ORIGINAL ARTICLE

Cytopeutics umbilical cord-derived mesenchymal stem cells are associated with earlier clinical improvement compared to bone marrow aspirate concentrate with scaffold in knee cartilage injury: A Phase 1 feasibility and Phase 2 randomized controlled trial

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ABSTRACT

Introduction: Despite advances in the development of mesenchymal stem cells (MSCs), the ultimate benefits of MSCs against current cell-based therapies are still limited. This study aimed to assess the safety, feasibility, and efficacy of Cytopeutics® umbilical cord-derived MSCs (Chondrocell-EX) in patients with knee cartilage injury.

Materials and Methods: The study was conducted in two parts: a phase I feasibility study (PI) followed by a phase II randomized controlled trial (PII). Both studies were approved by UKM Research Ethics Committee (PI: UKM PPI/111/8; PII: UKM PPI/111/8/JEP-2019-304). Six patients were involved in the PI study in which all patients received Chondrocell-EX and 28 patients in the following PII study, where 17 patients received Chondrocell-EX with Hyaluronic acid (HA) (Arm A) and 11 patients received commercially available cell-based therapy, which is Bone Marrow Aspirate Concentrate (BMAC) with Hyaluronic acid-based scaffold (HA-S) (Arm B). Safety was assessed based on the occurrence of adverse events, while clinical outcomes were assessed based on the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Pain Visual Analog Scale (VAS). Second-look arthroscopy and histological assessment were performed to assess their structural outcomes at 12 months.

Results: In the PI feasibility study, significant pain reduction began at 3 months, with mean VAS decreasing from 6.83 ± 0.98 at baseline to 4.83 ± 1.17 ($p < 0.01$), 3.00 ± 0.00 at 6 months ($p < 0.01$), and 1.83 ± 0.75 at 12 months ($p < 0.01$). In the PII study, Arm A (Chondrocell-EX + HA) demonstrated significant VAS improvements at all follow-up points compared to baseline ($p < 0.001$), whereas Arm B (BMAC + HA-S) showed significant reductions only from 3 months onward. After adjustment for baseline age and VAS, Arm A achieved significantly lower pain scores than Arm B at 6 months (2.56 ± 1.41 vs 3.09 ± 1.22; $p = 0.015$) and 12 months (2.27 ± 1.49 vs 2.50 ± 1.35; $p = 0.043$), indicating earlier and sustained pain relief with Chondrocell-EX injection. Functional outcomes mirrored pain improvements. In PI, KOOS scores improved significantly from 3 months, reaching 85.83 ± 11.87 at 12 months ($p < 0.01$). In PII, KOOS increased significantly in both arms ($p < 0.001$), but Arm A demonstrated earlier gains at 3 months and significantly higher adjusted KOOS scores than Arm B at 6 ($p = 0.009$) and 12 months ($p = 0.037$). In KOOS subdomains analysis, it showed significantly greater improvements in Arm A, particularly in symptoms and stiffness, activity of daily living (ADL), pain, sport and recreation, and quality of life (QoL) at key time points.

Conclusion: Chondrocell-EX+HA treatment is more convenient, feasible, and minimally invasive with the findings suggesting that it is associated with faster functional improvement and pain relief, along with demonstration of hyaline-like cartilage regeneration, compared to the BMAC+HA-S method.

Trial Registration: NCT05016011; NMRR-19-54-46020.

KEYWORDS:
Cartilage injury, mesenchymal stem cells, BMAC, HA-based scaffold

INTRODUCTION

Knee cartilage injury is a common condition that normally occurs as a result of trauma (e.g., sports injuries), chronic

This article was accepted: 18 January 2026
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repetitive use, or progressive degeneration –often known as wear and tear – which frequently progresses to osteoarthritis (OA) due to cartilage's limited capacity for regeneration.[1] Cartilage lesions are present in over 60% of arthroscopic knee procedures, including those in athletes and OA patients.[2] With increasing age and post-injury OA risk, this prevalence is expected to grow, leading to substantial healthcare costs and early workforce exit.[3]

Current treatments focus on symptom relief rather than cartilage recovery, highlighting the need for more effective therapeutic options.[4] Bone marrow aspirate concentrate (BMAC), such as Marrow Cellution, combined with hyaluronic acid-based scaffolds (HA-S) like Hyalofast®, is widely used.[5-6] Mesenchymal stem cell (MSC) therapy is a promising approach for knee cartilage repair due to its immunomodulatory and regenerative effects via paracrine signalling, potentially delaying the need for total knee replacement.[7-8] In particular, umbilical cord-derived MSCs (UC-MSCs) have shown encouraging results in preclinical and clinical settings.[7,9] The approval of umbilical cord blood-derived MSCs (Cartistem®) in Korea for large cartilage defects further supports the clinical potential of MSCs.[10] Our previous studies demonstrated that 60% of patients with moderate to severe osteoarthritis showed improved MRI findings at 12 months post-UC-MSC treatment, including increased cartilage thickness and reduced joint pathology.[11] We also observed full cartilage regeneration in defects >2.5 cm² on arthroscopy, beyond the mainly subjective improvements reported in earlier studies.[12]

Despite progress in MSC-based therapies for knee cartilage repair, direct comparisons with established cell-based treatments remain limited. We conducted a randomized controlled trial to assess the safety and efficacy of Chondrocell-EX with hyaluronic acid (HA) versus BMAC with HA-S. This investigator-led study includes comprehensive clinical and histological evaluations.

MATERIALS AND METHODS

This study is in two phases. The first phase of the study (P1) is a feasibility study which was approved as compassionate use and designed as a single-arm, open-label trial conducted from 2016 to 2018 for patients with International Cartilage Repair Society (ICRS) grade 3 knee articular defects. The primary objective of our PI study was to assess the feasibility and safety of our intra-articular injection of Chondrocell-EX, with a secondary objective to assess the clinical and functional improvement of patients at 1-, 3-, 6-, and 12-month post-infusion.

The second phase of this study (PII) was designed as a prospective, randomized, open-label trial involving patients with ICRS grade 3 or 4 knee cartilage injury due to trauma or osteoarthritis (PII). Both studies were conducted at Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia (HCTM-UKM).

Criteria for Eligibility of Patients

In the PI study, patients were included if they had ICRS Grade 3 chondral knee injuries with cartilage defects larger than 2.5 cm² confirmed by arthroscopy, a VAS pain score above 3/10, normal blood parameters, including kidney and liver function, and were able to follow the post-operative rehab program. Exclusion criteria included autoimmune or inflammatory joint diseases, serious comorbidities, immunosuppressive drug use within six weeks, underlying knee ligament instability, significant malalignment, smoking, alcohol abuse, or a history or risk of neoplasia.

In the PII study, eligible patients were aged 18–50, with ICRS Grade 3 or 4 lesions of at least 1.0 cm², and symptoms such as swelling, pain, stiffness, or mechanical dysfunction. Patients were excluded if they had limb deformities over 10° varus or valgus, BMI ≥ 30, recent intra-articular hyaluronic acid (HA) or steroid injections (within three months), or other conditions deemed high-risk by the investigator.

Sample Size Determination

The sample size for the PII study was calculated using a formula from previous literature (Saw et al. 2013). Based on prior data, with a standard deviation (S) of 12.56 and a detectable mean difference (D) of 7.68 and using a significance level of 0.05 with 80% power, the constant (C) was set at 7.85. A minimum of 23 patients per group was required. Accounting for a 10% dropout rate, the target sample size was 25 per group (N = 50). However, due to COVID-19 restrictions, only 28 patients were successfully recruited.

Treatment Groups

In the PI study, all patients received a single intra-articular injection of 25 million cells (25×10^6) one week after undergoing a microfracture procedure. Additionally, patients were administered 2 ml of HA at 2-week intervals over four weeks, including the day of Chondrocell-EX injection.

In the PII study, patients were randomly assigned to two arms: Arm A (Chondrocell-EX+HA) and Arm B (BMAC+HA-S). Permuted block randomisation was generated using Microsoft Excel, and the sequence was concealed in sealed, opaque envelopes prepared by personnel not involved in recruitment. After enrolment, the investigator notified Cytopeutics, who opened the next envelope and assigned the patient to Arm A (Chondrocell-EX + HA) or Arm B (BMAC + HA-S). All patients underwent arthroscopic debridement prior to receiving their assigned treatment. For those patients in Arm B who refused or were unable to undergo BMAC and those patients whose cartilage defects were too large for HA-S treatments, the principal investigator can allow them to Arm A.

Preparation and Administration of Chondrocell-EX+HA (PI & PII: Arm A)

Chondrocell-EX was derived from umbilical cords of full-term, healthy infants with written parental consent. Donors underwent three generational screening for genetic, infectious, and hereditary conditions.[7,13-14] Samples were processed in a GMP-certified laboratory in Cyberjaya, Malaysia, following national stem cell research guidelines. MSCs were isolated through enzymatic digestion and cultured under standard conditions using a proprietary medium. Non-adherent cells were removed after three days,

and adherent MSCs were expanded to the desired quantity. Early-passage cells were cryopreserved for future use, and quality control included immunophenotyping, differentiation assays, and contamination testing. Details of the preparation of the cells were explained in previous literature.[7,13-14]

On the treatment day, the final cell preparation, involving thawing, washing, and suspension of 25-30 x 10^6 viable cells resuspended in 2 mL of saline, was conducted at the treatment center. Under local anesthesia, Chondrocell-EX was injected into the intra-articular route space, followed by 2 mL of HA (Orthovisc, Anika Therapeutics).

Preparation and Administration of BMAC+HA-S (PII: Arm B)

Briefly, under spinal or general anesthesia, a total of 5 mL of BMAC was extracted from the patient's posterior iliac crest using the Marrow Cellution system (Aspire Medical Innovation, Munich, Germany). A HA-S known as Hyalofast® (Fidia Advanced Biopolymers, Abano Terme, Italy) was utilized as a supporting framework for the 5 mL of cells from the Marrow Cellution. Marrow Cellution-filled Hyalofast® was positioned within the knee cartilage defects. The stability of the implanted stamps was assessed from flexion to extension using an arthroscope.

Outcome Measures

Primary Outcomes

The primary endpoints of our PI study, which were the safety assessments, included both local joint evaluation (pain at the site, persistent bleeding, knee swelling, difficulty moving the knee, and signs of infection) and basic systemic monitoring such as temperature and screening for fever, hypersensitivity, or other systemic symptoms. Assessments were performed at baseline, 1, 3, 6, and 12-months. Following that, the PII primary endpoints were based on clinical and functional assessments using the following tools: pain visual analog scale (VAS) and symptoms and functional Knee Injury and Osteoarthritis Outcome Score (KOOS) function score.

Secondary Outcomes

The PI secondary endpoints were VAS and KOOS scores, which assessed treatment efficacy in terms of symptoms and functional outcomes. Additionally, second-look arthroscopy and histological evaluations using Hematoxylin and Eosin (H&E) and Safranin-O staining were performed to assess overall tissue morphology, proteoglycan distribution, and glycosaminoglycan content of the cartilage. The OARSI histopathological grading system was employed for H&E staining assessment, meanwhile immunohistochemical (IHC) staining for collagen type I and collagen type II was evaluated semi-quantitatively using the immunoreactive score (IRS) method, a widely used and established approach for assessing IHC expression.[15-16]

In the PII, secondary endpoints included arthroscopic evaluations, which were conducted at baseline and at 12 months to assess cartilage lesions and regeneration in randomized patients from Arms A and B, whenever feasible. The biopsy samples for histological and immunohistochemical evaluation were obtained only from patients who consented to undergo second-look arthroscopy evaluation at 12 months. No routine biopsies were taken from patients who declined to do the procedure. Additionally, all reported adverse events and serious adverse events were documented and closely monitored throughout the study period.

Statistical Analysis

Descriptive data were presented as the mean (standard deviation [SD]), median (interquartile range [IQR]), and frequency (%). A t-test or Mann-Whitney test was used for between-group comparison, while a repeated measure ANOVA with Bonferroni correction for multiple comparison was used for pre- and post-treatment analysis. To account for significant baseline differences among patients following group reassignment in the PII study, age- and baseline VAS-adjusted analyses were performed using ANCOVA to evaluate outcome measures. All data were analyzed using SPSS ver. 27 (SPSS, Inc., Chicago, IL, USA), and a p-value < 0.05 was considered statistically significant. Outcome assessments were performed by the study investigators independently of sponsor involvement. Statistical analyses were conducted by independent biostatistician.

Ethics approval and consent to participate

This study was approved by UKM Research Ethics Committee (PI: UKM PPI/111/8; PII: UKM PPI/111/8/JEP-2019-304). The PII study was registered in the National Institute of Health registry of Clinical Trials (NCT05016011) and the National Medical Research Register of Malaysia (NMRR-19-54-46020). The study was conducted in accordance with the declaration of Helsinki and the Good Clinical Practice (GCP) Guidelines. Written informed consent was obtained from all participants before they enrolled as per Good Clinical Practice (GCP) Guidelines.

RESULTS

Demographics and Other Baseline Characteristics

Our PI feasibility study involved six women (mean age of 47 ± 6 years). Two patients each were classified as normal weight, overweight, and obese, respectively. The mean duration of knee pain prior to recruitment was 53 weeks (range: 3–96 weeks). All patients had previously undergone at least three months of standard management such as IA HA injections, rest, physiotherapy, and medications for pain relief. All patients completed the full 12-month follow-up period.

In our PII randomized controlled trial, 31 patients with knee cartilage injuries were initially screened for eligibility. Of these, three patients withdrew consent prior to treatment, resulting in a final cohort of 28 participants. Patients were randomized into two groups: Chondrocell-EX+HA (Arm A) and BMAC+HA-S (Arm B). Initially, 13 patients were assigned to Arm B; however, due to the lesion sizes being too large for HA-S treatment, two patients were reallocated to Arm A. As a result, Arm A included 17 patients and Arm B included 11 patients (Figure 1). These patients were analysed in the arm corresponding to the treatment they received as the reassignment happen before they received any treatment.

Table I: Baseline demographics of the study participants (N=34)

Variables	PI	PII		p-value*
	Chondrocell-EX+HA (n=6)	Chondrocell-EX+HA (n = 17)	BMAC+HA-S (n = 11)	
Age, years (mean ± SD)	47 ± 6	46 ± 10	38 ± 9	0.04
Sex				0.41
Male	0 (0.0)	4 (23.5%)	5 (45.5%)	
Female	6 (100.0%)	13 (76.5%)	6 (54.5%)	
BMI, kg/m^2 (mean ± SD)	27.11 ± 4.07	29.33 ± 6.76	28.94 ± 4.20	0.87
KOOS (mean ± SD)	46.49 ± 11.51	37.29 ± 12.28	46.27 ± 12.32	0.07
VAS (mean ± SD)	6.83 ± 0.98	7.29 ± 1.11	6.27 ± 1.35	0.022
Diagnosis				0.26
Chondral injury	-	14 (82.4%)	11 (100%)	
Osteoarthritis	6 (100.0%)	3 (17.6%)	0	

*Comparison between groups in PII (Chondrocell-EX+HA compared with BMAC+HA-S)

This resulted in the patients in Arm A being older and with a higher pain VAS score at baseline compared to Arm B (Table I and Figure 2)

Table I shows baseline demographics and characteristics for the patients. Patients in PII Arm A receiving Chondrocell-EX+HA were much older and, in more pain, based on VAS. The baseline differences observed between groups can be attributed to patient reassignment following randomization due to ineligibility for the HA scaffold procedure based on lesion conditions. No differences were observed in other baseline characteristics of patients between arms.

Safety

A total of 6 injections of Chondrocell-EX+HA. were administered in PI, and 17 injections were given in PII. Additionally, 11 administrations of BMAC+HA-S were performed for patients in Arm B of the PII. In the PI study, three out of six patients showed a minimal degree of knee effusion and swelling up to 1-month post-procedure, but resolved afterwards, and no further side effects were reported from the 3-month mark through the 12-month follow-up (Supplementary Table 1). No side effects were reported following Chondrocell-EX injections in the PII study throughout the entire 12-month follow-up period.

Efficacy

Clinical Outcomes

Visual Analog Scale (VAS) & Knee Injury and Osteoarthritis Outcome Score (KOOS)

Our PI study showed nearly no change in pain scores at 1 month. It demonstrated a significant reduction in pain scores from 3-month post-treatment, with mean VAS scores decreasing from a baseline of 6.83 ± 0.98 to 4.83 ± 1.17 (p<0.01). This reduction persisted at subsequent time points, with scores further declining to 3.00 ± 0.00 at 6 months and 1.83 ± 0.75 at 12 months (both p<0.01). In the PII study, mean VAS score in Arm A (Chondrocell-EX+HA) decreased consistently from baseline (7.21 ± 1.05) to 12-month post treatment (2.00 ± 1.11), with all follow-up time points showing significant reductions compared with baseline (all p < 0.001). In Arm B, VAS scores also declined from baseline (6.30 ± 1.42) to 12-month post treatment (2.50 ± 1.35). However, significant reduction can only be observed from 3-month onwards. Additionally, between-group comparison using age-adjusted analysis showed no significant differences in VAS at 1- and 3-month post treatment with Arm A (Chondrocell-EX+HA) group demonstrated significantly lower VAS scores compared with the Arm B (BMAC+HA-S) at 6-month (2.56 ± 1.41 vs 3.09 ± 1.22; p = 0.015) and 12-month (2.27 ± 1.49 vs 2.50 ± 1.35; p = 0.043).

In term of functional outcomes, KOOS scores in PI study significantly improved from 59.50 ± 3.56 at 3-month to 69.69 ± 6.14 at 6-month, reaching 85.83 ± 11.87 at 12-month (all p<0.01). In the PII study, when comparing with baseline, both groups demonstrated a significant improvement in KOOS scores over time (both p < 0.001). In the Arm A (Chondrocell-EX+HA) group, mean KOOS increased from 38.4 ± 12.7 at baseline to 66.1 ± 14.7 at 3-month, 72.0 ± 13.5 at 6-month, and 73.7 ± 19.2 at 12-month, with all improvements from 3-month onwards being statistically significant (p < 0.001). Similarly, Arm B (BMAC+HA-S) showed a significant change in KOOS over time (p < 0.001), with mean scores increasing from 45.8 ± 12.9 at baseline to 65.4 ± 12.6 at 6-month and 69.4 ± 12.3 at 12-month with the improvements were statistically significant only at 6- and 12-month. After adjustment for age and baseline VAS, there were no significant differences in KOOS scores between both groups at baseline, 1-month, or 3-month. However, Arm A (Condrocell-EX+HA) demonstrated significantly higher adjusted KOOS scores compared with Arm B at 6-month (p = 0.009) and 12-month (p = 0.037).

This mirrors the PII study where a significant improvements can be seen in Arm A KOOS subdomains of symptoms and stiffness (3-month: 80.4 ± 12.4, p=0.005; 6-month: 82.2 ± 16.1, p<0.001; 12-month: 85.5±14.3 p<0.001), ADL (3-month: 77.0±13.3, p=0.008; 6-month: 81.4±12.0 p<0.001; 12-month: 85.4±11.4, p= p<0.001), pain (3-month: 73.1±15.8, p=0.001; 6-month: 78.5±14.2, p<0.001; 12-month: 85.5±12.4, p<0.001) and QoL (3-month: 53.1±18.7, p<0.001; 6-month: 54.5±20.6, p<0.001; 12-month: 56.5±22.3, p<0.001). Meanwhile sports and recreation showed delayed gains, with significant changes only after 6-month (55.0 (32.5,70.0), p=0.003)

In contrast to Arm A, Arm B showed significant improvement only in QoL (3-month: 44.9±19.1, p=0.038; 6-month: 48.9±12.1, p=0.004; 12-month: 50.6±16.0, p=0.001), pain (12-month: 78.9±13.0, p=0.017) and sport and recreation (12-month: 52.5 (38.8,61.3, p=0.047).

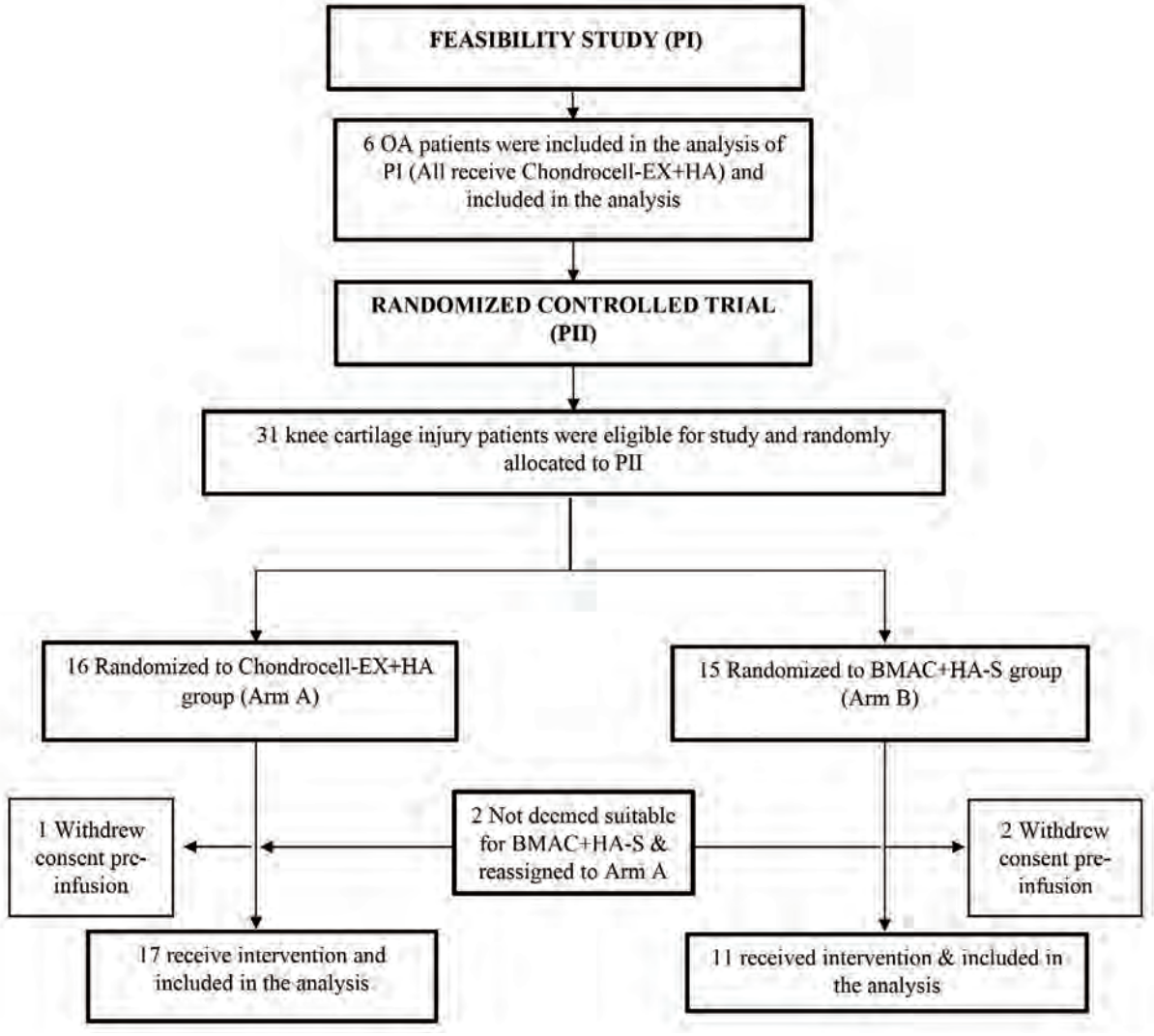

Fig. 1: Patients disposition

Between-group comparisons of KOOS subdomains were assessed using ANCOVA adjusted for age and baseline VAS. Significant difference can be observed in all of subdomains at different time point such as symptoms and stiffness subdomains showed significant differences at 6-month (p=0.037), pain subdomain at 6-month (p=0.002), ADL at 3-month (p=0.001) and 6-month (p=0.018), sport and recreation at 6-month (p=0.030) and 12-month (p=0.024) and QoL at 12-month (p=0.022). The significant differences observed in all of these subdomains were favouring Arm A compared to Arm B as Arm A showed greater improvement compared to Arm B. Details of the scores, 95% CI, effect size (Cohen'f) and p-value were provided in Supplementary Table 2-8.

Structural Outcomes

Second-look arthroscopy was performed on consented patients who had been informed about the purpose of the procedure. In our PI study, all patients showed more than 90% area of coverage with similar integrity to the non-injured cartilage surface area (Figure 3a and b) during second-look arthroscopy.[12] In our PII study, although initial lesions on the counterface area among patients in both arms were healed, patients in Arm A (Figure 3c and d) had larger lesions and exhibited improved healing of articular cartilage lesions without any incorporation of scaffold, compared to those in Arm B (Figure 3e and f). This apparent recovery eliminated the need for further invasive treatment.

Histological (H&E) & Immunohistochemical Staining Evaluation

Representative histological images of the regenerated cartilage sample post-treatment from our PI feasibility study are shown in Figure IV. H&E staining (Figure 4 A & B) of the articular cartilage biopsy specimen showed changes in the contour of the articular surface with notable bone remodelling at the articular surface. Safranin-O staining exhibited hyperchromatic and metachromatic staining, which indicates the presence of matrix proteoglycans.

The regenerated cartilage samples obtained from the five consented patients in the PI study were also stained for type I and type II collagen via immunohistochemical staining (Figure 4 C & D). Results showed that the tissues were

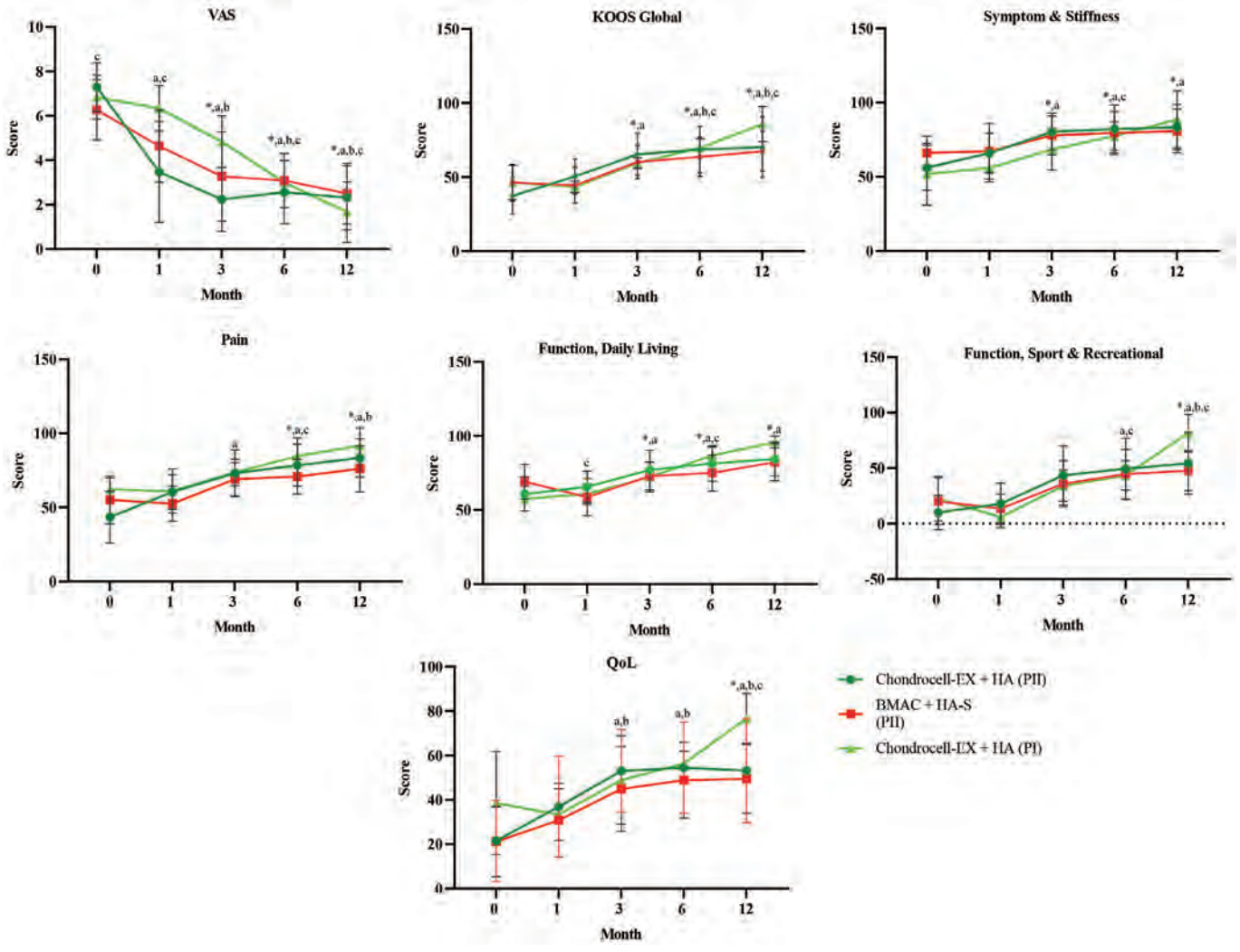

Fig. 2: Comparison of VAS, KOOS and KOOS subdomain of all patients in PI and PII throughout 12-months follow-up. p<0.05 is considered significant [*=from baseline in PI; a= from baseline in Arm A (PII); b= from baseline in Arm B (PII); c=between arms (PII)]

positively stained for type II collagen, with over 75% of the area showing positivity, whereas only foci and weak staining was observed for type I collagen. These results indicated a hyaline cartilage formation rather than fibro-cartilage formation.

DISCUSSION

Current treatments for severe knee cartilage injuries or lesions, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and viscosupplements such as HA, are primarily aimed at providing symptomatic relief rather than cartilage repair and regeneration. While autologous chondrocyte implantation (ACI) promotes hyaline-like cartilage regeneration, it has drawbacks such as the need for cell harvesting, reduced efficacy in older patients, and donor site morbidity.[15,17] Consequently, BMAC, especially with HA-based scaffolds like Hyalofast® has become a more accepted cell-based therapy for knee cartilage injuries and osteoarthritis.[18-19] BMAC provides more sustained benefits than HA alone, with clinical improvements becoming more evident beyond 12 months.[19-20] However, as an autologous therapy, it requires bone marrow aspiration, which adds procedural risk and patient discomfort. It's also unsuitable for larger lesions and shows variability in stem cell yield influenced by patient characteristics such as gender, age and health, harvest site, and technique.[21-23] Since the beneficial effects of BMAC is linked to its MSC content, this variability often translates into inconsistent clinical outcomes.[22]

A recent meta-analysis of 15 studies (n = 585) found MSCs significantly improved outcomes; BM-MSCs were superior in pain and ROM, while hUC-MSCs excelled in overall function.[20,24] While these findings highlight the therapeutic potential of hUC-MSCs, to date, no study has directly compared allogeneic hUC-MSCs with established cell-based therapies such as HA, PRP, or BMAC. Our present study addressed this important gap by comparing Chondrocell-EX, an allogeneic hUC-MSC product, to BMAC, a widely used autologous cell-based therapy.

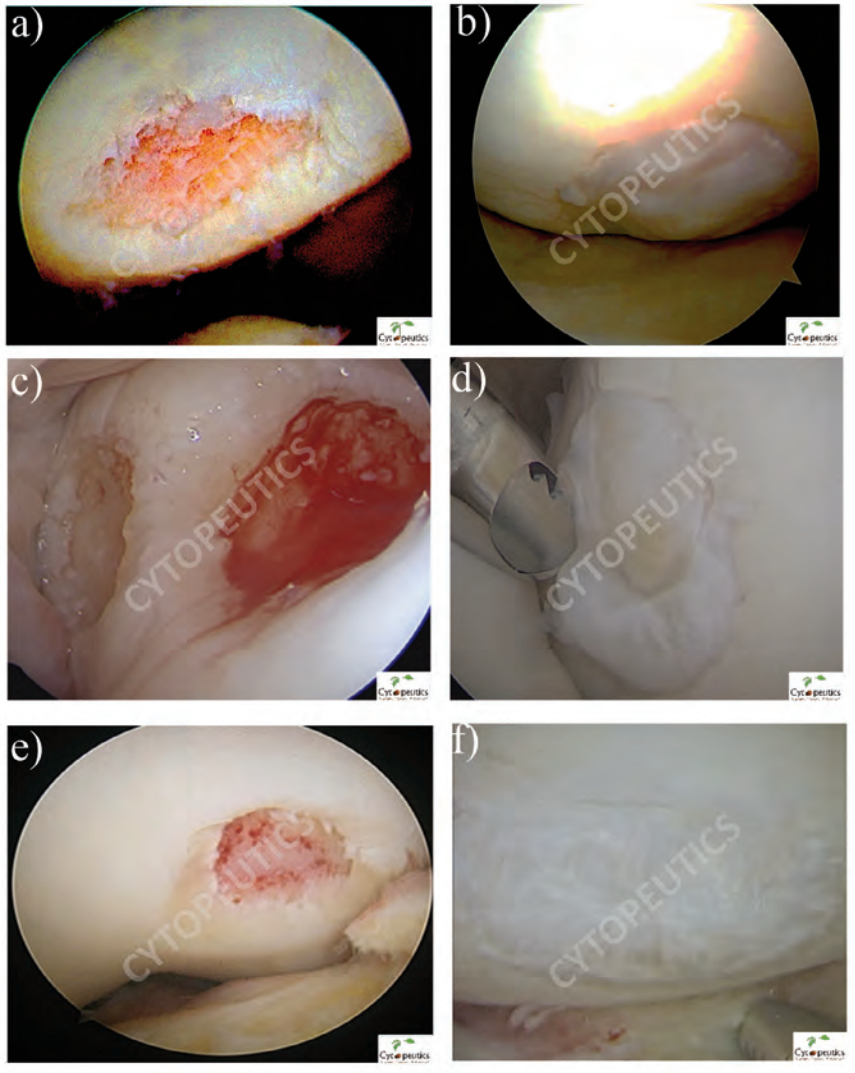

Fig. 3: PI: a) severe cartilage erosion with underlying exposed bone at baseline in PI and b) corresponding cartilage regeneration following treatment with Chondrocell-EX at 12 months follow-up. PII: c) Before Chondrocell-EX: Multiple, large cartilage lesions with complete absence of articular cartilage. d) After Chondrocell-EX: Formation of regenerated cartilage; white smooth surface and firm hyaline-like cartilage which covers the majority of cartilage defects (without HA-S). e) Before BMAC+HA-S: Single, small lesion with nearly complete absence of articular cartilage. f) After BMAC+HA-S: Formation of white regenerated cartilage covering the lesion (HA-S applied). No hypertrophy or abnormal calcification was identified in either of the arms.

Allogeneic hUC-MSCs offer a safe and consistent cell source for cartilage repair, further revolutionizing knee cartilage lesion treatment. Preclinical and clinical studies have demonstrated the safety and efficacy of intra-articular MSC injections, showing benefits such as pain reduction, functional improvement, and cartilage volume gain.[12,25-26] However, most studies have focused on bone marrow-derived MSCs, and clinical evidence specifically for hUC-MSCs in knee cartilage repair remains limited.[27]

The promising results observed in our PI study that showed significant improvements in VAS scores and KOOS functional outcomes, along with evidence of hyaline cartilage regeneration on arthroscopy, histology, and immunohistochemical staining have prompted us to further investigate these findings in our PII study. However, considering the prolonged rehabilitation period required after microfracture that delayed patient recovery, the microfracture procedure was excluded from our PII study protocol. In fact, in the PI study, pain reduction was only significant after 3 months post-Chondrocell-EX administration, likely due to the microfracture procedure performed a week prior. This delayed recovery aligns with previous findings that reported increased immobility, pain, and stiffness when MSCs were injected following microfracture.[28]

The PII study compared Chondrocell-EX+HA with BMAC+HA-S in patients with severe knee cartilage injuries. BMAC was harvested using Marrow Cellution, known for yielding higher-purity bone marrow.[3] Hyalofast®, a biodegradable HYAFF-based scaffold, was used with BMAC to support cell attachment and tissue regeneration and is an established, cost-effective option for cartilage repair.[19,29,30] Meanwhile, UC-

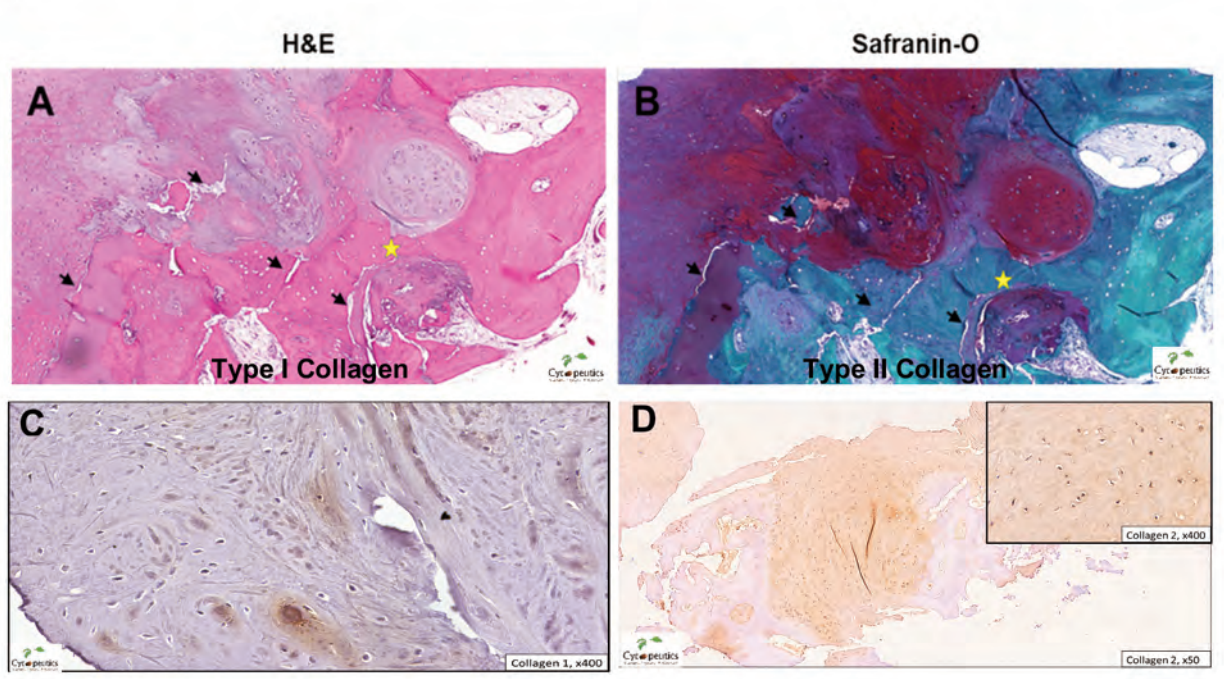

Fig. 4: Microscopic examination of a similar area reveals chondroid-rich cartilage samples post-treatment with Chondrocell-EX in A) H&E (100x), where the cartilage is stained red with Safranin-O (B) (100x). Immunohistochemical studies show that C) only a few foci of the arthroscopic biopsy are stained with type I collagen (400x), compared to D) more areas are stained with type II collagen (50x). These findings correspond to hyaline cartilage formation post-treatment with Chondrocell-EX

MSCs combined with HA have been used clinically – such as in Cartistem®, approved in 2012 with evidence showing that the combination slows cartilage degradation more effectively than HA alone.[31-32] To our knowledge, this is the first study directly comparing UC-MSCs with an active CE-marked comparator therapy widely approved in Europe and Asia.[33] Regarding the safety of Chondrocell-EX, minor side effects were observed in the PI study, that was mainly due to the microfracture, with three out of six patients experiencing mild knee effusion and swelling that resolved within a month. No major adverse events occurred beyond three months. In the PII study, no side effects were reported in either treatment arm throughout the 12-month follow-up. These findings support the safety of intra-articular UC-MSC injections, consistent with previous reviews reporting MSC therapies as generally safe.[27,34] The mild stiffness and swelling observed paralleled previous studies that observed only minor and non-significant side effects.[35] Furthermore, a 7-year follow-up study reported no long-term adverse effects after MSC injection.[31] Collectively, these results reinforce the favourable safety profile of Chondrocell-EX for knee cartilage repair.

Although the study used randomization, there were baseline differences between groups in the PII study, particularly in pain severity, patient age, and lesion size. These differences occurred because some patients were reassigned when their lesion characteristics were unsuitable for the BMAC+HA-S procedure. Despite being older and presenting with more severe pain, patients treated with Chondrocell-EX+HA showed significant pain improvement as early as one month, based on VAS score, compared with patients treated with BMAC+HA-S that only showed significant pain reduction after 3-months. This could be explained by the consistent quality and quantity of allogeneic UC-MSCs, which are derived from younger cells, do not require bone marrow aspiration, and avoid the variability in stem cell yield often observed with autologous BMAC sources.[13,21,23] Similar findings have been reported in several meta-analyses, where MSCs demonstrated pain reduction, although typically observed around six months post-treatment.[36-38] In addition to pain relief, patients treated with Chondrocell-EX with HA also experienced earlier and greater improvement in KOOS and its subdomain such as symptom and stiffness, ADL and QoL, compared to those receiving BMAC+HA-S. Cartilage regeneration was assessed via arthroscopy at baseline and 12 months. In the PI study, all six patients showed over 90% cartilage coverage after treatment with Chondrocell-EX.[12] Similar improvements were seen in both arms of the PII study, with smooth, hyaline-like cartilage covering most defects. Notably, patients in the Chondrocell-EX+HA group were generally older and had larger or multiple lesions in which HA-S use was less practical. Despite this, Chondrocell-EX still resulted in complete cartilage regeneration, as confirmed by arthroscopic evaluation.

Histological analysis confirmed type II collagen expression and increased proteoglycan content, indicating active tissue regeneration. This may be attributed to the production of ECM molecules, as well as the paracrine and anti-inflammatory effects of the treatment.[8] The immunomodulatory properties of Chondrocell-EX have also been reported.[7] The observed improvements in the Chondrocell-EX arm are particularly noteworthy, as they

were achieved through a minimally invasive approach involving a simple intra-articular injection. This contrasts with the more invasive BMAC+HA-S treatment, which requires bone marrow aspiration as well as an arthroscopy procedure that introduces additional complexity, risks, and recovery time. While achieving results equivalent or non-inferior to existing treatments would have been a significant outcome in itself, the better results demonstrated by Chondrocell-EX further emphasize its efficacy and clinical feasibility. Furthermore, Chondrocell-EX applies to patients with larger and more severe lesions, as well as older patients, who often present greater treatment challenges. This makes Chondrocell-EX a promising option, particularly in clinical settings where such patient populations require effective yet less invasive solutions.

Our study has certain limitations. These include the absence of data on important structural factors that may affect cartilage healing and clinical outcomes, such as limb alignment, lesion size or depth, and Kellgren-Lawrence grading for osteoarthritis, which may hinder a full understanding of treatment effectiveness. Secondly, baseline differences in age, VAS, and lesion complexity occur because of patients that were reassigned from the BMAC+HA-S arm to the Chondrocell-EX+HA arm when their lesions were deemed unsuitable for scaffold treatment. Although adjusted analyses were performed to mitigate these imbalances, this reassignment itself represents a limitation. Had those patients remained in Arm B, their unsuitability would have been considered treatment failure and would have lowered the efficacy estimate for BMAC+HA-S. By reassigning them to Arm A, the observed differences between groups were reduced, masking what may have been a larger treatment benefit favouring Chondrocell-EX. In addition, analyses were conducted on a per-protocol basis, which should be considered when interpreting the results. Besides that, the 12-month follow-up restricts the ability to determine the long-term durability of the regenerated cartilage. Nevertheless, previous international MSC studies have reported sustained clinical improvement for up to five years and maintained function with high survival rates up to nine years, suggesting the potential for longer-term benefit.[39-40] Finally, histological evaluation was only performed in patients who consented to second-look arthroscopy, and biopsy samples were limited to accessible, well-healed lesions, which may introduce selection bias. Nevertheless, the consistent clinical and arthroscopic improvement observed across multiple outcome measures supports the strength of our findings.

CONCLUSION

In conclusion, the present study demonstrated the safety, feasibility, and efficacy of Chondrocell-EX, which has potential for earlier pain improvement and functional gains compared to the commercially available cell-based therapy for severe knee cartilage injury. Despite using a minimally invasive intra-articular injection, findings of this study suggested that Chondrocell-EX was associated with earlier pain improvement, faster and sustained functional recovery, and showed evidence of hyaline-like cartilage regeneration, with predominant expression of collagen type II hyaline cartilage, even in older patients with multiple large cartilage injuries.

CONFLICT OF INTEREST

Sze-Piaw Chin advises Cytopeutics Sdn Bhd on regulatory, clinical and research activities. Soon-Keng Cheong sits on the medical advisory board. Nik Syazana Izyan Saffery and Muhammad Fahmi Yakop are the research project coordinators at Cytopeutics Sdn Bhd.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia (HCTM-UKM) for helping us conduct the study.

FUNDING

This study was supported by an unconditional research grant from Cytopeutics Sdn Bhd.

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Supplementary File

Table 1: Adverse events (AEs) recorded in the study

Adverse Events	Phase	N (%)	Severity	Remarks
Knee swelling / effusion	Phase I	3 (50%)	Mild	Resolved within 1 month; no recurrence
Injection-site discomfort	Phase II	–	–	–
Stiffness	Phase I	3 (50%)	Mild	Resolved within 1 month; no recurrence
Fever/systemic reaction	Phase I & II	–	–	–
Infection	Phase I & II	–	–	–
Allergic reaction	Phase I & II	–	–	–
Serious adverse events (SAEs)	Phase I & II	–	–	–

Table 2: VAS mean scores for PI and PII throughout 12-months follow-up

VAS	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	6.83 ± 0.98	7.29 ± 1.10	6.27 ± 1.35	0.022[c]	(0.20 , 2.28)	0.49
1 Month	6.33 ± 1.03	3.47 ± 2.27*	4.64 ± 1.63	0.134	(-3.36 , 0.48)	0.32
3 Month	4.83 ± 1.17*	2.24 ± 1.44*	3.27 ± 2.00*	0.125	(-2.91 , 0.38)	0.32
6 Month	3.00± 0.00*	2.56 ± 1.41*	3.09 ± 1.22*	0.015	(-2.48 , -0.29)	0.58
12 Month	1.67 ±1.37*	2.27 ± 1.49*	2.50 ± 1.35*	0.043	(-2.34 , -0.04)	0.50

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)
[c]Adjusted only for age

Table 3: KOOS Global mean scores for PI and PII throughout 12-months follow-up

KOOS Global Score	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	46.49 ± 11.51	37.3± 12.3	46.3 ± 12.3	0.493	(-15.82 , 7.83)	0.14
1 Month	43.40 ± 3.83	50.4 ± 11.8	44.5 ± 12.1	0.132	(-2.86 , 20.58)	0.32
3 Month	59.50 ± 3.56*	65.3 ± 14.0*	60.2 ± 11.3	0.153	(-3.65 , 21.89)	0.30
6 Month	69.69 ± 6.14*	68.7 ± 15.7*	63.7 ± 13.2*	0.009	(4.83 , 29.60)	0.60
12 Month	85.83 ± 11.87*	71.9 ± 19.8*	69.4 ± 12.3*	0.037	(0.73 , 21.01)	0.50

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 4: KOOS Symptom & Stiffness subdomain mean score for PI and PII throughout 12-months follow-up

KOOS Symptom & Stiffness	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	51.79 ± 20.79	56.2 ± 15.1	66.0 ± 11.4	0.319	(-20.42 , 6.92)	0.21
1 Month	55.95 ± 9.22	65.9 ± 13.3	67.2 ± 18.9	0.537	(-20.32 , 10.85)	0.13
3 Month	68.45 ± 14.00*	80.4 ± 12.4*	77.9 ± 13.0	0.587	(-9.30 , 16.08)	0.11
6 Month	77.38 ± 9.50*	82.2 ± 16.1*	79.5 ± 14.5	0.037	(0.97 , 28.66)	0.46
12 Month	88.69 ± 19.22*	85.5 ± 14.3*	83.2 ± 13.2	0.159	(-2.92 , 16.62)	0.33

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 5: KOOS Pain subdomain mean score for PI and PII throughout 12-months follow-up

KOOS Pain	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	62.04±7.79	43.5 ±17.5	55.1 ± 16.1	0.152	(-21.49 , 3.57)	0.32
1 Month	61.11±14.80	60.5 ± 11.6	52.5 ± 11.7	0.065	(-0.70 , 22.23)	0.40
3 Month	73.61±8.91	73.1 ± 15.8*	69.0 ± 11.3	0.199	(-4.91 , 22.40)	0.27
6 Month	84.72±12.27*	78.5 ± 14.2*	70.8 ± 11.7	0.002	(7.77 , 29.18)	0.74
12 Month	91.67±12.30*	85.5 ± 12.4 *	78.9 ± 13.0*	0.063	(-0.57 , 19.60)	0.44

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
aANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
bCohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 6: KOOS Activity of Daily Living (ADL) subdomain mean scores for PI and PII throughout 12-months follow-up

KOOS Activity of Daily Living (ADL)	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	57.60±8.29	60.8 ± 11.5	69.2 ± 11.7	0.085	(-21.28 , 1.47)	0.37
1 Month	60.78±6.75	65.7 ± 10.6	58.7 ± 12.4	0.001	(5.56 , 19.17)	0.80
3 Month	72.30±10.08*	77.0 ± 13.3*	72.9 ± 9.4	0.337	(-6.28 , 17.63)	0.20
6 Month	86.77±5.81*	81.4 ± 12.0*	75.0 ± 12.2	0.018	(2.46 , 23.42)	0.53
12 Month	95.84±3.99*	85.8 ± 11.4*	85.0 ± 9.5	0.266	(-4.35 , 14.93)	0.26

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 7: KOOS Sport & Recreation subdomain mean scores for PI and PII throughout 12-months follow-up

KOOS Sport & Recreation	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	22.50 ± 19.94	5.0 (0.0,20.0)	10.0 (5.0,40.0)	0.664	(-12.14 , 18.69)	0.09
1 Month	5.83 ± 9.17	10.0 (5.0,25.0)	10.0 (0.0,25.0)	0.440	(-7.60 , 16.93)	0.16
3 Month	34.17 ± 13.93	50.0 (25.0,70.0)	30.0 (20.0,50.0)	0.392	(-14.16 , 34.89)	0.18
6 Month	43.33 ± 13.29	55.0 (32.5,70.0)*	40.0 (35.0,65.0)	0.030	(2.59 , 46.82)	0.48
12 Month	81.67 ± 16.93*	65.0 (50.0,75.0)*	52.5 (38.8,61.3)*	0.024	(2.80 , 35.75)	0.56

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 8: KOOS QoL subdomain mean scores for PI and PII throughout 12-months follow-up

KOOS QoL	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	38.54±23.19	21.5 ± 18.5	21.2 ± 15.8	0.222	(-6.26 , 25.61)	0.25
1 Month	33.33±11.64	36.9 ± 22.7	30.8 ± 16.5	0.105	(-3.42 , 33.92)	0.34
3 Month	48.96±19.93	53.1 ± 18.7*	44.9 ± 19.1*	0.113	(-2.91 , 25.58)	0.35
6 Month	56.25±5.59	54.5 ± 20.6*	48.9 ± 17.1*	0.136	(-4.65 , 32.27)	0.31
12 Month	76.71±11.26*	56.5 ± 22.3*	50.6 ± 16.0*	0.022	(2.34 , 27.35)	0.57

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)