

# An Open-Label Single-Arm Phase I/IIa Study to Evaluate the Safety of Human Allogeneic Bone-Marrow-Derived Mesenchymal Stromal Cell Product StromaForte<sup>®</sup> for the Treatment of Knee Osteoarthritis

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## Research Article

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# Abstract

**Results:** MSCs were well tolerated, with no serious adverse events or major treatment-related safety signals observed during 6 months of follow-up. Treatment was associated with improvements in pain and knee-related function over this period. Immune profiling of peripheral blood mononuclear cells demonstrated a significant increase in central memory CD4<sup>+</sup> and CD8<sup>+</sup> T-cell subsets, together with enrichment of BAFF receptor-positive CD19<sup>+</sup> regulatory B-cell populations, 6 months after treatment compared to baseline. In parallel, intermediate and non-classical monocyte subsets increased 6 months after injection, suggesting sustained immunological remodeling following local MSCs administration.

**Conclusion:** A single intra-articular injection of  $50 \times 10^6$  allogeneic BM-MSCs was safe and well tolerated in grade 2–3 knee OA patients with observed improvements in clinical outcomes. The accompanying changes in adaptive and innate immune cell compartments support further investigation of MSCs-associated systemic immunomodulatory effects in osteoarthritis.

**Introduction:** Knee osteoarthritis (OA) is a highly prevalent and disabling chronic joint disorder characterized by pain, impaired function, and low-grade inflammation, for which there are currently limited disease-modifying treatment options. Mesenchymal stromal cells (MSCs) have emerged as a promising therapeutic strategy due to their immunomodulatory, anti-inflammatory, and regenerative properties. This study aimed to evaluate the safety, tolerability, and preliminary clinical efficacy of a single intra-articular injection of the allogeneic bone-marrow-derived MSCs product StromaForte<sup>®</sup> in patients with grade 2–3 knee OA.

**Methods:** In an open-label, single-arm phase I/IIa trial (ClinicalTrials.gov identifier: NCT06084988), 12 participants with Kellgren–Lawrence grade 2–3 knee OA received a single ultrasound-guided intra-articular injection of allogeneic BM-MSCs.

## 1. Introduction

Osteoarthritis (OA) is a chronic, progressive and debilitating joint disorder characterized by degeneration of articular cartilage, synovial inflammation, subchondral bone remodeling, and progressive loss of joint function, which most commonly affects the knee, hip and hand. OA is the most prevalent musculoskeletal disorder, affecting an estimated 595 million individuals in 2020,<sup>1</sup> with knee OA accounting for approximately 60% of all cases and projected to increase by 74.5% by 2050.<sup>1</sup> Hallmarks of OA include persistent joint pain, stiffness, effusion, inflammation, and impaired mobility, all of which contribute substantially to disability, reduced quality of life and loss of productivity.<sup>2,3</sup>

Age remains a risk factor for OA<sup>4</sup> development, however obesity, dietary factors, metabolic dysfunction, prior joint injury, and excessive mechanical loading are important modifiable contributors to disease onset and progression. In addition, genetic factors are estimated to account for approximately 30–60% of OA susceptibility.<sup>5</sup> OA causes substantial pain and disability, with a high burden of comorbid mental,<sup>6</sup> cardiovascular,<sup>7</sup> and metabolic disease.<sup>8</sup> Some of this burden may be linked to current management

strategies, particularly NSAID use, which is associated with gastrointestinal and cardiovascular risks.<sup>9</sup> Additional complications may arise from pain-related inactivity and the chronic inflammatory processes underlying OA. Standard treatments, including physiotherapy, weight loss, corticosteroids, and hyaluronic acid (HA),<sup>10</sup> often provide limited long-term benefit, and joint replacement remains the final option when conservative care fails. Together, these factors make OA a major source of socioeconomic cost and healthcare utilization.<sup>11–16</sup>

The Osteoarthritis Research Society International (OARSI) has in part defined OA as “a disorder involving movable joints characterized by cellular stress and extracellular matrix degradation initiated by micro- and macro-injury, which activates maladaptive repair responses, including pro-inflammatory pathways of innate immunity.”<sup>10,17</sup> And in this context, it is no surprise that mesenchymal stromal cells (MSCs) have emerged as a promising therapeutic treatment for knee OA. In addition to its well-known anti-inflammatory, regenerative, pro-angiogenic, anti-fibrotic, and immunomodulatory properties,<sup>18</sup> MSCs are known to play a vital role in both innate and adaptive immunity, and their immunomodulatory effects are exerted mainly through interactions with immune cells through cell-to-cell contact and paracrine release of bioactive factors.<sup>18</sup>

Pre-clinical and clinical studies have demonstrated the therapeutic potential of MSC-based therapies to stimulate the regeneration of cartilage, improvement in cartilage quality,<sup>19–22</sup> and pain reduction.<sup>23–25</sup> While few studies have used allogeneic BM-MSC products in patients with knee osteoarthritis, most have instead focused on adipose-derived MSCs (AD-MSCs) or autologous BM-MSCs.<sup>19,22,26</sup>

Importantly, MSCs derived from different tissue sources exhibit distinct biological and safety profiles. In particular, AD-MSCs have been reported to express higher levels of tissue factor (CD142), which may confer a greater procoagulant activity compared to BM-MSCs,<sup>27</sup> raising theoretical considerations regarding thrombotic risk. In contrast, BM-MSCs typically exhibit lower tissue factor expression and a more favorable hemocompatibility profile, potentially enhancing their safety and suitability for clinical translation.

One Phase 3 Clinical Trial in India used allogeneic BM-MSCs in combination with HA compared to HA alone and found superior results in change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score leading to market approval.<sup>28</sup> No approved product exists with MSC treatment alone in knee OA and few studies have investigated the use of allogeneic BM-MSCs for knee OA. Intra-articular administration of MSC therapy in knee OA has been associated with modulation of the local synovial inflammatory milieu in human studies, although mechanistic evidence remains limited and heterogeneous.<sup>29</sup> In a clinical study, Yanuarso et al. demonstrated that treatment with umbilical cord–derived MSCs resulted in substantial reductions in pro-inflammatory cytokines in synovial fluid, including IL-1 $\beta$ , IL-6, IFN- $\gamma$ , IL-17A, and IL-18, together with decreased matrix-degrading enzymes such as MMP-1, MMP-7, and MMP-13 at 12 weeks post-injection, supporting a direct anti-inflammatory and tissue-protective effect within the joint environment.<sup>30</sup> Consistent with these findings,

clinical and translational observations by Pers et al. demonstrated that intra-articular injection of AD-MSCs was associated with immunomodulatory effects, including shifts toward regulatory immune phenotypes and reduction of inflammatory activity in osteoarthritis patients<sup>31</sup>. Finally, human synovial analyses summarized by Sekiya et al. suggest that MSCs may enhance anti-inflammatory and homeostatic mediators such as TSG-6 and PRG-4 within the joint, contributing to reduced inflammation and improved joint lubrication.<sup>32</sup>

To date, clinical evidence supporting the use of allogeneic BM-MSCs in knee OA remains limited. Collectively, these human data support the concept that MSC therapy exerts its effects, at least in part, through modulation of the local immune and inflammatory environment of the osteoarthritic joint, although the precise cellular mechanisms and their relationship to clinical outcomes remain to be fully elucidated.

Accordingly, the present open-label, single-arm Phase I/IIa study aimed to evaluate the safety and tolerability of StromaForte<sup>®</sup>, an allogenic BM-MSC product, administered via intra-articular injection in patients with knee OA. Secondary objectives included preliminary assessment of clinical efficacy, including pain reduction and improvement in OA-related symptoms and functional outcomes.

## **2. Methods**

### **2.1 Study design:**

#### **2.1.1 Consent to participate**

All participants provided written informed consent prior to enrollment and before undergoing any study-related procedures. Participants were informed about the nature, purpose, potential risks, and benefits of the study and were given the opportunity to ask questions before providing consent. No identifiable personal information is included in this manuscript.

#### **2.1.2 Human ethics**

The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable regulatory requirements. The study was approved by the Institutional Review Board (IRB) of Burjeel Medical City, Abu Dhabi, United Arab Emirates, the Abu Dhabi Health Research and Technology Ethics Committee, Department of Health – Abu Dhabi (Approval Ref: DOH/CVDC/2023/462; approved on 16 March 2023), and the Ministry of Health and Prevention (MOHAP), United Arab Emirates (CT Ref No: RCMOHP/CT1/0146/2023; approved on 11 May 2023). The clinical trial was registered at ClinicalTrials.gov (Identifier: NCT06084988).

#### **2.1.2 Study regulatory informations**

This was an Open-Label Single-Arm Phase I/IIa Study conducted at the Burjeel Medical City Hospital in the United Arab Emirates (UAE). The study was monitored by an international independent Data and

Safety Monitoring Board (DSMB). Enrolled patients has documented X-Ray diagnosis of mild/moderate knee OA defined as Kellgren-Lawrence Grade 2–3. The full inclusion and exclusion can be found in Supplementary Table 1. A defined allogenic bone marrow derived MSCs (BM-MSCs) named StromaForte® was provided by the trial sponsor Cellcolabs Clinical SPV Limited Abu Dhabi, UAE.

This was an Open-Label Single-Arm Phase I/IIa Study conducted at the Burjeel Medical City Hospital in the United Arab Emirates (UAE). The study was monitored by an international independent Data and Safety Monitoring Board (DSMB). All participants provided written informed consent prior to enrollment and were aged  $\geq 18$  years, with documented X-Ray diagnosis of mild/moderate knee OA defined as Kellgren-Lawrence Grade 2–3. The full inclusion and exclusion can be found in Supplementary Table 1. A defined allogenic bone marrow derived MSCs (BM-MSCs) named StromaForte® was provided by Cellcolabs AB, Stockholm, Sweden.

## 2.2 MSC preparation and administration

### 2.2.1 Donor Process

The study utilized allogenic MSCs derived from the bone-marrow of healthy volunteers aged between 18–30 years old who were residing in Sweden.

All donors were screened by a primary care physician through physical examination, oral medical history interview, review of electronic health records, self-reported written questionnaire and blood tests for general haematology and biochemistry, to assess their health status and potential risk factors for diseases. Donors were required to test negatively on two occasions for HIV-1/2, HTLV-1/2, Hepatitis B, Hepatitis C and Syphilis before donation. All donors were informed of possible risks and consented to the donation of bone marrow.

Bone marrow was collected via aspiration from the posterior iliac crest under sterile conditions. In each batch produced, the MSCs were isolated and expanded from a single donor. All screening and donation procedures were performed in accordance with Swedish laws and regulations, entailing, SOSFS 2009:30, the National Board of Health and Welfare's regulations on donation and procurement of tissues and cells, and the act (2008:286) on quality and safety standards in the handling of human tissues and cells. The directive 2004/23/EC of the European parliament and of the council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells was also applied.

The BM-MSCs product StromaForte was produced under Good Manufacturing Practices in accordance with permits received from the Swedish Medical Products Agency; Tissue Establishment 5.9.2-2024-038163 and Approval for Investigational Medicinal Product (IMP) manufacturing for human use, SE-HI-MIA-23-094868.

### 2.2.2 Preparation of allogenic BM-MSCs:

The StromaForte® production process consists of isolation of MSC from bone marrow (BM) aspirate. The BM-MSCs are expanded in a growth medium supplemented with human platelet lysate (hPL). After expansion to passage 2 (P2), the cells were harvested and cryopreserved at a concentration of 10 million cells/mL in 4 ml of a cryoprotectant containing 10% DMSO and aliquoted in cryovials. The cells were tested for phenotype, cellular impurities, viability, genomic stability (karyotyping), mycoplasma, endotoxin level and sterility before release of the product, and adhered to the ISCT release criteria for MSCs.<sup>33</sup>

## **2.2.3 Injection of StromaForte**

On the day of injection, cryopreserved MSC vials were removed from liquid nitrogen storage and thawed in a 37°C water bath until a small ice chip remained. The entire reconstitution process was performed within a biosafety cabinet (BSC). Following thawing, cells were transferred into a 50 mL centrifuge tube containing 2% human serum albumin (HSA) in CliniMACS buffer (wash solution) and subjected to two sequential centrifugation steps at 500 × g for 7 minutes at room temperature, with supernatant discarded after each spin to remove the cryoprotectant. The resulting cell pellet was resuspended in wash solution for enumeration. Cell count and viability were determined using a manual hemocytometer, with a minimum viability threshold of 70% required for release. After counting, the cells were washed and centrifuged once again at 500xg for 7 minutes and then diluted to the final concentration of 50 million in 4mL of infusion solution comprising equal volumes of 20% HSA and 0.9% sodium chloride (10% HSA final concentration).

Prior to injection the knee was prepared using standard sterile techniques. All injections were administered under ultrasound guidance by an experienced orthopedic surgeon using a superolateral patellar approach under aseptic conditions. The resuspended MSCs were injected into the intra-articular knee space within 2 hours of syringe preparation. Participants were provided with post injection analgesia as required.

## **2.3 Safety and adverse events**

### **2.3.1 Safety monitoring and follow-up**

Following administration of StromaForte®, participants remained at the clinic for 2 hours for observation. Safety monitoring continued until Day 168 post-injection through a combination of onsite visits and scheduled telephone contacts. From Day 1 to Day 7, participants were contacted daily by telephone, followed by weekly contacts (± 3 days) during the first month, and then monthly contacts (± 3 days) until study completion. In addition, onsite visits were scheduled at 28d (± 7), 84d (± 7), and 168d (± 7) post-injection.

All safety data, including adverse events (AEs) and serious adverse events (SAEs), were recorded in the electronic case report form (eCRF). Both active monitoring and spontaneous reporting were used to collect safety information. Unscheduled visits or contacts outside of the planned schedule were permitted if participants experienced AEs or SAEs that required additional assessment.

## **2.4 Efficacy measurements**

### **2.4.1 Patient reported outcomes**

The following questionnaires were collected from all patients forms were provided in Arabic or English.

#### **2.4.1.1 Numeric Rating Scale (NRS)**

Pain intensity was assessed using the NRS, an 11-point scale where 0 = no pain and 10 = worst imaginable pain. Patients were instructed to choose a single number from the scale that best indicated their level of pain in the 7 days preceding.<sup>16,15</sup> The NRS was administered at baseline, 84d and 168d post injection.

#### **2.4.1.2 Knee Injury and Osteoarthritis outcome score (KOOS)**

The KOOS consists of five subscales: Pain, Other Symptoms, Activities of Daily Living (ADL), Sport and Recreation Function (Sport/Rec), and knee-related Quality of Life (QOL). Participants rated their experiences over the previous week using standardized 5-point Likert options (0–4). Scores for each item were transformed to a 0–100 scale, with 100 representing no symptoms and 0 representing extreme symptoms.<sup>34</sup> The KOOS was administered at baseline, 84d and 168d post injection.

#### **2.4.1.3 Oxford Knee Score (OKS)**

The OKS was originally developed to assess outcomes after total knee arthroplasty (TKA), it has been validated and increasingly used in non-surgical populations as well, particularly those with moderate knee OA.<sup>35</sup> The OKS comprises 12 questions, each with 5 response options, and includes questions on pain severity, mobility, and activities of daily living. For each question, answers were coded from 4 to 0 with lower values indicating worse symptoms. Individual patient scores overall were computed by adding coded answers on corresponding questions total scores were calculated with a minimum score of 0 indicating worse symptoms and 48 indicating better symptoms. Overall were computed by adding coded answers on corresponding questions and then standardized to range from 0 to 100 with higher values indicating better symptoms. The OKS was administered at baseline, 84d and 168d post injection.

#### **2.4.1.4 Lequesne Index Assessment**

The Lequesne Index Assessment evaluates three domains: pain or discomfort, maximum distance walked, and activities of daily living (ADLs). Each domain comprises specific questions, and the total score ranges from 0 (no disability) to 24 (maximum disability), with higher scores indicating greater severity.<sup>36</sup> The Lequesne Index Assessment was administered at baseline, 84d and 168d post injection.

#### **2.4.1.5 SF-36**

The SF-36 comprised of 8 subscales including; physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional wellbeing, social functioning, pain, general health and a single question at the end which asks: 'Compared to one year ago, how would you rate your health in general now?'. The SF-36 was administered at baseline and at 168d post injection.

## **2.4.2 MRI acquisition and analysis**

Magnetic resonance imaging (MRI) was performed at baseline and at 168 days post-injection using a 1.5 Tesla scanner (Toshiba Vantage Titan, Otawara, Tochigi, Japan) equipped with a dedicated knee coil. Participants were positioned supine with the knee in slight flexion to optimize joint visualization and minimize motion artefacts. No intravenous contrast agent was administered.

The imaging protocol consisted exclusively of non-contrast sequences acquired with a uniform slice thickness of 3 mm. The protocol included the following sequences: T1-weighted sagittal (TR 400–700 ms; TE 10–20 ms), proton density fat-suppressed (PD-FS) sagittal (TR 2,000–4,000 ms; TE 30–40 ms), T1-weighted coronal (TR 400–700 ms; TE 10–20 ms), PD-FS coronal (TR 2,000–4,000 ms; TE 30–40 ms), PD-FS axial (TR 2,000–4,000 ms; TE 30–40 ms), and T2-weighted axial (TR 3,000–6,000 ms; TE 80–120 ms). All sequences were acquired with a field of view ranging from 16 to 21 cm, depending on the imaging plane.

Structural assessment of osteoarthritis (OA) features was performed using the MRI Osteoarthritis Knee Score (MOAKS), a validated and reliable semi-quantitative scoring method.<sup>37–39</sup> The following features were assessed: (i) Hoffa-synovitis and effusion-synovitis (ii) Bone Marrow Lesions (BMLs) (iii) articular cartilage morphology and (iv) osteophytes.

All MRI scans were read by an experienced radiologist (A.G) who was blinded to treatment allocation.

## **2.5 Blood sampling and analysis**

### **2.5.1 Blood sample collection and peripheral blood mononuclear cell analysis**

Venous blood samples were collected from patients by a trained nurse. For immune and cytokine analysis 2 samples per time point were collected with vacutainers containing SST. Samples sat at room temperature for 15 minutes before being centrifuged as 3500 RPM for 10 minutes for collection of serum, aliquoted in 0.2 mL cryotubes and stored at -80°C until analysis. Peripheral blood mononuclear cells (PBMCs) were isolated from patient buffy coat using Ficoll density-gradient centrifugation. PBMCs were cryopreserved in 10% DMSO and stored in barcoded cryotubes at -180°C in liquid nitrogen.

### **2.5.2 Serum protein analysis**

Protein concentrations were quantified in serum samples using a multiplex bead-based immunoassay (MILLIPLEX® Human Cytokine/Chemokine/Growth Factor Panel A, Merck) performed at RISE, Sweden,

according to validated in-house method RISE-5813. The panel included 20 cytokines: CCL2, CCL3, CCL4, CXCL10, Eotaxins, IFN- $\gamma$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-7, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, TGF- $\alpha$ , TNF- $\alpha$ , TNF- $\beta$ , and VEGF-A.

Samples were thawed on ice, vortexed, and centrifuged to remove particulates. Standards, quality controls, and samples were prepared and added to 96-well plates together with antibody-conjugated magnetic beads, followed by overnight incubation at 2–8°C with agitation. After washing, detection antibodies and streptavidin-phycoerythrin were sequentially added with intermediate incubation steps. Plates were analyzed on a Bio-Plex 200 system (Bio-Rad), and fluorescence intensity was measured for each analyte. Concentrations were calculated using a five-parameter logistic (5PL) standard curve generated in Bio-Plex Manager software. All samples were analyzed in duplicate, and assay performance was validated using internal quality controls and predefined acceptance criteria, including standard recovery (70–130%) and coefficient of variation  $\leq$  30% between replicates.

## 2.5.3 Flow cytometry analysis

Immune cell phenotyping was performed on PBMCs using multiparametric flow cytometry at RISE, Sweden, according to the internal RISE method “FACS -phenotypic analysis of circulating immune cells”. The assay was designed to quantify the relative proportions of 26 major immune cells and their subsets, including T cells, B cells, natural killer (NK) cells, and monocytes, using three antibody panels (Supplementary Table 4).

Data acquisition was performed on a BD FACSLyric™ flow cytometry system equipped with three lasers and 12 fluorescence channels, allowing simultaneous measurement of up to 14 parameters per cell. Flow cytometry data were analyzed in FlowJo to determine immune cells percentages. All assays met predefined acceptance criteria, and internal controls performed as expected.

## 2.6 Statistical Analysis

### 2.6.1 Safety and efficacy

Safety was analysed using counts and frequency distributions (per events and per patients) to summaries TE-SAE, SAE, and AEs along with their causality, severity, expectedness, and outcomes. Normality of the numeric continuous questionnaires NRS, Lequesne Index Assessment, KOOS, and 36-Item Short Form Health Survey (SF-36) was assessed using Q-Q plots and histograms. Data was summarized at baseline, 84 days and 168 days post treatment and analysed by Friedmans test, except for the SF-36 which was only measured at baseline and 168 days post treatment and was analysed by Wilcoxon signed rank test. For the health change question, answers between baseline and visit 5 were compared using the McNemar-Bowker test. Statistical analysis was conducted using IBM-SPSS (version 29, Armonk, NY), figures were made using GraphPad Prism version 10. For all data the level of statistical significance was set to  $p < 0.05$ , all data is presented as mean  $\pm$  standard deviation.

### 2.6.2 MRI Analysis

Hoffa-synovitis and effusion-synovitis data is summarized descriptively and categorized into improvement, no change (stable), and worsening with Wilcoxon Signed-Rank test applied to assess for differences. BMLs were summarized in each of 15 subregions by BML size score (a single grade for size inclusive of all BMLs into one score per subregion) and the number of BMLs per subregion (BML count). The change in total score was computed between timepoints (Delta-sum), along with changes in maximum score (maximum change across timepoints).<sup>40,41</sup> A paired t-test was used to detect mean differences and a Wilcoxon Rank-Sum test applied for median differences. A Bowker's test of symmetry was used to compare maximum BML grade between timepoints and McNemar's test to compare presence vs. absence of any BML between time points. Articular cartilage morphology was scored in 14 subregions and summarized separately for surface area extent and extent of full-thickness damage. The change in total score was computed between baseline and day 168 (Delta-sum). The number with any cartilage worsening, in either surface area extent or full-thickness damage, is presented. A paired t-test was used to detect mean differences; and Wilcoxon Rank-Sum test for median differences. Binomial test of proportions was used for any worsening ( $H_0: p = 0$ ). Osteophytes were scored in each of 12 locations and the change in total score was computed between baseline and day 168 (Delta-sum)<sup>41</sup> and the number with any osteophyte worsening is presented.

## 2.6.3 Immune phenotyping

Longitudinal changes in immune cell phenotypes and serum protein biomarkers following MSC treatment were analyzed using mixed-effects modeling to account for repeated measurements within individuals and relevant covariates. Time since treatment (days) was modeled as a continuous variable using natural cubic splines to allow for nonlinear temporal effects. All models included sex and mean-centered age at treatment as fixed effects, along with a subject-specific random intercept to account for within-subject correlation.

Immune cell phenotypes and serum protein biomarkers without censoring were analyzed using linear mixed-effects models with Gaussian residuals. For serum protein biomarkers with values below the assay-specific lower limit of detection (LOD), a censored modeling approach was applied. Biomarkers with fewer than 50% of observations below the LOD were analyzed using censored Gaussian mixed-effects models in a Bayesian framework, where values below the LOD were treated as left-censored.

For non-censored models, the overall effect of time was assessed using likelihood ratio tests comparing models with and without the time term. For censored models, model performance was evaluated using leave-one-out cross-validation, and evidence for a time effect was determined based on improvements in expected log predictive density. This strategy ensured appropriate handling of censoring while maintaining model parsimony when censoring was absent.

Evidence for a time-dependent effect was assessed using likelihood ratio tests ( $p < 0.05$ ) for non-censored biomarkers. For censored biomarkers, model performance was evaluated using leave-one-out cross-validation, and strong evidence for a time effect was defined as a standardized improvement in expected log predictive density ( $|\Delta\text{ELPD}| / \text{SD}(\Delta\text{ELPD})$ ) greater than 4.

## 3. Results

### 3.1 Participant characteristics:

A total of 19 patients were screened for this study; seven patients were excluded for non-eligibility and 12 were enrolled. There was no loss to follow-up with data collection achieved at all time points from all individuals. The age of the patients was  $55.1 \pm 14.7$  years (mean  $\pm$  SD) of which 7 were male and 5 were female. The BMI for all participants was  $26.9 \pm 3.1$  kg/m<sup>2</sup> (Table 1). Independent from knee OA, n = 8 (66.7%) had at least one other co-morbidity (Table 2).

### 3.2 Primary outcome: Safety and tolerability

Within the first 2 hours after treatment, no injection-related reactions or adverse events were observed. During this observation period, there were no changes in core temperature, systolic or diastolic blood pressure, respiratory rate, or heart rate (Supplementary Table 2).

Over the study duration of 6 months, among the 12 patients who received the MSCs, 10 (83.3%) reported at least one AE, with a total of 32 AEs reported overall (Table 3). Most of the adverse events were mild, with clinical symptoms such as swelling and pain at the injection site (Table 4), which were resolved within 3 to 7 days without any medication. Out of the 32 AEs reported, 26 (81.3%) were classified as mild. Only one AE was classified as severe, a case of pain in the right knee, which was treated and resolved within five days. There was one unresolved adverse event, classified as mild, unexpected, and considered unrelated to the treatment. Most AE were categorized as general disorders and administration site conditions (84.4%), while 15.6% were classified as respiratory, thoracic, mediastinal, gastrointestinal, or endocrine disorders (Table 3). Nineteen out of the 32 AEs were expected, with most being possibly or probably related to the MSC injection. These included swelling in the knee (n = 7), pain in the knee (n = 7), ecchymosis on the superior and lateral aspect of the left knee (n = 1), decreased mobility in the right knee (n = 1), vomiting (n = 1), tenderness in the right knee (n = 1), and a burning sensation in the right knee (n = 1) (Table 4). Two-thirds (65.5%) of the AEs did not require medication, and the majority resolved within 2 to 7 days. (Table 3).

There were no major issues or safety concerns identified during physical examinations or for vital signs registered during the follow-up. As for laboratory tests, there were no clinically significant events in all parameters over time (Supplementary Table 3). Finally, there were no serious adverse events (SAEs) or Treatment Emergent SAEs (TE-SAEs) reported in the study.

### 3.3 Secondary outcomes

#### 3.3.1 Numeric Rating Scale (NRS)

Self-reported pain assessed on the NRS showed significant reductions from baseline to 84d ( $5.8 \pm 0.9$  vs  $1.8 \pm 1.5$ ,  $p < 0.001$ , (mean  $\pm$  SD)) and 168d post injection ( $5.8 \pm 0.9$  vs  $1.2 \pm 1.3 < 0.001$ , Fig. 2).

#### 3.3.2 Knee Injury and Osteoarthritis outcome score (KOOS)

An overall treatment effect was detected in 4 of the 5 subscales of KOOS (Fig. 3), for the one remaining subscale (Symptoms and Stiffness) a strong trend for an effect was observed but was not statistically significant (Fig. 3,  $p = 0.052$ ). Where Wilcoxon signed rank tests were applied, changes from baseline scores were evident at 84d post-injection for all 5 subscales ADL, Pain, Sports and Recreation and Quality of life and Symptoms and Stiffness. Where at 168d post-injection compared to baseline Wilcoxon signed rank tests only reported effects in ADL ( $p = 0.006$ ) and Quality of life ( $p = 0.028$ ) subscales. Other subscales indicated strong trends including Symptoms & Stiffness ( $p = 0.052$ ), Sports and Recreation ( $p = 0.063$ ) and Pain ( $p = 0.07$ ).

### 3.3.3 Oxford Knee Score (OKS)

Friedmans test revealed an overall treatment effect in the OKS overall score from baseline to 84d and 168d post-injection ( $66.5 \pm 25.7$ ,  $84.2 \pm 14.1$  and  $82.5 \pm 19.8$  respectively, mean  $\pm$  SD,  $p = 0.012$ , Fig. 2). When the OKS was scored into the Pain subscale an overall treatment effect was seen from baseline at 84d ( $18.5 \pm 19.4$ ,  $p = 0.014$ ) and 168d post-injection ( $\Delta 17.9 \pm 13.5$ ,  $p = 0.002$ ). OKS Function similarly demonstrated an overall treatment with Wilcoxon signed rank tests indicating improvement at 84d ( $\Delta 16.7 \pm 18.3$ ,  $p = 0.010$ ) and a trend at 168d post-injection ( $\Delta 13.3 \pm 21.1$ ,  $p = 0.09$ ).

### 3.3.4 Lequesne Index

There was a mean 43% ( $8.4 \pm 3.1$  vs  $4.8 \pm 3.6$ , mean  $\pm$  SD,  $p < 0.05$ ) and 44% decrease ( $8.4 \pm 3.1$  vs  $4.7 \pm 4.0$ ,  $p < 0.05$ ) in Lequesne severity index scores from baseline to 84d and 168d post-injection, respectively (Fig. 2,  $p = 0.017$ ).

### 3.3.5 Short-Form 36 (SF-36)

Injection of StromaForte® had no effect on any of the 8 subdomains of the SF-36 from baseline to 168d post-injection ( $p > 0.05$ ). There was a tendency for improvements on the pain subscale to be improved but this was not significantly different from baseline ( $65.0 \pm 29.2$  vs  $86.7 \pm 20.5$ ,  $p = 0.12$ ).

### 3.3.6 MRI

Over the 168d follow-up period,  $n = 10$  had stable effusion-synovitis and  $n = 2$  who were previously classified with Grade 1 effusion were then classified as Grade 0 at 168d (Table 4A, Fig. 4). No participants had change in Hoffa-synovitis from baseline to 168d post treatment (Table 5C, 5D).

Overall, Bone Marrow Lesions (BMLs) were relatively stable over the 168d period (Table 6). Three participants had within grade-improvement, and one had within grade-worsening (Table 6).

MRI confirmed no worsening of cartilage loss in knee OA patients from baseline to 168d post-injection (Table 7), with  $n = 1$  displaying within-grade improvements of cartilage surface area damage within the posterior medial femur cartilage subregion and the central medial tibia cartilage subregion. Finally, no changes in osteophyte size were observed in any participant over the 168d follow-up (Table 8).

### 3.3.7 Cytokines-Immune Cells

To evaluate the effect of the MSC therapy on the immune system, we measured the concentrations of 20 serum proteins and the frequencies of 26 immune cells in all study participants at 7 days before and 28, 84, and 168 days after MSC therapy. We found no significant changes in the levels of any of the serum proteins following MSC therapy (Supplementary Table 5 and Supplementary material 1). For the blood immune cell frequencies, we found after correction for multiple testing (FDR < 0.05) that the levels of non-classical monocytes, intermediate monocytes, CD8 + central memory T cells, and BAFFR + B-cells increased following MSC therapy, while the levels of CD8 + effector memory T cells decreased (Fig. 5, Supplementary Table 6 and Supplementary material 2).

## Discussion

This Phase I/II clinical trial was an open-label, single-arm study in adults with mild-to-moderate knee osteoarthritis to assess the safety and tolerability of a single intra-articular human allogeneic BM-MSC product StromaForte® (50 x 10<sup>6</sup>) for up to 6 months, with secondary outcomes included to assess any potential efficacy of StromaForte® regarding patient reported pain, function and structural MRI changes. As an exploratory outcome, we also investigated whether local injection of StromaForte® had any peripheral effects on cytokine or immune cells. The study was successful in meeting its primary outcome of being safe and tolerated by participants. In the immediate two hours following intra-articular injection there were no immediate reactions or AEs observed.

While many participants reported AEs (83.3%), the majority of these were considered mild and classified as general disorders or administration site conditions (84.4%) with 96.9% resolved by the close of the study. The one remaining unresolved AE was an endocrine disorder, which was considered not related to the study treatment. The observed AE profile is consistent with the literature, where systematic reviews and research papers report common AEs following intra-articular injections were typically seen at the injection site.<sup>23</sup>

The laboratory safety testing completed in the current study showed no changes in blood profiles throughout the study period, further supporting a favorable safety profile of StromaForte®. Finally, with no serious adverse events (SAEs) or treatment-emergent SAEs (TE-SAEs) reported, the results from this study are in agreement with the literature where MSC products have been used in the treatment of OA via administration of intra-articular injections.<sup>23,42</sup> Overall, MSCs have been reported to have a strong safety profile, with a 2021 systematic review reporting from 62 randomized control trials (RCTs) with a total of 3546 participants that received MSCs.<sup>43</sup> Common side effects from local implantation include swelling, and pain at injection site which is reflective in the current clinical trial.

Our study examined various self-reported questionnaires as secondary outcomes to assess the potential efficacy of StromaForte. The NRS assessment was 69% lower at 84 days and 80% lower at 168 days respectively following the injection. These changes are large and comparable to if not larger than that reported in the literature for both VAS and NRS across numerous studies with MSCs.<sup>23,25,44</sup> One consideration for the large reduction in pain may be related to a high responder rate observed in our

study with 10/12 patients responding to treatment defined by OARSI/OMERACT criteria defined as improvements in pain or function of  $\geq 50\%$  and absolute changes  $\geq 20\text{mm}$ .<sup>45</sup> Because our study did not include a control group, we cannot exclude the possibility that the observed improvements may, at least in part, reflect a placebo or expectancy effects, thereby warranting further investigations in rigorously controlled studies. Notably, control groups with saline intra-articular injections have reported 38% reduction in VAS at 12 months in mild-moderate knee OA patients, the results showed no differences compared to an AD-MS. <sup>46</sup>

KOOS, OKS total score and Lequesne Index were also generally positive throughout the study period, in general agreement with the literature assessing improvements in pain and function assessment following intra-articular injections of MSCs. <sup>23,25,26</sup> While this study was not designed to assess efficacy, the study showed promising results which support the need for larger scale studies investigating therapeutic benefit and long-term safety of StromaForte®.

There was no improvement in the SF-36 score from baseline to 6-months, to our knowledge, limited data exist with allogenic BM-derived MSCs have investigated the SF-36 and so comparisons to the literature here are hard to make. The results, while not supportive of improvement in the current study, this should be interpreted with caution. The validity of the SF-36 is well established and clear; it is considered a strong tool to assess general health status <sup>47</sup>. There may be some limitations in various aspects of assessing QoL across the entire OA spectrum which may have been missed by using the SF-36 nonetheless, our improvements in QoL as assessed by KOOS may indicate a level of improvement in QoL in knee OA patients.

An important consideration for potential disease-modifying therapies in knee OA is the absence of further structural damage to the knee joint attributable to the investigational therapy. The MOAKS analysis performed in this study reported no further worsening of knee cartilage breakdown in the 6-month period following the intra-articular injection of StromaForte®. This finding is aligned with the literature, where no incidence of damage to the knee has been reported following intra-articular injection of MSCs. We report no overall group changes were found across any MOAKS variables, which is unsurprising given the short-term follow-up and low sample size of the study which was designed to assess safety. However, a few results seen on an individual level, support the need for longer term studies with StromaForte in knee OA patients. Typically, at least 12-months of follow-up and larger sample sizes are required to see changes within the knee joint, which might include improved slowing of cartilage breakdown and reduced progression in osteophyte formation previously seen at 12-months with AD-MS. <sup>24</sup> Regardless, in this study we can confirm the safety of the StromaForte® on knee structure within 168d following a single intra-articular injection.

Despite MSC injections being administered locally within the intra-articular space, we observed effects on the systemic immune response up to six months after treatment. Among the most significant changes was an increase in CD8 + Central Memory T Cells and changes in monocytes subsets distributions. Pers et al. reported that a single intra-articular injection of autologous adipose-derived

MSCs was associated with a significant increase in circulating regulatory T cells (CD4<sup>+</sup>CD25<sup>high</sup>FOXP3<sup>+</sup>) as early as 1 month post-injection, together with expansion of transitional B-cell populations (CD24<sup>high</sup>CD38<sup>high</sup>) and a reduction in classical CD14<sup>+</sup> monocytes by 3 months, indicating a shift toward a more regulatory immune phenotype<sup>31</sup>. Also, in a randomized controlled trial, Sadri et al. observed changes in circulating T-cell compartments following intra-articular administration of allogeneic adipose-derived MSCs, including reductions in CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> T cells and modulation of activation markers over a 6–12 month period, further supporting systemic immunomodulatory effects despite local delivery.<sup>48</sup> The synovial cavity harbors a complex immune landscape, including CD4<sup>+</sup> and CD8<sup>+</sup> T cells, monocytes/macrophages, and other innate and adaptive immune populations, providing a dynamic interface for MSC–immune cell interactions. Accumulating evidence indicates that MSCs do not act in isolation but are rapidly engaged by resident immune cells following intra-articular administration. In particular, MSCs have been shown to be efficiently engulfed by monocytes/macrophages, a process that may be further enhanced by complement components present within the joint microenvironment.<sup>49</sup> Notably, MSC phagocytosis has been associated with reprogramming of classical monocytes toward intermediate monocyte subsets exhibiting anti-inflammatory properties,<sup>50</sup> supporting the concept that MSC-driven immunomodulation may be mediated, at least in part, through their active clearance and subsequent immune cell re-education. These observations raise the possibility that MSC–immune cell interactions within the joint may not remain confined to the local environment. In particular, phagocyte populations that have engaged with MSCs may subsequently recirculate, potentially contributing to the peripheral immune changes observed following intra-articular administration.

Collectively, these findings suggest that MSC therapy may exert broader immunological effects beyond the joint microenvironment; however, systematic immune profiling remains limited across clinical trials, and the relationship between these systemic changes and clinical outcomes remains to be fully established. To the contrary, we did not observe significant changes in circulating cytokine levels following MSC therapy. This finding should be interpreted with caution, as the detection threshold of the Luminex-based assays used in this study may limit sensitivity for low-abundance cytokines. In addition, the local intra-articular delivery of MSCs, together with the relatively low level of systemic immune activation typically observed in osteoarthritis, may contribute to an underestimation of subtle systemic immunological effects. These factors raise the possibility of false-negative results in the cytokine analysis. Future studies incorporating more sensitive and high-dimensional approaches, such as multiplex proteomics and complementary systems-level analyses, together with larger and controlled cohorts, will be required to more comprehensively characterize the systemic immunological impact of MSC therapy.

## Limitations

This study has several limitations. The small sample size and open-label, single-arm design without a control group limit conclusions regarding efficacy. The 6-month follow-up period may be insufficient to evaluate long-term clinical and structural outcomes. In addition, immune analyses were performed in

peripheral blood rather than within the synovial compartment and should therefore be considered exploratory. Larger randomized controlled studies with longer follow-up and integrated mechanistic analyses are required to confirm these findings.

## Conclusions

This Phase I/IIa trial demonstrated that a single intra-articular injection of the BM-MSC–derived product StromaForte at a dose of  $50 \times 10^6$  was safe and tolerated in a cohort of patients with grade 2–3 knee OA. The treatment was associated with reductions in pain assessed by NRS and improvements in function and disease severity including KOOS, OKS, and Lequesne Index. The accompanying changes in adaptive and innate immune cell compartments support the concept that MSC therapy may exert immunomodulating effects not only in the local joint, but also systemically. Larger, controlled trials with longer follow-up are warranted to confirm these findings and to determine the durability of clinical benefits and the potential for structural effects.

## Declarations

### Ethics approval and consent to participate

The clinical study was conducted in accordance with a clinical trial authorization issued by the Ministry of Health and Prevention of the United Arab Emirates (CT Ref No: RCMOHP/CT1/0146/2023). Approval to conduct the trial was granted by the Ministry of Health and Prevention following regulatory review of the submitted documentation, and ethical approval by the Abu Dhabi Health Research and Technology Ethics Committee (Ref: DOH/CVDC/2023/462; Date: 16<sup>th</sup> March 2023; Study title: An Open-Label Single-Arm Phase I/IIa Study to Evaluate the Safety of Human Allogeneic Bone-

Marrow-Derived Mesenchymal Stromal Cell Product StromaForte for the Treatment of Knee Osteoarthritis). The study was also approved by the Institutional Review Board at Burjeel Medical City (Ref No: BH/REC/040/22). All participants provided written informed consent for participation in the study and the use of samples.

### Consent for Publication

Not applicable.

### Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to participant confidentiality and restrictions related to the clinical study documentation, but may be available from the corresponding author upon reasonable request and subject to applicable regulatory, ethical, and data protection requirements.

### AI Declaration

The authors declare that they have not used AI-generated work in this manuscript.

## **Authorship contributions**

O.C. served as the physician principal investigator, performed the intra-articular injections, and was responsible for patient follow-up and clinical oversight. V.L.W. performed data analysis, interpreted data, generated the figures, and wrote the first draft of the manuscript. N.K. conceived and designed the study, developed the clinical protocol, led the scientific direction of the project, performed immunological analyses, and critically revised the manuscript.

M.B.S. contributed to the study design and protocol development, coordinated interactions with the contract research organization (CRO), supported regulatory and operational oversight, and revised the manuscript. A.O. contributed to immunological data analysis and interpretation and revised the manuscript. A.G. and J.E.C. contributed to imaging analysis, data interpretation, and manuscript revision. C.K. contributed to clinical coordination, data collection, and manuscript revision. M.M., S.M., A.S.A., and H.A.S. contributed to study discussions, interactions with regulatory authorities (Department of Health), data interpretation, and manuscript revision.

H.S. contributed to protocol development, inclusion of trial participants, study oversight, including interactions with the Data Safety Monitoring Board (DSMB), and revised the manuscript. A.L.B. contributed to manuscript revision. K.L.B. contributed to scientific input, data interpretation, and critical revision of the manuscript. A.H. contributed to clinical coordination, data acquisition, and manuscript revision. All authors reviewed and approved the final version of the manuscript.

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## **Funding Declaration**

No funding was used to support this trial. **Competing Interests**

V.L.W, A.O, A.L.B and M.B.S are full-time employees of Cellcolabs AB. N.K is a consultant for Cellcolabs AB. H.S. has been an employee of Cellcolabs AB during the trial period. Current workplace for H.S. is Tandem Health AB, Stockholm, Sweden. MM, SM and HSA have no competing interests to declare. A.G is consultant to TissueGene, ICM, Medipost, Scarcell, Peptinov, 4Moving, Pacira, Paradigm, Novartis, Coval, Formation Bio, and Levicept. He is shareholder of BICL, LLC.

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**Tables**

**Table 1. Participant Baseline Characteristics**

|                                      |                        |
|--------------------------------------|------------------------|
| <b>Characteristic</b>                |                        |
| Age (years)                          | 55.1 ± 14.7            |
| <b>Gender</b>                        |                        |
| Male (n, %)                          | 7 (58.3%)              |
| Female (n, %)                        | 5 (41.7%) <sup>†</sup> |
| <b>Race</b>                          |                        |
| White (n, %)                         | 4 (33.3%)              |
| Asian (n, %)                         | 1 (8.3%)               |
| other (n, %)                         | 7 (58.3%)              |
| <b>Ethnicity</b>                     |                        |
| Arab (n, %)                          | 9 (75%)                |
| Other (n, %)                         | 3 (25%)                |
| <b>Physical Characteristic</b>       |                        |
| Weight (kg)                          | 76.8 ± 9.7             |
| Height (cm)                          | 169 ± 10.2             |
| Body Mass Index (kg/m <sup>2</sup> ) | 26.9 ± 3.1             |
| <b>Smoking Status</b>                |                        |
| Smoker (n, %)                        | 1 (8.3%)               |
| Non-smoker (n, %)                    | 11 (91.7%)             |
| <b>Baseline questionnaire data</b>   |                        |
| NRS                                  | 5.8 ± 0.93             |
| KOOS Pain                            |                        |
| KOOS Symptoms and Stiffness          | 75.00 ± 14.04          |
| KOOS ADL                             | 72.18 ± 19.78          |
| KOOS Sports & Recreation             | 41.25 ± 28.53          |
| KOOS QoL                             | 44.79 ± 22.43          |
| OKS Total                            | 66.49 ± 16.20          |
| Lequesne Index                       | 8.4 ± 3.1              |

ADL, Activities of Daily Living; QoL, Quality of Life; OKS, Oxford Knee Score; <sup>†</sup> Indicates two females of childbearing age. Data is presented as mean ±SD or n, %.n=12.

**Table 2. Participants comorbidities at baseline**

| Comorbidities                                  | N (%)     |
|------------------------------------------------|-----------|
| Medical history other than knee Osteoarthritis | 8 (66.7%) |
| Hyperlipidemia*                                | 3 (25.0%) |
| Diabetes*                                      | 2 (16.7%) |
| Type I                                         | 1 (8.3%)  |
| Type II                                        | 1 (8.3%)  |
| Hypertension*                                  | 2 (16.7%) |
| Benign prostatic hyperplasia*                  | 1 (8.3%)  |
| Factor 5 deficiency*                           | 1 (8.3%)  |
| Gastritis*                                     | 1 (8.3%)  |
| Insertion of multi component penile prothesis  | 1 (8.3%)  |
| Total knee replacement (left knee)             | 1 (8.3%)  |
| Arthroscopic right knee surgery                | 1 (8.3%)  |

\*Ongoing at study enrolment

**Table 3. List of Adverse Events and resolution status**

| Variable                             | Safety analysis data set (n=12) |                |
|--------------------------------------|---------------------------------|----------------|
|                                      | n (%)                           | n (%)          |
|                                      | (events)                        | (participants) |
| <b>AE</b>                            | 32                              | 10 (83.3%)     |
| <b>AE Severity</b>                   |                                 |                |
| Mild                                 | 26 (81.3%)                      | 10 (83.3%)     |
| Moderate                             | 5 (15.6%)                       | 3 (25.0%)      |
| Severe                               | 1 (3.1%)                        | 1 (8.3%)       |
| Life Threatening                     | 0 (0%)                          | 0 (0%)         |
| <b>AE Seriousness</b>                |                                 |                |
| Serious                              | 0 (0%)                          | 0 (0%)         |
| Not serious                          | 32 (100%)                       | 10 (83.3%)     |
| <b>Serious AE</b>                    | 0                               | 0 (0%)         |
| Death                                | 0                               | 0 (0%)         |
| Life Threatening                     | 0                               | 0 (0%)         |
| Hospitalization                      | 0                               | 0 (0%)         |
| Disability/Incapacity                | 0                               | 0 (0%)         |
| Congenital anomaly or birth defect   | 0                               | 0 (0%)         |
| Other medically important AE         | 0                               | 0 (0%)         |
| <b>TE-SAE</b>                        | 0 (0%)                          | 0 (0%)         |
| <b>AE related to study treatment</b> |                                 |                |
| Yes                                  | 20 (62.5%)                      | 8 (66.7%)      |
| No                                   | 12 (37.5%)                      | 5 (41.7%)      |
| <b>Action taken</b>                  |                                 |                |
| Not applicable                       | 31 (96.9%)                      | 10 (83.3%)     |
| Unknown                              | 1 (3.1%)                        | 1 (8.3%)       |
| <b>Relationship to the Therapy</b>   |                                 |                |
| None                                 | 6 (18.8%)                       | 4 (33.3%)      |
| Unlikely                             | 6 (18.8%)                       | 4 (33.3%)      |
| Possible                             | 4 (12.5%)                       | 2 (16.7%)      |
| Probable                             | 7 (21.9%)                       | 3 (25.0%)      |
| Definite                             | 9 (28.1%)                       | 5 (41.7%)      |

|                                |            |           |
|--------------------------------|------------|-----------|
| <b>Expectedness</b>            |            |           |
| Expected                       | 19 (59.4%) | 8 (66.7%) |
| Not Expected                   | 13 (40.6%) |           |
| <b>Medication given for AE</b> |            |           |
| Yes                            | 11 (34.4%) | 7 (58.3%) |
| No                             | 21 (65.6%) |           |
| <b>AE outcome</b>              |            |           |
| Recovered/resolved             | 31 (96.9%) | 9 (75%)   |
| Recovering/resolving           | 0 (0%)     | 0 (0%)    |
| Not recovered/not resolved     | 1 (3.1%)   | 1 (8.3%)  |
| Resolved with sequelae         | 0 (0%)     | 0 (0%)    |
| Fatal                          | 0 (0%)     | 0 (0%)    |
| Unknown                        | 0 (0%)     | 0 (0%)    |

AE, Adverse events; Treatment Emergent- Serious Adverse Events, (TE-SAE).

**Table 4:Adverse Event Descriptions**

| <b>AE Description</b>                                       | <b>n (%)</b>      |
|-------------------------------------------------------------|-------------------|
| <b>General Disorders and Administration Site Conditions</b> | <b>27 (84.4%)</b> |
| Pain in the right knee                                      | 6 (18.8%)         |
| Swelling in the right knee                                  | 5 (15.6%)         |
| Pain in left knee                                           | 3 (9.4%)          |
| Swelling at the left knee                                   | 3 (9.4%)          |
| Tenderness in right knee                                    | 1 (3.1%)          |
| Rash on the left knee                                       | 1 (3.1%)          |
| Hamstring pain in the right knee                            | 1 (3.1%)          |
| Hamstring tendinitis due to over activity                   | 1 (3.1%)          |
| Hypopigmentation in the left knee                           | 1 (3.1%)          |
| Ecchymosis superior and lateral aspect of left knee         | 1 (3.1%)          |
| Burning sensation in the right knee                         | 1 (3.1%)          |
| Decreased mobility in the right knee                        | 1 (3.1%)          |
| Body pain                                                   | 1 (3.1%)          |
| Fever                                                       | 1 (3.1%)          |
| <b>Respiratory, Thoracic, and Mediastinal Disorders</b>     | <b>3 (9.4%)</b>   |
| Sore throat                                                 | 1 (3.1%)          |
| Dry cough                                                   | 1 (3.1%)          |
| Nasal congestion                                            | 1 (3.1%)          |
| <b>Gastrointestinal Disorders</b>                           | <b>1 (3.1%)</b>   |
| Vomiting                                                    | 1 (3.1%)          |
| <b>Endocrine Disorders</b>                                  | <b>1 (3.1%)</b>   |
| Nodule of the left thyroid lobe TIRADS 3*                   | 1 (3.1%)          |

\*Mild, not serious, not related to study treatment, not expected, still ongoing

**Table 5A-D. Effusion-synovitis and Hoffa-synovitis grading at baseline and 168 d post a single intra-articular injection of StromaForte®**

Table 5A. Effusion-synovitis grading (0–3)

| Grade | Baseline, n (%) | 168 d post, n (%) |
|-------|-----------------|-------------------|
| 0     | 6 (50.0%)       | 8 (66.7%)         |
| 1     | 5 (41.7%)       | 3 (25.0%)         |
| 2     | 1 (8.3%)        | 1 (8.3%)          |
| 3     | 0 (0%)          | 0 (0%)            |

n=12 at baseline and 168d post.

**Table 5B. Change summary of effusion-synovitis grading**

| Outcome            | Improved, n (%) | Stable, n (%) | Worsened n (%) | Median change | p-value* |
|--------------------|-----------------|---------------|----------------|---------------|----------|
| Effusion-synovitis | 2 (16.7%)       | 10 (83.3%)    | (0%)           | 0             | 0.5000   |

\*Wilcoxon Signed-Rank test was applied. n=12 at baseline and 168d post.

**Table 5C. Hoffa-synovitis (0–3)**

| Grade | Baseline, n (%) | 168d post, n (%) |
|-------|-----------------|------------------|
| 0     | 6 (50.0%)       | 6 (50.0%)        |
| 1     | 4 (33.3%)       | 4 (33.3%)        |
| 2     | 2 (16.7%)       | 2 (16.7%)        |
| 3     | 0 (0%)          | 0 (0%)           |

n=12 at baseline and 168d post.

## 5D. Change Summary

| Outcome         | Improved n (%) | Stable n (%) | Worsened n (%) | Median change | p-value |
|-----------------|----------------|--------------|----------------|---------------|---------|
| Hoffa-synovitis | 0 (0%)         | 12 (100%)    | 0 (0%)         | 0             | --      |

n=12 at baseline and 168d post.

**Table 6. Bone Marrow Lesion scores from MOAKSat baseline and 168 d post a single intra-articular injection of StromaForte®**

| Variable                             | Baseline                                     | 168 d post                                                  | Change<br>(Post–Baseline)                                        | p-value |
|--------------------------------------|----------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------|---------|
| BML_sum mean ± SD                    | 2.8 ± 3.1                                    | 3.1 ± 3.3                                                   | 0.25 ± 1.1                                                       | 0.4627  |
| BML_sum median [IQR]                 | 2.5 [0.0, 4.5]                               | 2.0 [0.0, 5.5]                                              | 0 [0, 1.0]                                                       | 0.6250  |
| BML_count median [IQR]               | 2.5 [0.0, 5.5]                               | 2.0 [0.0, 6.0]                                              | 0 [0, 0]                                                         | 1.0     |
| BML_max grade distribution (0/1/2/3) | 0: 5 (41.7%)<br>1: 4 (33.3%)<br>2: 3 (25.0%) | 0: 4 (33.3%)<br>1: 5 (41.7%)<br>2: 1 (8.3%)<br>3: 2 (16.7%) | 0: 7 (58.3%)<br>1 [worsen by 1 grade]: 5 (41.2%)                 | 0.8088  |
| BML_any n (%)                        | 7 (58.3%)                                    | 8 (66.7%)                                                   | None-none: 4 (33.3%)<br>Any-any: 7 (58.3%)<br>None-any: 1 (8.3%) | 0.3173  |

BML, bone marrow lesions; data analysed by Wilcoxon Rank-Sum test for median differences; Bowker's test of symmetry for paired categorical data; McNemar's test for paired binary data. n=12 at baseline and 168d post.

**Table 7. Articular cartilage morphology (14 subregions) assessed by MOAKSat baseline and 168 d post a single intra-articular injection of StromaForte®**

| Variable                      | Baseline       | 168 d post     | Change<br>(Post–Pre) | p-value |
|-------------------------------|----------------|----------------|----------------------|---------|
| Cart_Area_sum mean ± SD       | 9.0 ± 7.0      | 9 ± 7.0        | 0 ± 0                | --      |
| Cart_Area_sum median [IQR]    | 7.5 [3, 15]    | 7.5 [3, 15]    | 0 [0, 0]             | --      |
| Cart_FT_sum mean ± SD         | 4.4 ± 4.5      | 4.3 ± 4.6      | -0.2 ± 0.6           | 0.3388  |
| Cart_FT_sum median [IQR]      | 3.5 [0.5, 6.5] | 2.5 [0.5, 6.5] | 0 [0, 0]             | 1.0     |
| Any cartilage worsening n (%) |                |                | 0 (0%)               | 1.0     |

Cart\_Area\_sum, summed MOAKS cartilage area score across all 14 subregions. Cart\_FT full-thickness cartilage loss score across 14 subregions. paired t-test for mean differences; Wilcoxon Rank-Sum test

for median differences; binomial test of proportions for any worsening (H0: p=0).n=12 at baseline and 168d post.

Table 8A.Osteophyte size (Safety evaluation) (12 locations)

| Variable                            | Baseline                                                    | 168 d post                                                  | Change                      | p-value |
|-------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-----------------------------|---------|
| OP_sum mean ± SD                    | 3.3 ± 4.3                                                   | 3.3 ± 4.3                                                   | 0 ± 0                       | --      |
| OP_sum median [IQR]                 | 1.5 [0.0, 6.0]                                              | 1.5 [0.0, 6.0]                                              | 0 [0, 0]                    | --      |
| OP_max grade distribution (0/1/2/3) | 0: 5 (41.7%)<br>1: 4 (33.3%)<br>2: 2 (16.7%)<br>3: 1 (8.3%) | 0: 5 (41.7%)<br>1: 4 (33.3%)<br>2: 2 (16.7%)<br>3: 1 (8.3%) | No participants with change | --      |

OP, Osteophyte.n=12 at baseline and 168d post.

Table 8B. Additional Osteophyte Safety analysis.

| Safety Outcome                             | n (%)  | 95% CI       |
|--------------------------------------------|--------|--------------|
| Participants with any osteophyte worsening | 0 (0%) | (0% - 26.5%) |

Figures

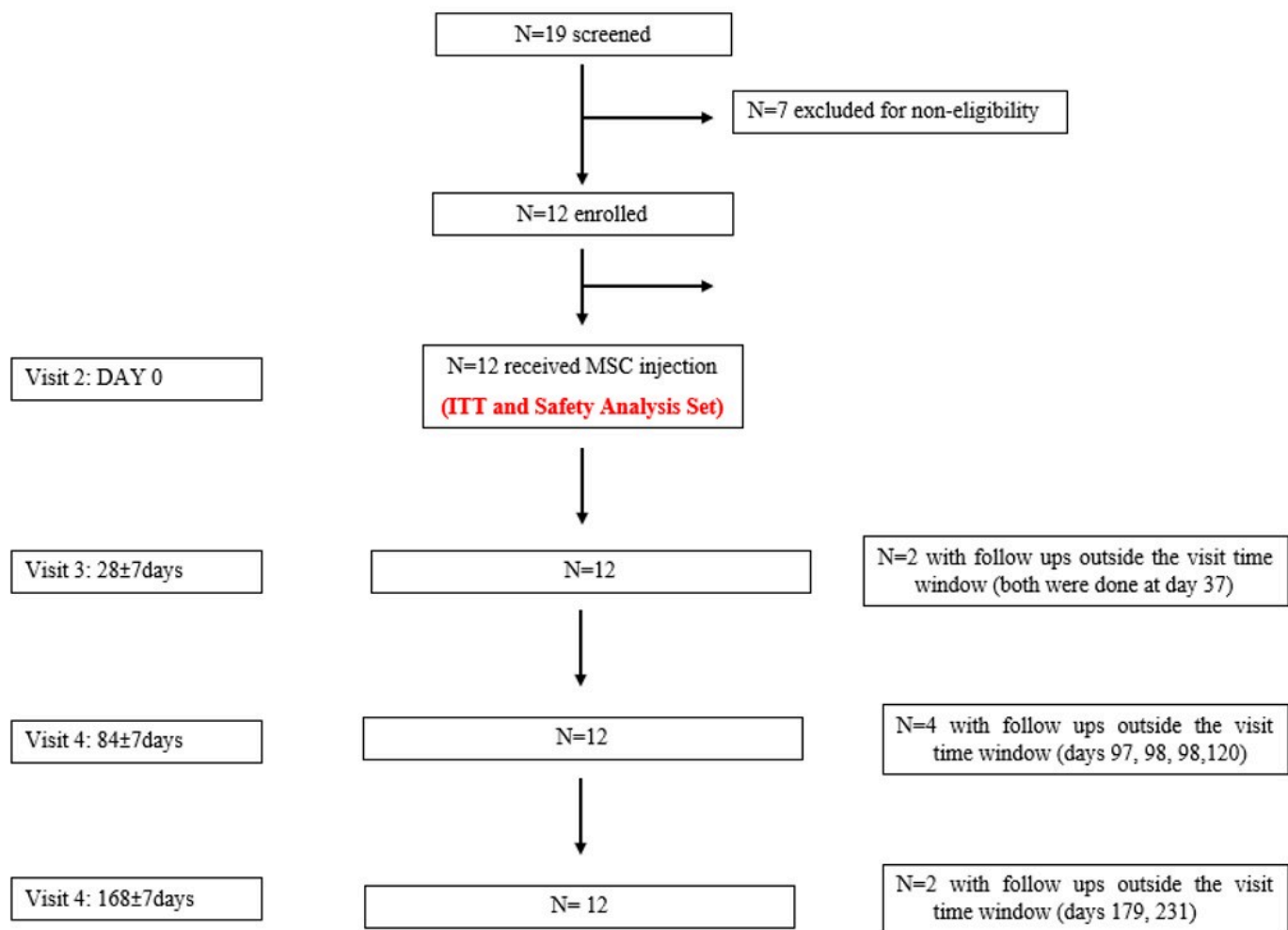


Figure 1

Participants flow chart for enrolment and trial completion

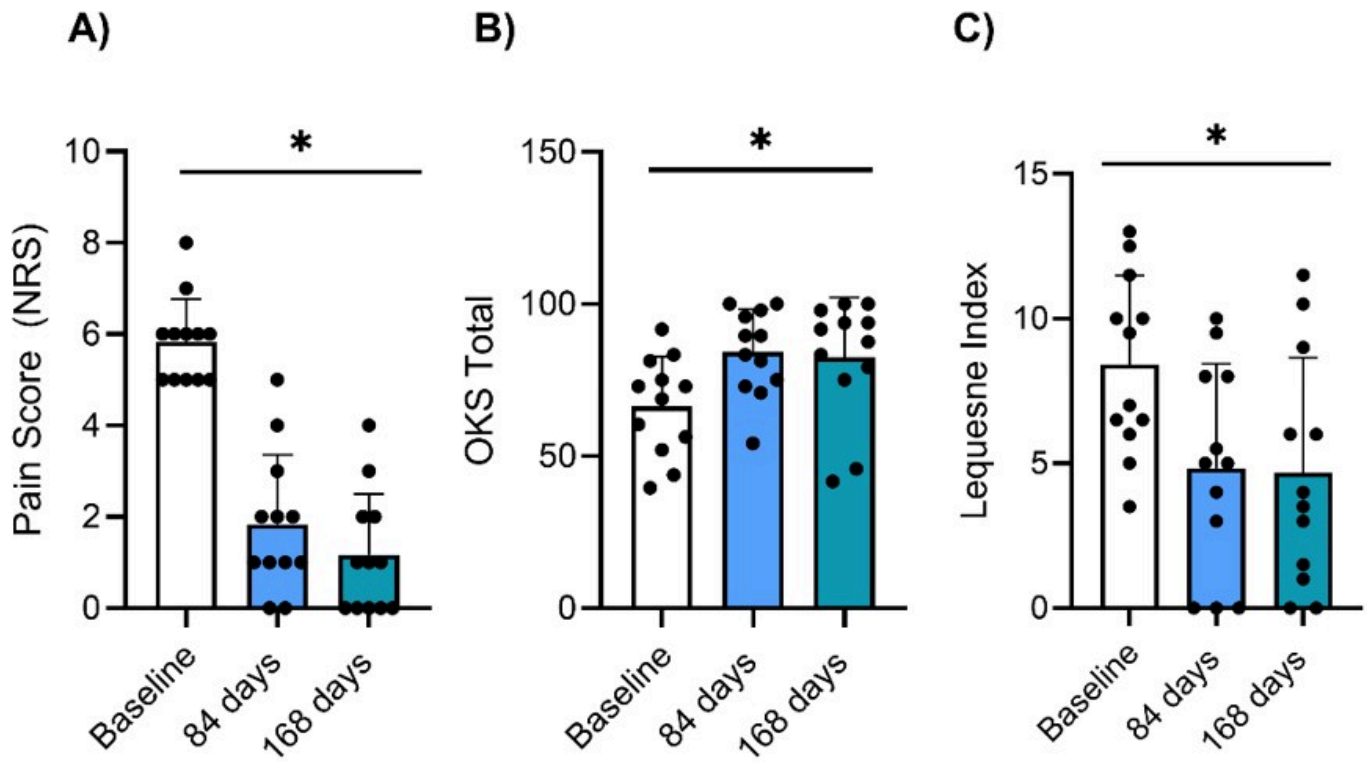


Figure 2

### NRS, OKS and Lequesne index score's following a single injection of StromaForte®

Participants self reported scores from the A) Numeric Rating Score (NRS), B) Oxford Knee Score (OKS) total and C) Lequesne Index. Data shown from baseline, 84 d and 168d following a single intra-articular injection of StromaForte®. Data analysed by Friedmans test, \*indicates  $p < 0.05$ . Data presented as mean  $\pm$  SD.  $n = 12$  at baseline and 168d post.

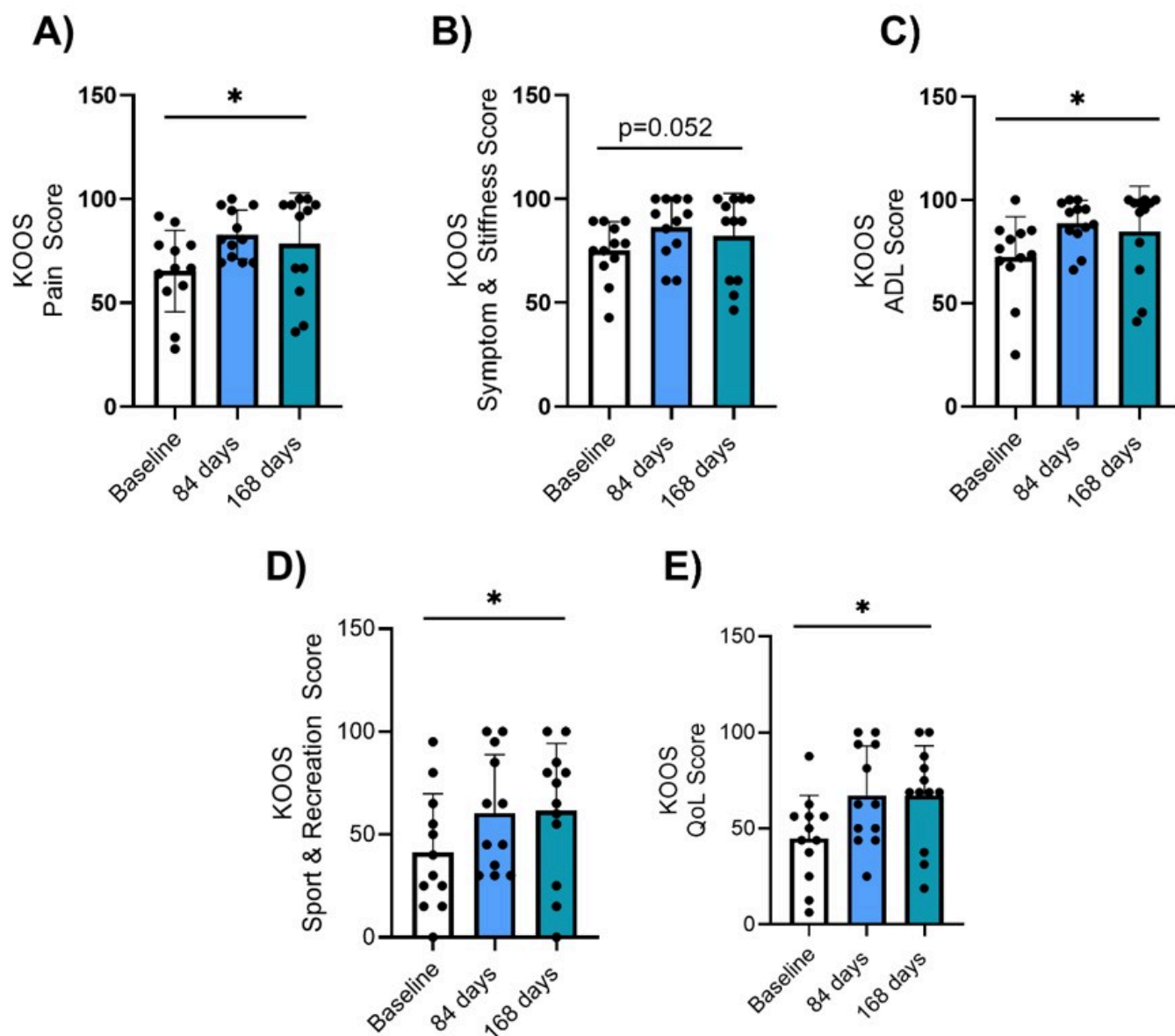
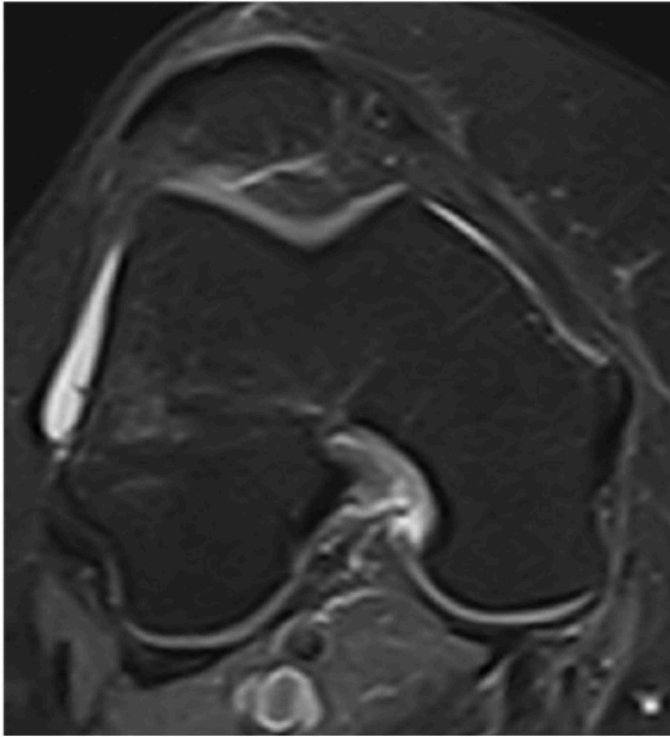


**Figure 3**

### KOOS subscale scores following a single injection of StromaForte®

Participants self-reported scores from the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales A) Pain, B) Symptoms and Stiffness, C) Activities of Daily Living (ADL) score, D) Sport & Recreation Score, E) Quality of Life (QoL) score. Data shown from baseline at baseline, 84 d and 168d following a single intra-articular injection of StromaForte®. Data analysed by Friedmans test, \*indicates  $p < 0.05$ . Data presented as mean ± SD. n=12 at baseline and 168d post.

**A)**



**B)**

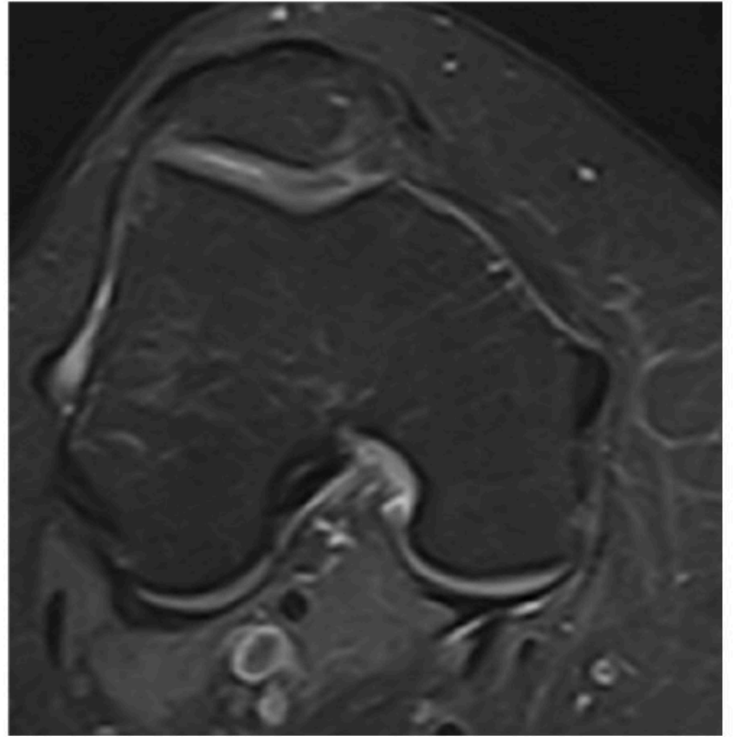


**Figure 4**

**MRI image of improved grading of effusion and synovitis scored by MOAKS at baseline (A) and 168 d post MSC treatment (B).**

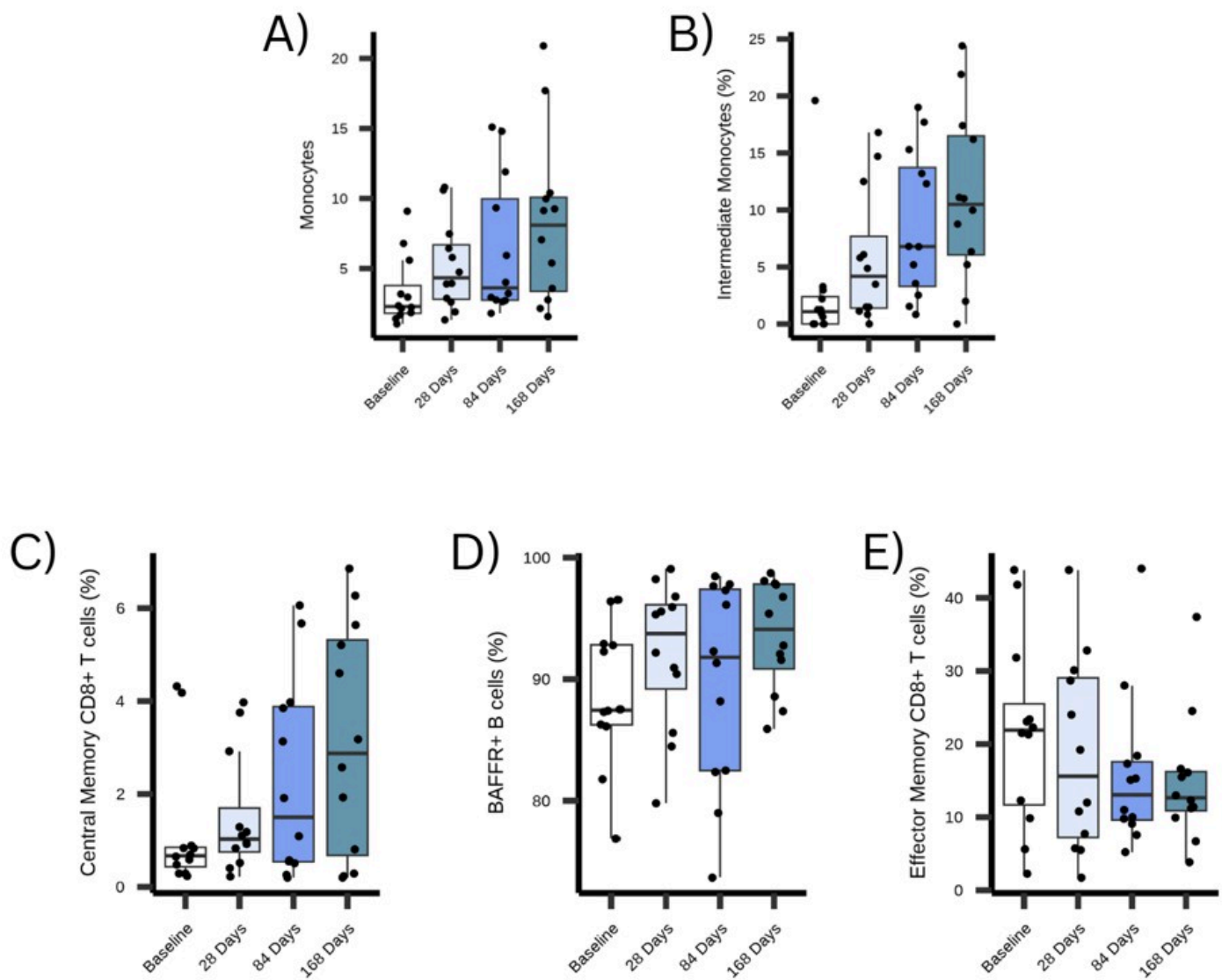


**Figure 5**

### **Blood immune cell frequencies following a single injection of StromaForte®**

Participant blood immune cell frequencies in peripheral blood mononuclear cells (PBMCs) of A) monocytes as a percentage of all PBMCs, B) intermediate monocytes as a percentage of all monocytes, C) CD8+ central memory T cells as a percentage of CD8+ T cells, D) BAFFR+ B cells as a percentage of all B cells, and E) CD8+ effector memory T cells as a percentage of CD8+ T cells. Boxes show the interquartile range (25th–75th percentiles) with the median indicated by the central line, whiskers extend to the most extreme values within 1.5×IQR. Raw data points are shown as a jitter.

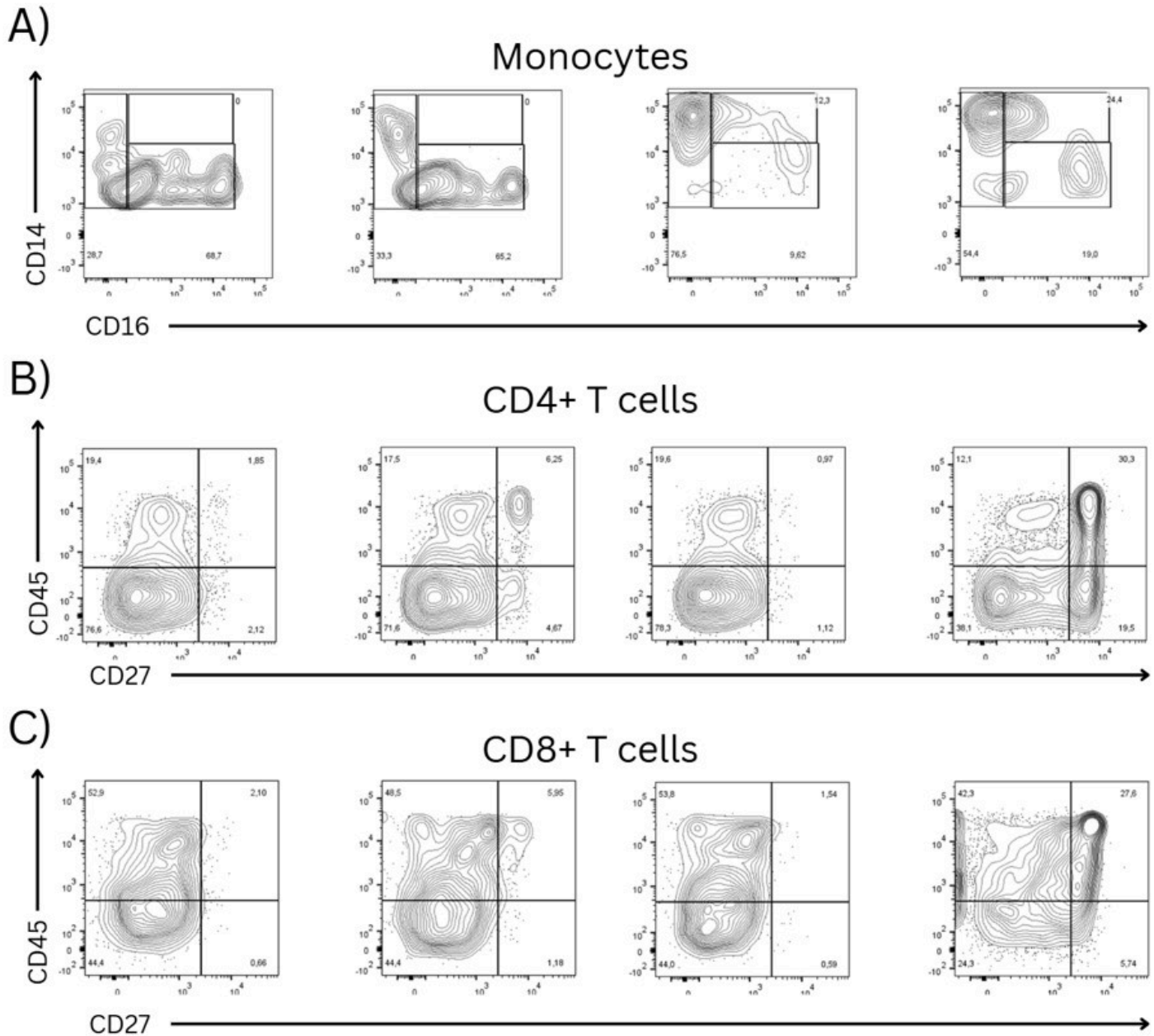


**Figure 6**

### Flow cytometry gating examples

Flow cytometry gating examples for A) monocyte subsets, B) CD4+ T cell subtypes, and C) CD8+ T cell subtypes.