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Original Research

Safety of an allogeneic, human, umbilical cord blood-derived mesenchymal stem cells-4% hyaluronate composite for cartilage repair in the knee

Brian J. Cole[a,*], Joshua T. Kaiser[b], BS, Kyle R. Wagner[b], BS, and Andreas H. Gomoll[b]

[a] Rush University Medical Center, Chicago, IL, USA
[b] Hospital for Special Surgery, New York, NY, USA

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ABSTRACT

Introduction: Knee osteoarthritis treatments that functionally restore diseased/damaged cartilage are limited.

Objective: To evaluate the safety and effectiveness of allogeneic, human, umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) + 4% hyaluronate composite for knee cartilage defects.

Methods: In a 24-month, open-label, non-randomized phase 1/2a study, adults ≥18 years with single, full-thickness, ICRS grade 3 to 4 knee cartilage defects were recruited sequentially based on initial defect size (Dose A: 2-5 cm^2; Dose B: >5 cm^2). The hUCB-MSCs composite (0.25×10^7 cells/cm^2) was surgically implanted into the defects. Safety (adverse events [AEs] and dose-limiting toxicities) was the primary objective, and efficacy was secondary.

Results: Twelve patients (mean 38 years; 83% male; BMI 27.6 kg/m^2) completed the study. All patients reported ≥1 treatment-emergent AE (TEAE): 42 with Dose A (n = 6); 27 with Dose B (n = 6); most common were decreased range of motion (100%) and arthralgia (92%). Seven patients (58%) had 10 treatment-related TEAEs. No discontinuations due to TEAEs, serious AEs, or deaths were reported. There were no dose-limiting toxicities; maximum tolerated dose was established as 2.0×10^7 cells. The IKDC score and other knee function and pain scores significantly improved from baseline to months 12 and 24. Clinically significant abnormal MRI findings declined from 91.7% (n = 11) at baseline to 16.7% (n = 2) at month 24.

Conclusion: hUCB-MSCs + 4% hyaluronate composite implantation appears to be safe over 24 months in US patients with ICRS grade 3 to 4 knee cartilage defects, with improvements in function, pain, and cartilage repair evidence.

Introduction

Osteoarthritis of the knee affects approximately 5% of the US population, or 14 million people according to data from 2010,[1] with medical care costs exceeding $27 billion annually.[2,3] Given the prevalence of osteoarthritis as well as other common causes of chondral defects such as trauma or aging, and the poor healing ability of articular cartilage, new strategies are needed to halt disease progression and functionally repair or regenerate diseased and damaged articular cartilage.

Current procedures to repair damaged cartilage, including osteochondral allograft transplantation,[4,5] autologous chondrocyte implantation,[6] and microfracture,[7,8] are generally intended for the treatment of focal chondral defects in younger patients. Arthritic

* Corresponding author: Brian J. Cole, Rush University Medical Center, 1725 West Harrison Street, Suite 1063, Chicago, IL 60612.
Email address: bcole@rushortho.com (B.J. Cole).

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lesions in older patients are more diffuse and often involve both knees; any positive results of these treatments tend to deteriorate over time.[9,10] The use of multipotent mesenchymal stem cells (MSCs) has been proposed for cartilage repair or regeneration in knees with chondral defects due to aging, trauma, or degenerative disease.[11] Human, allogeneic, umbilical cord blood-derived MSCs (hUCB-MSCs) have unique properties compared with MSCs from other tissues, with immunomodulatory, anti-inflammatory, and pro-regenerative cytokine/chemokine activity,[12,13] as well as noninvasive cell collection and hypo-immunogenicity.[14,15]

The investigational composite of hUCB-MSCs and 4% lyophilized sodium hyaluronate (CARTISTEM; MEDIPOST Co. Ltd.) has been shown in preclinical studies[16-18] and a Korean phase 1/2 trial with 7-year follow-up[19] to be safe and effective for cartilage repair of osteoarthritic, full-thickness cartilage lesions. The hUCB-MSC composite also showed significant improvement in cartilage regeneration, with no serious adverse events, when compared with microfracture in a multicenter, phase 3, Korean, randomized trial with 60-month follow up; favorable results included the subgroup of patients aged >50 years.[20] The product was market authorized in Korea for the treatment of knee articular cartilage defects in patients with osteoarthritis (International Cartilage Repair Society [ICRS] Grade 4) as a result of degenerative disease or repeated trauma.

The present study is the first US study of the hUCB-MSC composite for cartilage repair of the knee in American patients for FDA approval. The primary purpose of this phase 1/2a, open-label, nonrandomized study was to evaluate the safety of the allogeneic hUCB-MSCs + 4% hyaluronate composite in patients with articular cartilage defects of the knee recruited at 2 US sites using a dose-escalation scheme to identify the maximum tolerated dose (MTD), with a secondary objective of evaluating cartilage regeneration and pain reduction.

Methods

Study design

This open-label, nonrandomized phase 1/2a study, conducted at 2 US sites between 2013 and 2017, was designed to evaluate the safety and exploratory efficacy of the hUCB-MSCs–hyaluronate composite (investigational product) in patients with articular cartilage defects measuring ≥2 cm^2 over 24 months. Because this was a safety study to detect dose-limiting toxicity (DLT) and MTD, a dose-escalation design was used with no control group.

The study protocol was reviewed and approved by an independent ethics committee or institutional review board at each study site, and the study was conducted in accordance with Good Clinical Practice, relevant laws and regulations regarding studies of investigational products, and ethical principles of the Declaration of Helsinki. All participants provided written informed consent before undergoing any study procedures.

Participants

Participants (aged ≥18 years; body mass index [BMI] ≤35 kg/m^2) with a single, full-thickness cartilage defect of the knee (ICRS grade 3 or 4) measuring ≥2 cm^2 due to aging, trauma, or degenerative disease with scores for swelling, tenderness, and active range of motion less or equal to Grade 2, as well as joint pain of 20 to 60 mm on a 100-mm visual analog scale (VAS), were enrolled. Major exclusion criteria were underlying necrotic, autoimmune, inflammatory, or infectious etiology; recent surgery or radiation (within 6 weeks), or co-morbidities that contraindicate surgery; ligament instability >Grade 2; uncorrected lower-extremity malalignment (>5°); partial meniscectomy (<5 mm meniscal rim remaining); and recent immunosuppressant (within 6 weeks) or corticosteroid or viscosupplementation injection in the target knee (within 3 months).

Study treatment and procedures

Participants received the study treatment and were followed for 24 months for the primary (safety) and secondary (efficacy) objectives. Study treatment was a single administration of the investigational product at a cell density of 0.25×10^7 cells/cm^2 (0.5 mL/cm^2 with 0.5×10^7 cells/mL) with the total dosage depending on the final defect size visually confirmed via arthroscopy on the day of surgical implantation. A small longitudinal arthrotomy was used to expose the cartilage defect. Following debridement of the defect and perforation of the subchondral plate with a drill bit, the product was implanted directly into the drill holes, as previously reported.[19] Participants were recruited into groups sequentially based on initial cartilage defect size of 2 to 5 cm^2 ($n = 6$; Dose A). If no DLT was observed with Dose A 3 months after implantation, a second group with defect size of >5 cm^2 ($n = 6$; Dose B) was enrolled. Dose ranges selected for this study were derived from preclinical and clinical studies. If a DLT occurred in 1 to 2 participants at Dose A, 3 more patients were to be enrolled at Dose A, while DLTs in any 3 subjects at either dose mandated trial termination. Postoperative rehabilitation entailed use of a continuous passive motion device from postoperative day 1 through week 6 and increased weight-bearing during weeks 6 to 12; patients had to refrain from high-impact activities for 20 to 24 weeks.

During the study, corticosteroids or viscosupplementation were not permitted. Other medications that would not affect the efficacy assessment were allowed. All medication and physical therapy interventions during the study period were recorded.

Outcome measures

The primary outcome was safety as evaluated by adverse events (AEs, serious AEs [SAEs], and treatment-emergent AEs [TEAEs]) at weeks 2, 4, 8, 12, and 24, and at months 12 and 24. AEs were assessed for intensity (Grades 1 to 4 defined as mild, moderate, severe,

Table 1
Demographic and clinical characteristics at baseline.

	Investigational product*		
Characteristic	Dose A (n = 6)	Dose B (n = 6)	Total (N = 12)
Age, years			
Mean (SD)	36.3 (8.2)	39.7 (8.0)	38.0 (7.9)
Range	27-47	27-47	27-47
Sex, n (%)			
Male	5 (83.3)	5 (83.3)	10 (83.3)
Female	1 (16.7)	1 (16.7)	2 (16.7)
Race, n (%)			
White	5 (83.3)	5 (83.3)	10 (83.3)
Black	1 (16.7)	1 (16.7)	2 (16.7)
BMI, kg/m^2			
Mean (SD)	28.6 (4.1)	26.6 (4.5)	27.6 (4.3)
Range	24.0-34.6	19.8-32.3	19.8-34.6
Cause of cartilage defect, n (%)			
Degenerative diseases	4 (66.7)	3 (50.0)	7 (58.3)
Trauma	2 (33.3)	2 (33.3)	4 (33.3)
Other	0	1 (16.7)	1 (8.3)
ICRS grade, n (%)			
3	6 (100)	4 (66.7)	10 (83.3)
4	0	2 (33.3)	2 (16.7)
Physical exam, n (%)			
Swelling			
Grade 0	4 (66.7)	2 (33.3)	6 (50)
Grade 1	2 (33.3)	4 (66.7)	6 (50)
Tenderness			
Grade 0	2 (33.3)	3 (50)	5 (41.7)
Grade 1	4 (66.7)	3 (50)	7 (58.3)
Active range of motion			
Grade 0	5 (83.3)	5 (83.3)	10 (83.3)
Grade 1	1 (16.7)	1 (16.7)	2 (16.7)
VAS			
Mean (SD)	46.5 (8.4)	36.7 (20.6)	41.6 (15.8)
Range	34-54	3-61	3-61
IKDC			
Mean (SD)	43.3 (19.1)	37.0 (14.1)	40.2 (16.3)
Range	17-69	23-62	17-69

Abbreviations: BMI, body mass index; ICRS, International Cartilage Repair Society; IKDC, international knee documentation committee; VAS, visual analog scale.

* Human umbilical cord blood-derived mesenchymal stem cells and lyophilized sodium hyaluronate.

or life-threatening, respectively) and treatment relatedness. Routine clinical laboratory tests, coagulation tests, immunogenicity tests, vital signs, physical examination, and magnetic resonance imaging (MRI) of the focal lesion site for possible tumorigenicity were also evaluated for safety.

A DLT was defined as toxicity or AEs of Grade 3 or higher (≥80 points for pain) in ≥2 events in the knee (swelling, tenderness, range of motion, or pain) at any follow-up visit, or as an adverse drug reaction (ADR) of Grade 3 or higher according to the Common Toxicity Criteria for Adverse Events Version 4.0 (CTCAE, v4.0) that failed to resolve within 7 days despite intervention. The MTD was defined as Dose B if a DLT occurred in ≤2 patients at Dose B; alternatively, the MTD was defined as Dose A if a DLT occurred in ≥3 patients at Dose B. If a DLT occurred in ≥3 patients treated with Dose A, then the MTD would remain undetermined.

The primary efficacy endpoint was self-reported change in knee function on the International Knee Documentation Committee (IKDC) score from baseline to month 12. The IKDC score ranged from 0 to 100, with 100 = no activity limitations or absence of symptoms. Secondary efficacy outcomes were patient-assessed knee function by the Lysholm Score (range, 0-100, with 100 = no symptoms or disability), and the Knee Injury and Osteoarthritis Outcome Score (KOOS) with subscales for activities of daily living (ADL), pain, quality of life, sports, and symptoms (range, 0-100 for all knee scales, with 100 = no problems); and joint pain on a 100-mm VAS.[21] All outcome scores were measured before treatment and at weeks 4, 8, 12, and 24, and months 12 and 24; VAS was also measured at week 2. Cartilage regeneration and morphologic makeup of the repair tissue were assessed using high-resolution (1.5 or 3 Tesla) MRI, including evaluation for tumorigenicity, and the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score (range, 0-100, with 100 = best outcome) at week 24, and months 12 and 24; and by standard radiographs at baseline and month 12.

Table 2
Number and percentage of patients with treatment-emergent adverse events*.

Adverse event	Dose A (n = 6)	Dose B (n = 6)	Total (N = 12)
TEAEs, n (%)	6 (100)	6 (100)	12 (100)
Number of events	42	27	69
Preferred term			
Joint range of motion decreased	6 (100)	6 (100)	12 (100)
Arthralgia	5 (83.3)	6 (100)	11 (91.7)
Muscle atrophy	5 (83.3)	1 (16.7)	6 (50)
Joint effusion	3 (50)	3 (50)	6 (50)
Joint swelling	3 (50)	3 (50)	6 (50)
Prehypertension	3 (50)	0	3 (25)
Bone marrow edema	1 (16.7)	2 (33.3)	3 (25)
Joint crepitation	2 (33.3)	0	2 (16.7)
Blood creatine phosphokinase increased	1 (16.7)	0	1 (8.3)
Blood pressure increased	1 (16.7)	0	1 (8.3)
Chondromalacia	1 (16.7)	0	1 (8.3)
Chondropathy	1 (16.7)	0	1 (8.3)
Exostosis	1 (16.7)	0	1 (8.3)
Hemarthrosis	1 (16.7)	0	1 (8.3)
Joint lock	1 (16.7)	0	1 (8.3)
NMRI abnormal	0	1 (16.7)	1 (8.3)
Plica syndrome	0	1 (16.7)	1 (8.3)
Procedural pain	1 (16.7)	0	1 (8.3)
Sinusitis	1 (16.7)	0	1 (8.3)
Soft tissue injury	1 (16.7)	0	1 (8.3)
Tendonitis	0	1 (16.7)	1 (8.3)
TEAEs related to treatment†	4 (66.7)	3 (50)	7 (58.3)
Arthralgia	3 (50)	2 (33.3)	5 (41.7)
Bone marrow edema	1 (16.7)	1 (16.7)	2 (16.7)
Exostosis	1 (16.7)	0	1 (8.3)
Joint lock	1 (16.7)	0	1 (8.3)
NMRI abnormal	0	1 (16.7)	1 (8.3)

Abbreviations: NMRI, nuclear magnetic resonance imaging; SOC, system organ class; TEAE, treatment-emergent adverse events.

* There were no significant differences in TEAE incidence between dose groups.

† Definitely, probably, or possibly treatment related.

Statistical analysis

The safety population included all patients who received the investigational product, and the efficacy population included all patients who received the investigational product and had data for ≥1 efficacy endpoint. Missing values were not imputed. Because this was a phase 1/2a study of safety and exploratory efficacy, no formal sample size for statistical power was calculated; 6 patients in each dose group treated sequentially were considered sufficient.

Safety and efficacy endpoints are presented with summary statistics for both dose groups and for all patients combined. Safety variables were analyzed descriptively by incidence. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v20.0 or later and categorized by system organ class and preferred term.

Changes from baseline to the various follow-up time points for the primary and secondary efficacy endpoints were analyzed descriptively and compared between dose groups using *t* tests. When changes from baseline for the efficacy variables were not significantly different between doses, the changes from baseline were analyzed for all 12 patients (regardless of dose group) using paired *t* tests post hoc. Results include 95% confidence intervals for actual values and changes from baseline to week 24, month 12, and month 24.

All analyses were performed with Statistical Analysis System v9.2 or higher (SAS Institute Inc.). All tests were 2-sided, with significance defined as $P < .05$.

Results

Participant disposition and demographics

Of 21 patients who were screened, 12 received treatment and completed the study. Nine patients were excluded, either due to failure to meet eligibility criteria ($n = 7$), defect found to be untreatable ($n = 1$), or defect size found to be larger intra-operatively ($n = 1$). Six patients had final cartilage defects sized (visually confirmed arthroscopically at implantation) 2.2 to 4.4 cm^2 and received 0.55×10^7 to 1.1×10^7 cells (Dose A); 6 patients had final defects sized 5.2 to 8.0 cm^2 and were treated with 1.3×10^7 to 2.0×10^7 cells (Dose B).

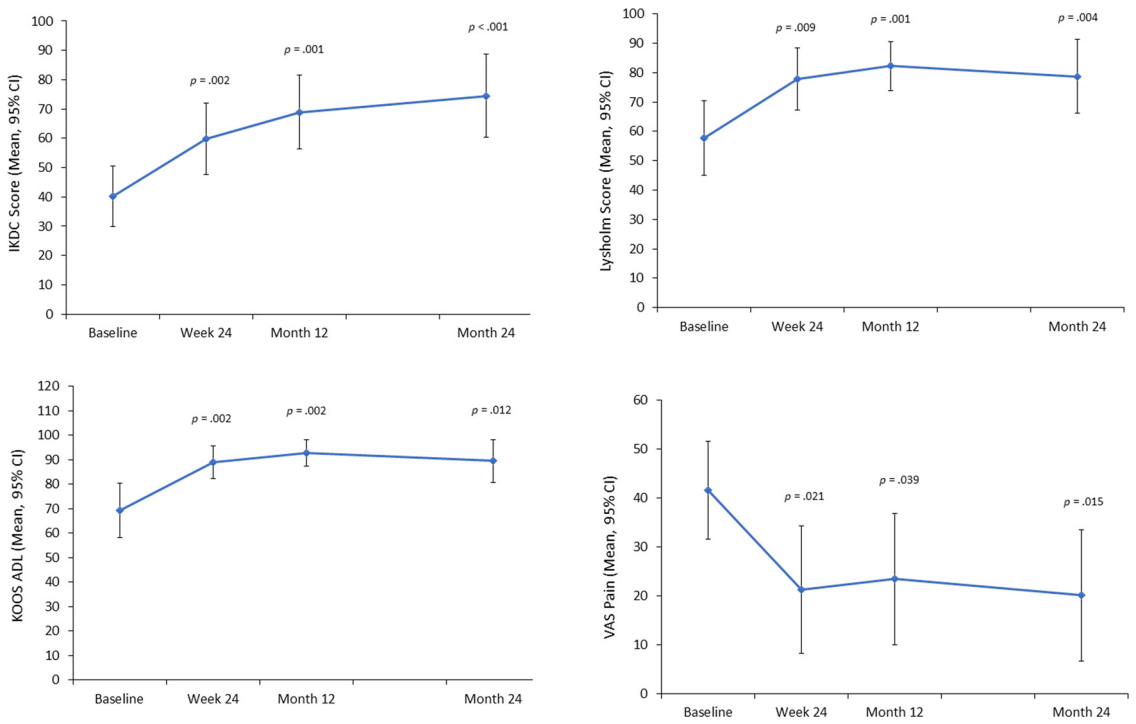

Fig. 1. Mean (a) International Knee Documentation Committee (IKDC) (b) Lysholm (c) Knee injury and Osteoarthritis Outcome Score (KOOS) activities of daily living (ADL) subscale, and (d) Visual Analog Scale (VAS) Pain scores at baseline, at week 24 and at months 12 and 24.

Patients had a mean age of 38.0 years and a mean BMI of 27.6 kg/m^2, and most patients were male (83%) and white (83%) (Table 1). Cartilage defects were caused by degenerative disease in 58.3%, trauma in 33.3%, and osteochondritis dissecans in 8.3%; all defects were ICRS grade 3 or 4, and patients' mean VAS at baseline was 41.6 mm and mean IKDC score was 40.2. All patients had prior surgeries, primarily chondroplasty (33%) and fracture treatment (17%). Demographic and clinical characteristics were similar between dosage groups.

Safety

None of the TEAEs met the criteria for a DLT. Therefore, as per protocol, the MTD was established as Dose B (2.0×10^7 cells).

All patients in both dose groups reported ≥1 TEAE during the study, for a total of 69 TEAEs (42 with Dose A; 27 with Dose B) (Table 2). The most common TEAEs were decreased range of motion (100% of patients), arthralgia (92%), muscle atrophy (50%), joint effusion (50%), and joint swelling (50%). Seven patients (58%) had 10 TEAEs considered possibly, probably, or definitely related to treatment; 4 (67%) with Dose A and 3 (50%) with Dose B. All TEAEs were grade 1 to 2 except for 1 grade-3 TEAE of tendonitis in a patient receiving Dose B, which resolved within 1 week; no grade 4 TEAEs were reported. There were no significant differences between dose groups in TEAE incidence. There were no SAEs, no premature study discontinuations due to TEAEs, and no deaths during the study. No clinically relevant effects of treatment or other abnormal findings were found for vital signs, laboratory parameters, physical exam, or imaging.

Efficacy

No significant differences were found in improvements of efficacy outcomes with Dose A and Dose B. Thus, combined results ($n = 12$) are shown for all outcomes. The IKDC as the primary outcome increased (improved) from a mean of 40.2 at baseline to 68.9 a month 12; mean scores at week 24 and month 24 were to 59.8 and 74.5, respectively; all changes from baseline were statistically significant ($P \leq .002$) (Table 3; Fig. 1). Lysholm scores, all KOOS subscales (including ADLs, pain, quality of life, sports, and symptoms), and pain scores significantly improved at all time points (Table 3; Supplemental Fig. 1).

Imaging parameters shown in Table 4 suggest regeneration of the defect and a decrease in clinically significant abnormal findings. MRI results showed that 11 patients (91.7%; 6 at Dose A and 5 at Dose B) had clinically significant abnormal findings at baseline (while all 12 met the inclusion criteria for measuring pain), whereas only 1 patient (8.3%) had clinically significant abnormal findings at month 12 (a new defect adjacent to the transplant following Dose A) and 2 (16.7%) had clinically significant abnormal findings at month 24, both with Dose B (2 cases of edema progression). Pre-operative cartilage defects can be seen on Proton Density Fat

Table 3
Efficacy outcomes: actual values and changes from baseline for overall group, and dose comparisons, at week 24 and months 12 and 24*.

Variable	Overall group			
	Actual score	Change from baseline*	*P* value†	Dose A – Dose B difference‡
IKDC score				
Baseline	40.2 (29.8-50.6)			
Week 24	59.8 (47.7-71.9)	19.7 (8.8-30.5)	.002	5.00 (-17.79 to 27.79)
Month 12	68.9 (56.4-81.5)	28.8 (14.3-43.3)	.001	6.50 (-23.96 to 36.96)
Month 24	74.5 (60.2-88.8)	34.3 (19.4-49.3)	.000	13.67 (-16.52 to 43.85)
Lysholm score				
Baseline	57.7 (45.0-70.3)			
Week 24	77.8 (67.2-88.5)	20.2 (6.1-34.2)	.009	6.33 (-23.13 to 35.80)
Month 12	82.3 (74.0-90.5)	24.6 (12.7-36.5)	.001	4.17 (-20.87 to 29.20)
Month 24	78.8 (66.1-91.4)	21.1 (8.3-33.9)	.004	21.83 (-0.53 to 44.19)
KOOS ADL				
Baseline	69.2 (58.1-80.4)			
Week 24	89.0 (82.2-95.7)	19.7 (9.1-30.5)	.002	8.58 (-13.22 to 30.37)
Month 12	92.6 (87.2-98.0)	23.4 (10.9-35.6)	.002	11.58 (-13.63 to 36.79)
Month 24	89.5 (80.8-98.2)	20.2 (5.5-34.9)	.012	15.93 (-13.22 to 45.08)
KOOS Pain				
Baseline	60.9 (51.7-70.0)			
Week 24	80.3 (70.2-90.4)	19.4 (10.4-28.5)	.001	1.85 (-17.29 to 20.98)
Month 12	82.2 (72.2-92.2)	21.3 (8.3-34.3)	.004	9.24 (-17.62 to 36.10)
Month 24	80.6 (69.5-91.6)	19.7 (7.6-31.8)	.004	7.86 (-17.28 to 33.00)
KOOS QOL				
Baseline	19.3 (8.4-30.2)			
Week 24	44.8 (32.5-57.1)	25.5 (12.7-38.4)	.001	11.46 (-14.57 to 37.49)
Month 12	55.8 (42.8-68.7)	36.5 (18.9-54.1)	.001	20.75 (-13.72 to 55.22)
Month 24	54.2 (37.0-71.4)	34.9 (13.6-56.1)	.004	30.21 (-9.57 to 69.99)
KOOS Sports				
Baseline	30.4 (14.8-46.0)			
Week 24	60.8 (43.8-77.9)	30.4 (14.4-46.5)	.002	-7.50 (-41.18 to 26.18)
Month 12	70.0 (52.4-87.6)	39.6 (20.4-58.8)	.001	-7.50 (-47.88 to 32.88)
Month 24	68.3 (49.1-87.6)	37.9 (16.9-58.9)	.002	2.50 (-42.07 to 47.07)
KOOS Symptom				
Baseline	65.2 (54.5-75.9)			
Week 24	84.8 (77.4-92.3)	19.6 (11.3-28.0)	.000	2.38 (-15.28 to 20.04)
Month 12	85.7 (78.8-92.6)	20.6 (12.8-28.3)	.000	0.57 (-15.87 to 17.01)
Month 24	81.6 (70.2-92.9)	16.4 (5.0-27.7)	.009	16.07 (-5.19 to 37.33)
VAS pain				
Baseline	41.6 (31.5-51.7)			
Week 24	21.3 (8.3-34.2)	-20.3 (-37.0 to -3.7)	.021	-3.67 (-38.95 to 31.62)
Month 12	23.4 (10.0-36.8)	-18.2 (-35.3 to -1.1)	.039	-11.33 (-46.75 to 24.08)
Month 24	20.1 (6.6-33.5)	-21.5 (-38.0 to -5.0)	.015	-20.33 (-52.32 to 11.65)

Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, knee injury and osteoarthritis outcome score; QOL, quality of life; VAS, visual analog scale.

* Data are presented as mean (95% CI).

† *P* values are from paired *t* test on score changes from baseline to the time point.

‡ Mean difference between dose groups in respective changes from baseline. None of the differences were statistically significant.

Suppressed (PDFS) MR sequence images from representative patients (Supplemental Fig. 2AB, open-arrows). At the 24-month post-operative timepoint, PDFS MR sequence images showed qualitative improvements with cartilage restoration (Supplemental Fig. 2CD, solid-arrows). Both dose groups had consistent MOCART scores that were sustained up to month 24, with no significant difference between doses (Table 4). Clinically significant findings on X-ray declined from 3 patients (25%) at baseline to none at month 12 (Table 4).

Discussion

This phase 1/2a safety study reported AE incidence in a small group of US patients (83% white and 17% black) with grade 3 to 4 articular cartilage defects of the knee after a single administration of the investigational composite of hUCB-MSCs + 4% sodium hyaluronate. It showed that the hUCB-MSC composite was safe and well tolerated in these patients over 24 months. Two dose groups showed no significant differences in AEs, and no DLTs were observed; therefore, the MTD was established as 2.0×10^7 cells. Exploratory efficacy outcomes showed statistically significant and clinically meaningful improvements in knee pain and function, while MRI demonstrated defect healing. More specifically, PDFS MR sequence images at 24 months showed cartilage restoration

Table 4
Imaging parameters of cartilage regeneration and repair.

Variable	Dose A (n = 6)	Dose B (n = 6)	Total (N = 12)
MRI, n (%)			
Baseline			
Normal	0	0	0
Abnormal, not clinically significant	0	1 (16.7)	1 (8.3)
Abnormal, clinically significant	6 (100)	5 (83.3)	11 (91.7)
Week 24			
Normal	2 (33.3)	2 (33.3)	4 (33.3)
Abnormal, not clinically significant	3 (50)	3 (50)	6 (50)
Abnormal, clinically significant	1 (16.7)	1 (16.7)	2 (16.7)
Month 12			
Normal	2 (33.3)	2 (33.3)	4 (33.3)
Abnormal, not clinically significant	3 (50)	4 (66.7)	7 (58.3)
Abnormal, clinically significant	1 (16.7)	0	1 (8.3)
Month 24			
Normal	3 (50)	0	3 (25)
Abnormal, not clinically significant	3 (50)	4 (66.7)	7 (58.3)
Abnormal, clinically significant	0	2 (33.3)	2 (16.7)
MOCART score, mean (SD)			
Week 24	86.0 (7.4)	60.0 (17.8)	74.4 (18.3)
Month 12	86.0 (10.8)	57.5 (10.4)	73.3 (18.0)
Change, Week 24 to Month 12	0.0 (5.0)	-2.5 (15.6)	-1.1 (10.2)
Month 24	79.0 (18.8)	60.0 (13.2)	71.9 (18.7)
Change, Week 24 to Month 24	-7.0 (13.0)	-5.0 (26.5)	-6.3 (17.3)
Dose A – Dose B comparison*			
Week 24 to Month 12	2.50 (-14.72 to 19.72)		
Week 24 to Month 24	-2.00 (-35.27 to 31.27)		
Osteoarticular X-ray, n (%)			
Screening			
Normal	3 (50)	3 (50)	6 (50)
Abnormal, not clinically significant	2 (33.3)	1 (16.7)	3 (25)
Abnormal, clinically significant	1 (16.7)	2 (33.3)	3 (25)
Month 12			
Normal	4 (66.7)	3 (50)	7 (58.3)
Abnormal, not clinically significant	2 (33.3)	3 (50)	5 (41.7)
Abnormal, clinically significant	0	0	0

Abbreviations: MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging.

* Mean difference (95% CI) between dose groups in respective changes from reference time point. Differences were not statistically significant.

(Supplemental Fig. 2CD, solid-arrows). MOCART scores in both study groups were also high, suggesting cartilage repair beginning at week 24 that was maintained up to month 24.

Previous clinical data from phase 1/2a and phase 3 trials demonstrated that the hUCB-MSC composite was safe and effective for treatment of knee articular cartilage defects in Korean patients.[19,20] Additional retrospective studies and case reports from Korea further confirmed the benefits of the hUCB-MSC composite. In a retrospective review of 128 patients with cartilage lesions and osteoarthritis, the hUCB-MSC composite significantly improved IKDC, VAS, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 1 year and at final follow up (mean follow-up 36 months); an ICRS-Cartilage Repair Assessment grade I was observed in 6 (43%) patients and grade II in 8 (57%) patients who had second-look arthroscopy after 1 year.[22] In addition, the authors reported no significant differences in 1-year or final follow-up clinical scores for patients of different ages or BMI; those with grade 1, 2, or 3 lesions; or according to lesion size; although there was a significant influence of lesion site.[22] Similar results were found in another retrospective review of 25 patients with a bipolar lesion in the medial knee compartment, in which IKDC, VAS, and WOMAC scores significantly improved from pre-operative to 1 and 2 years, and from 1 year to 2 years; and in which MRI scores improved after 1 year.[23] Comparable results were found between obese and non-obese patients, but significantly better results were found in younger patients and those with larger lesion sizes.[23] In other reported cases of malalignment with cartilage defects being treated with high tibial osteotomy (n = 125)[24] or distal femoral varus osteotomy (n = 2)[25] in conjunction with the hUCB-MSC composite, cartilage regeneration, as well as improved knee function and reduced pain, were observed up to 2 to 3 years after treatment.

The safety and efficacy outcomes found in the current study among US patients are consistent with those reported in the phase 1/2a trial with 7-year follow up of cartilage repair in Korean patients with osteoarthritic, full-thickness cartilage lesions,[19] and data from the phase 3 study conducted in Korea with hUCB-MSCs versus microfracture.[20] In particular, no unexpected safety signals were found in this or the previous reports.[19,20] Testing for immunogenicity in this study was also negative, as found in the phase 3 study.[20]

With regard to cartilage regeneration and clinical outcomes, the two doses in this study achieved improvements similar to those reported for Korean patients in the phase 3 study[20] and the retrospective reviews.[22,23] Significant pain improvements were found here at 1 year, similar to the significant pain reduction observed in the phase 3 study with hUCB-MSCs versus baseline at the same time point (and versus microfracture at 60 months).[20]

The main limitations of this study were the small sample size, open-label design, and lack of a control group, although these are features of phase 1/2 trials. While these efficacy results are preliminary, phase 3 data from Korea show that the hUCB-MSC composite offers similar benefits to patients who had articular cartilage defects of the knee, and our study build the foundation for future large-scale, phase 3 studies in the US.

In conclusion, both doses of the hUCB-MSCs + 4% sodium hyaluronate composite examined in this phase 1/2a safety study appeared to be safe and well tolerated by US patients with single ICRS grade 3–4 articular cartilage defects of the knee over 24 months. Furthermore, significant improvements were seen and maintained up to 24 months for all measured clinical outcomes compared with baseline.

Patient consent

All participants provided written informed consent before undergoing any study procedures.

Author contributions

B.J.C. contributed to the study conception and design, administrative support, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. A.H.G. contributed to the study conception and design, administrative support, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. J.T.K. and K.R.W. authors contributed in the form of provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcjp.2021.100037.

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