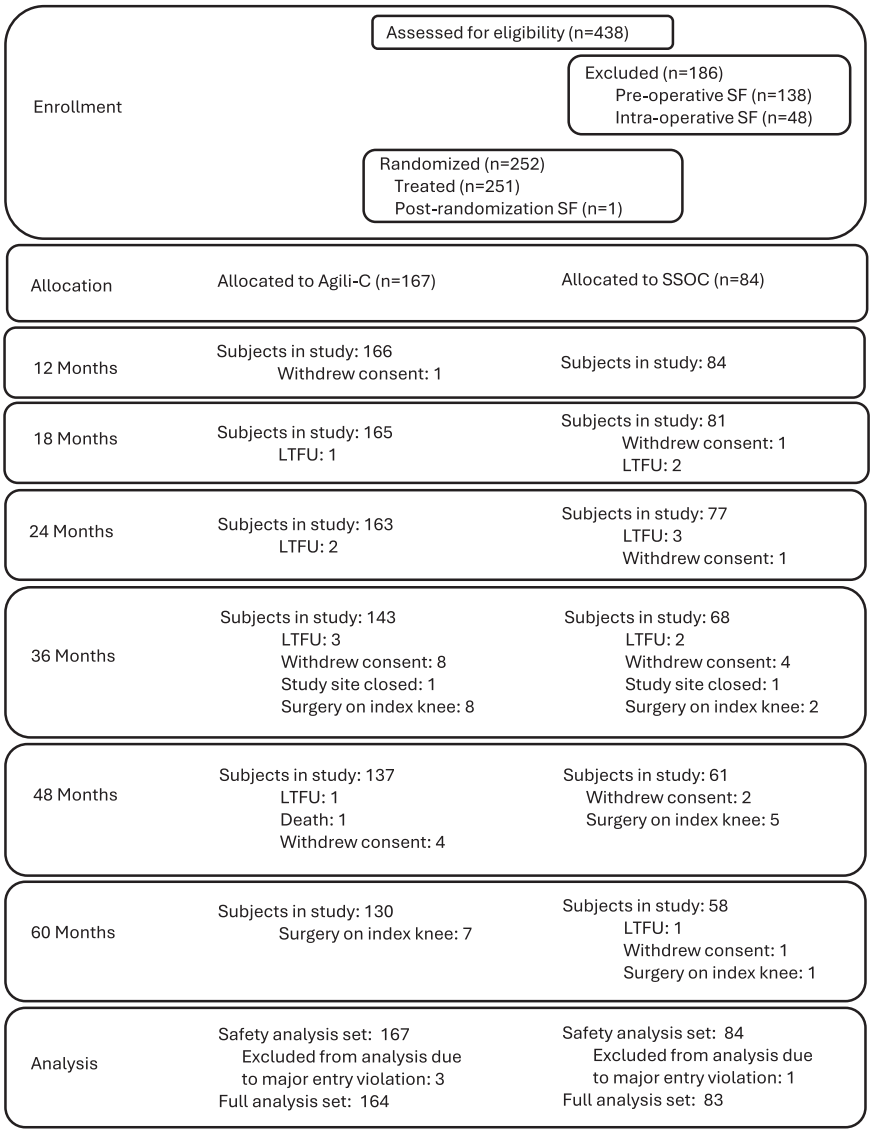

Figure 2. Patient randomization flowchart and distribution between the treatment groups. ''Subjects'' indicates the total number of participants at each time point, including both those with documented visits and those who missed visits but remained enrolled in the study. Agili-C, aragonite-based scaffold; LTFU, lost to follow-up; SF, screen failure; SSOC, surgical standard of care.

group among patients with mild to moderate OA. Based on the MMRM, the treatment group difference at 60 months for the KOOS overall score was 20.5 (95% CI, 10.7-30.4; $P < .001$) for no to minimal OA and 17.3 (95% CI, 9.0-25.5; $P < .001$) for mild to moderate OA, and the treatment-by-visit interaction was statistically significant ($P < .001$), demonstrating the increasingly larger group differences in mean improvements over time (Figure 3). There was no evidence that superiority margin was based on degree of OA ($P = .842$). The same was true for the KOOS Pain, QOL, ADL, Symptoms, and Sports Subscale values.

Among patients with no to minimal OA and mild to moderate OA, those in the implant group experienced greater mean improvements in all KOOS subscale values between baseline to 60 months compared to those in the SSOC group ($P < .05$). There was similar improvement in mean KOOS overall score and KOOS subscale values from baseline to 60 months between patients in the implant group with no to minimal OA and those with mild to moderate OA.

Among patients with no to minimal OA, the overall KOOS responder rate at 60 months was 74.7% (59/79 patients) in the implant group compared with 16.7% (4/24 patients) in the SSOC group. Among patients with mild to moderate OA, the overall KOOS responder rate at 60 months was 74.6% (50/67 patients) in the implant group compared with 36.2% (17/47 patients) in the SSOC group.

TABLE 2
Overall KOOS and Change From Baseline at All Follow-up Points Through 60 Months for Implant and SSOC Groups[a]

	Agili-C			SSOC			Score		Change From Baseline	
Visit, mo	No.	Score[c]	Change From Baseline[d]	No.	Score[c]	Change From Baseline[d]	Difference[e]	*P* Value[f]	Difference[e]	*P* Value[g]
0[b]	164	41.2 (13.1)	NA	83	41.7 (12.4)	NA	–0.5 (–3.9 to 2.8)	.622	NA	NA
6	164	68.7 (17.7)	27.6 (18.6)	81	61.4 (19.1)	19.3 (17.3)	7.4 (2.4 to 12.3)	.002	8.2 (3.5 to 13.0)	<.001
12	163	75.3 (18.1)	34.2 (19.8)	81	63.3 (22.3)	21.7 (19.3)	12.0 (6.4 to 17.6)	<.001	12.5 (7.3 to 17.7)	<.001
18	162	80.8 (17.6)	39.6 (19.6)	80	62.8 (23.2)	21.1 (19.7)	18.0 (12.2 to 23.7)	<.001	18.5 (13.2 to 23.7)	<.001
24	160	84.3 (17.6)	43.0 (20.1)	79	62.0 (23.9)	20.5 (20.9)	22.3 (16.3 to 28.2)	<.001	22.5 (16.9 to 28.0)	<.001
36	150	82.6 (20.4)	41.4 (21.3)	73	61.3 (23.5)	19.3 (19.2)	21.3 (15.0 to 27.6)	<.001	22.1 (16.6 to 27.7)	<.001
48	143	83.4 (20.6)	41.9 (21.6)	71	59.4 (25.6)	17.3 (20.0)	24.0 (17.2 to 30.9)	<.001	24.6 (18.8 to 30.4)	<.001
60	146	81.0 (23.0)	39.6 (23.4)	71	59.1 (25.2)	16.9 (20.4)	22.0 (15.0 to 28.9)	<.001	22.6 (16.6 to 28.7)	<.001

[a]Agili-C, aragonite-based scaffold; KOOS, Knee injury and Osteoarthritis Outcome Score; NA, not applicable; SSOC, surgical standard of care.
[b]Corresponds to the baseline visit.
[c]Data are presented as mean (SD).
[d]Data are presented as mean (SD). Based on the test of change from baseline to the time point. Change from baseline is statistically significant ($P < .001$).
[e]Data are presented as difference in means (95% CI).
[f]Based on the test of means between the Agili-C and SSOC score means at the time point.
[g]Based on the test of differences in change from baseline between the Agili-C and SSOC confidence intervals calculated using normal distribution. *P* values were calculated using the Student *t* distribution.
Independent *t* tests were used in these analyses.

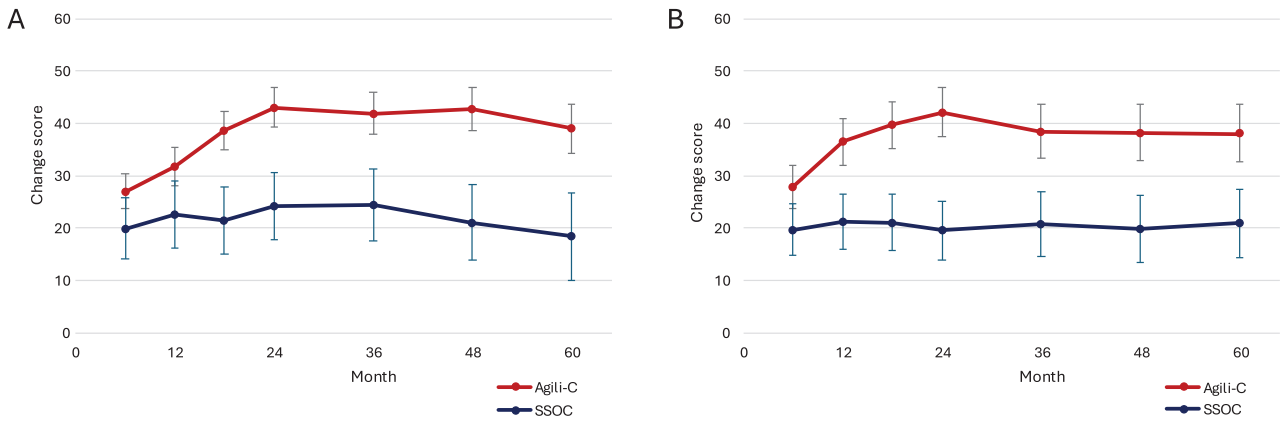

Figure 3. Mixed model for repeated measures: estimated change in the overall Knee injury and Osteoarthritis Outcome Score overtime by treatment group in patients (A) without osteoarthritis (Kellgren-Lawrence score 0 or 1) and (B) with osteoarthritis (Kellgren-Lawrence score 2 or 3). Agili-C, aragonite-based scaffold; SSOC, surgical standard of care.

DISCUSSION

The results from this randomized controlled trial confirm that the previously reported superiority of the aragonite-based scaffold over SSOC at 2 years[2] was maintained through 5 years. The scaffold continued to demonstrate superiority over SSOC across the primary and all secondary endpoints, with a comparatively low rate of treatment failure and a favorable safety profile.

For the primary outcome of improvement in overall KOOS, patients receiving the implant experienced significantly greater improvements than those receiving SSOC, and this benefit was sustained for the duration of follow-up. Superiority was confirmed via Bayesian posterior probability analysis (>0.999).

The KOOS is a multidimensional assessment tool encompassing various outcomes in patients impaired by knee pathology. KOOS has been validated in focal cartilage lesions,[5] and its subscales (particularly Sports and QOL) have been rated as being of the highest importance to patients.[13] Furthermore, this tool was created with the intent of being applicable in various knee injuries, including OA, which often occurs concurrent to (as in the current patient group) or after the development of these knee lesions.[26]

A ≥30-point improvement in KOOS was chosen as the threshold for defining clinical response, as it is in line with changes previously found to represent clinically important differences for KOOS subscales, which have been reported to range from 8.3 points for pain to 30.0 points for sports and recreation.[7] By this metric, the clear superiority of response rate in favor of the implant over SSOC in the current analysis (74.7% vs 29.6%) reflects notable improvements in pain, function, and QOL.

The implant also demonstrated a favorable safety profile, with lower rates of TEAEs, including transient/chronic pain. This is also reflected in the significantly lower rates of patients who required intra-articular injections among those receiving the implant, offering a proxy measure for decreased pain burden in this cohort.

Per regulatory requirements, reporting was inclusive of all TEAEs, regardless of their potential relationship with the study surgery or implant. As such, the safety of the implant is perhaps better demonstrated by the lower rates of reoperation as compared with SSOC, and the lack of patients in the implant cohort experiencing OA progression. Given that lesion progression and the need for reintervention are common challenges in this class of lesions, these findings are particularly relevant.

The results of the present evaluation suggest that the implant demonstrates stable clinical performance up to middle-term evaluation. This is confirmed both in its superiority compared with SSOC in terms of subjective scores and in the markedly lower rates of revision surgery (ie, osteotomies and knee replacements) at 5 years.

This trial's strengths include its status as the largest known randomized controlled study in surgical cartilage repair, as well as its multicenter, international design. This enabled the recruitment of a wide array of patients commonly encountered in clinical practice, who often present with multiple lesions of various types and substantial comorbidities. This is best exemplified by the inclusion of patients with mild to moderate OA and other commonly excluded characteristics (eg, multiple lesions and prior meniscectomy), a class of patients historically excluded from clinical trials of treatments for chondral/osteochondral lesions.[23] Additionally, the current trial was able to sustain robust follow-up rates despite being conducted during the COVID-19 pandemic, thereby minimizing the impact of missing visits on the findings.

However, this study has several limitations that should be considered when interpreting the results. First, although the treatment arms were generally well balanced for demographics and clinical characteristics, there were minor differences that may have biased the results. These included higher percentages of patients in the implant group with lesions >3 cm (58.7% vs 48.8%), larger total lesion size (3.9 vs 3.4 cm), ICRS grade 4b osteochondral lesions (37.7% vs 19.0%), and multiple lesions (34.7% vs 31.0%), as well as lower rates of mild to moderate OA (45.5% vs 64.3%). Second, the control group was limited to microfracture and debridement. Other repair treatments for chondral/osteochondral knee lesions, such as autologous chondrocyte implantation, matrix-induced autologous chondrocyte implantation, and osteochondral allograft transplantation, were not included, and comparison with these interventions remains to be conducted. This study did not compare the microfracture and debridement subgroups separately from the implant group, limiting our ability to determine the relative efficacy and safety of the implant versus these separate SSOC interventions. Finally, while this report focused on the impact of the presence of OA on primary and secondary outcomes, multiple predefined covariates of interest were collected. These are not reported herein due to size restrictions. However, these variables are nonetheless highly relevant to clinical decision-making and are worth exploring in future analyses to provide a more comprehensive understanding of the implant's safety and performance.

CONCLUSION

The aragonite-based scaffold demonstrated sustained superiority over SSOC in the treatment of chondral and osteochondral knee lesions at up to 5 years' follow-up. This superiority encompasses improvements in key outcomes (pain, function, and QOL) and extended to a wide variety of real-world patient and lesion types. Notably, the presence of mild to moderate OA did not jeopardize the performance of the scaffold at the final evaluation, proving that this approach is also effective in complex patients usually considered unsuitable for cartilage regenerative strategies.

These encouraging results open up new treatment opportunities for a challenging patient population, namely younger patients with early arthritis, that has historically been relegated to nonoperative management. While the latter can provide transient pain relief for some, many of these patients have had to live with significant restrictions in function and QOL.

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ORCID iDs

Kenneth R. Zaslav https://orcid.org/0000-0002-9709-6461
Berardo Di Matteo https://orcid.org/0000-0002-9807-0271
Dror Robinson https://orcid.org/0000-0003-2517-4069

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