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Safety and efficacy of an allogeneic adipose-derived mesenchymal stem cell preparation in the treatment of knee osteoarthritis: A Phase I/IIa randomised controlled trial

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ABSTRACT

Objectives: To assess the safety and efficacy of an allogeneic adipose-derived mesenchymal stem cell preparation (MAG200) in the treatment of knee osteoarthritis over 12 months.

Design: A single-centre, double-blind, ascending dose, randomised controlled trial. 40 participants with moderate knee osteoarthritis were randomised to receive a single intra-articular injection of MAG200 (dose cohorts:10, 20, 50, 100 $\times$ 10^6 cells) or placebo. Primary objectives were safety and efficacy according to a compound responder analysis of minimal clinically important difference in pain (numerical pain rating scale [NPRS]) and function (Knee Injury and Osteoarthritis Outcome Score - Function in Daily Living subscale [$KOOS_{ADL}$]) at month 12. Secondary efficacy outcomes included changes from baseline in patient reported outcome measures and evaluation of disease-modification using quantitative MRI.

Results: Treatment was well tolerated with no treatment-related serious adverse events. MAG200 cohorts reported a greater proportion of responders than placebo and demonstrated clinical and statistically significant improvement in pain and clinically relevant improvement in all KOOS subscales. MAG200 demonstrated a reproducible treatment effect over placebo, which was clinically relevant for pain in the 10 $\times$ 10^6 dose cohort (mean difference NPRS:-2.25[95%CI:-4.47,-0.03, p = 0.0468]) and for function in the 20 $\times$ 10^6 and 100 $\times$ 10^6 dose cohorts (mean difference $KOOS_{ADL}$:10.12[95%CI:-1.51,21.76, p = 0.0863] and 10.81[95%CI:-1.42,23.04, p = 0.0810] respectively). A trend in disease-modification was observed with improvement in total knee cartilage volume in MAG200 10, 20, and 100 $\times$ 10^6 dose cohorts, with progression of osteoarthritis in placebo, though this was not statistically significant. No clear dose response was observed.

Conclusion: This early-phase study provides supportive safety and efficacy evidence to progress MAG200 to later-stage trial development.

Trial registration: ACTRN12617001095358/ACTRN12621000622808.

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1. Introduction

Globally over 650 million individuals aged 40 years or more are affected by knee osteoarthritis (OA) [1]. This progressive condition is a leading cause of disability, and is associated with significant economic and healthcare burden [1]. In the absence of disease-modifying treatment, the current management of knee OA remains limited [2], with surgical total knee replacement (TKR) considered when conservative therapies have failed. Whilst registry data supports long-term durability of TKR [3], clinically meaningful pain reduction and functional outcomes can be sub-optimal in approximately 30% of patients [4], with the risk of serious post-surgical complications including infection, myocardial infarction, stroke and death not insignificant [5].

Intra-articular (IA) therapies, which aim to improve pain and function, are frequently considered [6]. The most common IA treatments are corticosteroids and viscosupplements (hyaluronic-acid) with increased use of orthobiological preparations including platelet-rich plasma [7]. Whilst corticosteroids are recommended in international guidelines there is an acceptance that they have limited benefit beyond 3–4 weeks and are associated with an observed increase in OA progression with repetitive use [8]. Comparably, viscosupplements demonstrate unpredictable improvement beyond 6 months and have limited benefit over placebo [9], with recent systematic review and meta-analysis not supporting their broad use in the treatment of knee OA [10]. Whilst PRP is associated with modest clinical benefit up to 12 months, its use is not recommended in current international clinical practice guidelines due to lack of evidence to definitively recommend its use [11]. Importantly, current therapies are not associated with disease-modification [12], and therefore have limited impact on the increasing incidence of TKR and associated socioeconomic burden.

The use of mesenchymal stem cells (MSCs) has emerged as a promising approach to address the unmet clinical need of OA [13]. MSCs are multipotent cells with the ability to differentiate into osteoblasts, adipocytes and chondroblasts [14]. MSCs are observed to directly modulate inflammation by suppression of inflammatory cell proliferation, reduction in pro-inflammatory cytokines (IL-1 and IL-6) with polarisation of M1 macrophages to an anti-inflammatory M2 phenotype in addition to inhibition of TNFα with expression of solubleTNF receptor-1 (sTNFR1) [15]. Reduction/inhibition of such inflammatory cytokines leads to reduced expression of nerve growth factor with inhibition of nociceptive sensitisation leading to improvement in pain [16]. Additionally, MSC secretion of trophic cytokines, including transforming growth factor (TGFβ1), may result in local tissue repair [17,18]. The ability of MSCs to differentiate into chondrocytes, as well as their observed immunomodulatory/anti-inflammatory and trophic/reparative actions [19], has fuelled interest in their application in OA [20]. A growing body of pre-clinical and clinical evidence supports sustained improvements in pain and function after IA injections of MSCs [21,22], in addition to observed disease-modification with stabilisation or delay in OA progression [13,23].

Whilst autologous MSC therapies continue to be investigated [24], methods to achieve isolated autologous MSC preparations are labour intensive, require a surgical harvest procedure and are costly, therefore limiting their widespread clinical application. Conversely, allogeneic MSC preparations offer the potential of a scalable 'off-the-shelf' therapy [25,26]. Importantly, due to lack of expression of immune relevant surface markers, MSCs are considered to be immune "evasive" [27], and are regarded as safe to use in genetically unmatched recipients [28].

Building on our prior research assessing the administration of autologous adipose-derived MSCs (ADMSCs) [29,30], the present study reports the effect of a defined allogeneic ADMSC cell-line in the treatment of knee OA. The overall purpose of this double blinded, placebo-controlled, randomised Phase I/IIa study was to evaluate the safety and preliminary efficacy of ascending doses of an allogeneic ADMSC therapy preparation to inform optimal dose selection for its application in knee OA and later-stage pivotal trials.

2. Methods

2.1. Design, randomisation and participants

This randomised, double blind, placebo-controlled, prospective study was conducted at the Melbourne Stem Cell Centre Research, Victoria, Australia. The study was approved by the Charles Sturt University Human Research Ethics Committee, NSW, Australia and conducted in accordance with ethical principles founded in the Declaration of Helsinki (Registration ACTRN12617001095358 / ACTRN12621000622808).

All participants provided written informed consent prior to screening. Eligible participants were aged 18–65 years inclusive, with documented radiological diagnosis of moderate knee OA (Kellgren-Lawrence Grade 2–3). All participants had attempted primary conservative management of OA and had an average pain score in the preceding week of $\geq$5 (Numeric Pain Rating Scale [NPRS]). (See Supplementary Table-S1. Eligibility Criteria).

A defined cell-line of allogeneic adipose-derived MSCs (ADMSCs) (company development code – MAG200) was provided by trial sponsor Magellan Stem Cells Pty Ltd (Victoria, Australia). The study comprised an ascending dose phase to determine short-term (3 months) safety of MAG200 administered as a single IA injection and a follow-up phase to evaluate preliminary efficacy and longer-term safety over 12 months. 40 participants were equally allocated to one of four ascending dose cohorts with each cohort comprising 10 participants randomized in a ratio of 4:1 to receive either MAG200 or placebo. This resulted in the four active treatment doses (MAG200 10, 20, 50, 100 $\times$ 10^6 cells) and placebo being represented equally with 8 participants (1:1:1:1:1) (Supplementary Fig. S1). As this was a 'first-in-human' study a sentinel group approach was used, with randomisation forced so that the first two participants in each dose cohort were allocated 1:1 to MAG200 or placebo. In the absence of any safety issues after 48 h, the remaining participants in each dose cohort were enrolled and randomised using a computer-generated randomisation schedule. Escalation to the next dose level occurred when safety data for the preceding dose level cohort was deemed acceptable at 1 month of follow-up.

Study participants and all study personnel directly involved with participant care/treatment were blinded to the treatment allocation throughout the trial.

2.2. Patient and public involvement

Prior to commencement of the study, we sought patient feedback regarding design and conduct of the study. This was to ensure that treatment reflected what would be acceptable in the broader community in addition to reducing chance of lost to follow-up.

2.3. Preparation of allogeneic ADMSCs

The ADMSCs were derived from a single donor and underwent isolation and expansion following good laboratory and clinical practices [31] in accordance with Magellan Stem Cells standard operating procedures [29,30]. Donation and testing relevant to the procurement of donor tissue was performed according to regulatory guidelines [32–35]. A lipoharvest was performed by a qualified clinician following previously reported protocols and transferred to the Magellan laboratory for manufacturing of the investigational product (MAG200) [29]. The lipoharvest underwent enzymatic digestion followed by centrifugation at 2000 rpm for 10 min. The pelleted cell mixture was then washed with sterile buffer solution with the final cell pellet resuspended in culture media and termed Stromal Vascular Fractions. The SVF was plated on to sterile tissue culture flasks for culture purification. After 72 h, non-adherent cells were removed and adhered cells were incubated with standard growth media containing fetal-bovine serum at 37 °C for 7–10 days until 80–90% confluence. Cells were expanded for a total of 4 passages (equivalent of 10–15 doublings). MAG200 was characterised

following International Society for Cell and Gene Therapy guidelines, including tri-lineage differentiation and expression of CD105, CD73, and CD90 (≥ 95% positive) and lack of expression of hematopoietic markers CD45, CD14, CD34, and CD19 (≤2% positive) [36]. Cell morphology, count and viability were recorded. In addition, MAG200 underwent sterility, mycoplasma and endotoxin analysis and karyotype stability testing.

MAG200 was stored in individual sterile cryovials stored in liquid nitrogen. Each cryovial contained 10 million cells in a volume of 1 mL cryoprotectant media (CryoStor®CS10, Biolife-Solutions, Washington, USA). When required, the appropriate number of cryovials were removed from the liquid nitrogen, thawed at 37 °C in a sterile water bath and centrifuged to remove cryoprotectant media. The resultant pelleted cells were reconstituted with 5 mL of sterile clinical grade injectable isotonic electrolyte solution (Plasma-Lyte 148 IV-Infusion, Baxter Healthcare Pty Ltd, NSW, Australia). Cell count and viability were confirmed using an automated cell counter (MUSE Cell Analyser, Merck, MA, USA) (Table 1). All treatments including placebo (5 mL Plasma-Lyte) were prepared and supplied to the clinical trial site in identical syringes with the syringe barrels covered in black tape to prevent unblinding.

2.4. Justification of the dose range

We chose 10×10^6 MSCs as an appropriate starting dose as past research suggested this was safe and associated with pain and functional improvement though not associated with disease-modification [37]. We have previously shown efficacy of high dose (100×10^6) ADMSC preparations with observed disease-modification and hence chose 100×10^6 cells as the maximal dose cohort [29].

2.5. Intervention

The area of injection site superficial to the knee joint capsule was first anaesthetised using 2 mL of 2% xylocaine. Intra-articular injection of the investigational product was performed under ultrasound guidance using a 21-gauge needle and via a superolateral patellofemoral approach. Post-treatment, participants were observed for 1 h and provided with a prescription for appropriate analgesia, a compression garment, and an ice pack. Full weight-bearing was allowed. We asked participants to refrain from strenuous weight-bearing exercise/activities for 1 week following treatment.

2.6. Study outcomes and participant assessments

The primary safety objective was to evaluate the safety of a single dose of MAG200 within the initial post-treatment period (0–3 months) via monitoring of adverse events (Common Terminology Criteria for Adverse Events-Version 5.0), physical examinations, concomitant medication usage and clinical laboratory tests.

The primary efficacy objective was to evaluate the effect of a single dose of MAG200 on knee pain and function at 12 months. The primary efficacy endpoint was a compound responder analysis as determined by improvement in pain (numeric pain rating scale [NPRS]) and function (Knee Injury Osteoarthritis Outcome Score Function in Daily Living subscale [$KOOS_{ADL}$]). A responder was defined as a participant in whom there was a clinically meaningful improvement (minimum clinically important difference [MCID]) in pain with no loss of function or a clinically meaningful improvement in function with no increase in pain. MCID were defined as a ≥2 point reduction (or ≥30% reduction) in NPRS for pain and a change from baseline of ≥8 points on the $KOOS_{ADL}$ subscale for function [38,39]. We chose a responder analysis as it provides a clinically relevant composite endpoint which takes pain and function into account, and has been shown to be more sensitive than mean changes in pain scores when assessing drug efficacy in knee OA [40,41].

Secondary efficacy objectives were to determine change from baseline to month 12 in patient reported outcome measures and knee joint structure. NPRS and $KOOS_{ADL}$ which formed part of the responder analysis were considered key secondary endpoints. PROMs were completed at baseline, months 1, 3, 6, 9 and 12 and included:

- Numeric Pain Rating Scale (NPRS): An 11-point scale was used with participants asked to rate their average knee pain over the previous week (0 = no pain, 10 = worst pain). NPRS is a validated primary outcome measure of OA pain intensity [42].
- Knee Injury and Osteoarthritis Outcome Score (KOOS): KOOS evaluates short and long-term consequences of knee injury and OA and consists of five subscales: pain, symptoms, function in daily living, function in sport and recreation, and knee-related quality of life. Each subscale is comprised of a series of questions assessed using a five-point Likert scale. A score of 0–100 is derived for each subscale (0 = extreme knee problems, 100 = no knee problems) [43].
- Orebro Musculoskeletal Pain Questionnaire Short Form (OMSPG-Short): The OMSPQ-Short was completed at baseline and was used to identify patients at risk of developing chronic pain; it comprises 10 questions each assessed with a score between 0 (no pain/difficulty) to 10. A total score >50 indicates an increased risk of long-term disability.
- Global Perceived Effect (GPE): A seven-point patient GPE scale was used, with participants indicating the overall change in their condition using a seven-point Likert scale ranging from 1 (completely recovered) to 7 (worse than ever).

We performed structural/disease-modification assessment using quantitative MRI (qMRI). The study knee was imaged in the sagittal plane on a 3-T whole body MRI (Ingenia, Philips Medical Systems, Netherlands) using a commercial transmit-receive extremity coil. The following sequence and parameters were used: a T1-weighted fat suppressed 3D gradient recall acquisition in the steady state; repetition time 18 msec; echo time 5 msec; flip angle 15°; field of view 16 cm; 640 × 640 matrix. Sagittal images were obtained at a partition thickness of 3.0 mm with 1.5 mm spacing between slices, and in-plane resolution of 0.25 × 0.25 mm. Two-dimensional fast spin-echo, T2-mapping sequencing was performed.

Cartilage volume within all compartments was determined, in addition to the medial and lateral tibial plateau area using validated methods [44]. The coefficient of variation was 2.0–3.4% for cartilage volume and 2.4% for tibial plateau bone area [44]. T2-mapping is

Table 1
MAG200 cell count and viability.

	MAG200 10×10^6 cells (N = 8)	MAG200 20×10^6 cells (N = 8)	MAG200 50×10^6 cells (N = 8)	MAG200 100×10^6 cells (N = 8)
Cell Count (x 10^6) (Mean ± SD)	10.74 ± 0.30	20.38 ± 0.85	50.54 ± 1.67	105.03 ± 4.44
Viability (%) (Mean ± SD)	92.55 ± 0.67	92.33 ± 0.22	91.43 ± 0.58	92.93 ± 1.55

SD = Standard deviation.

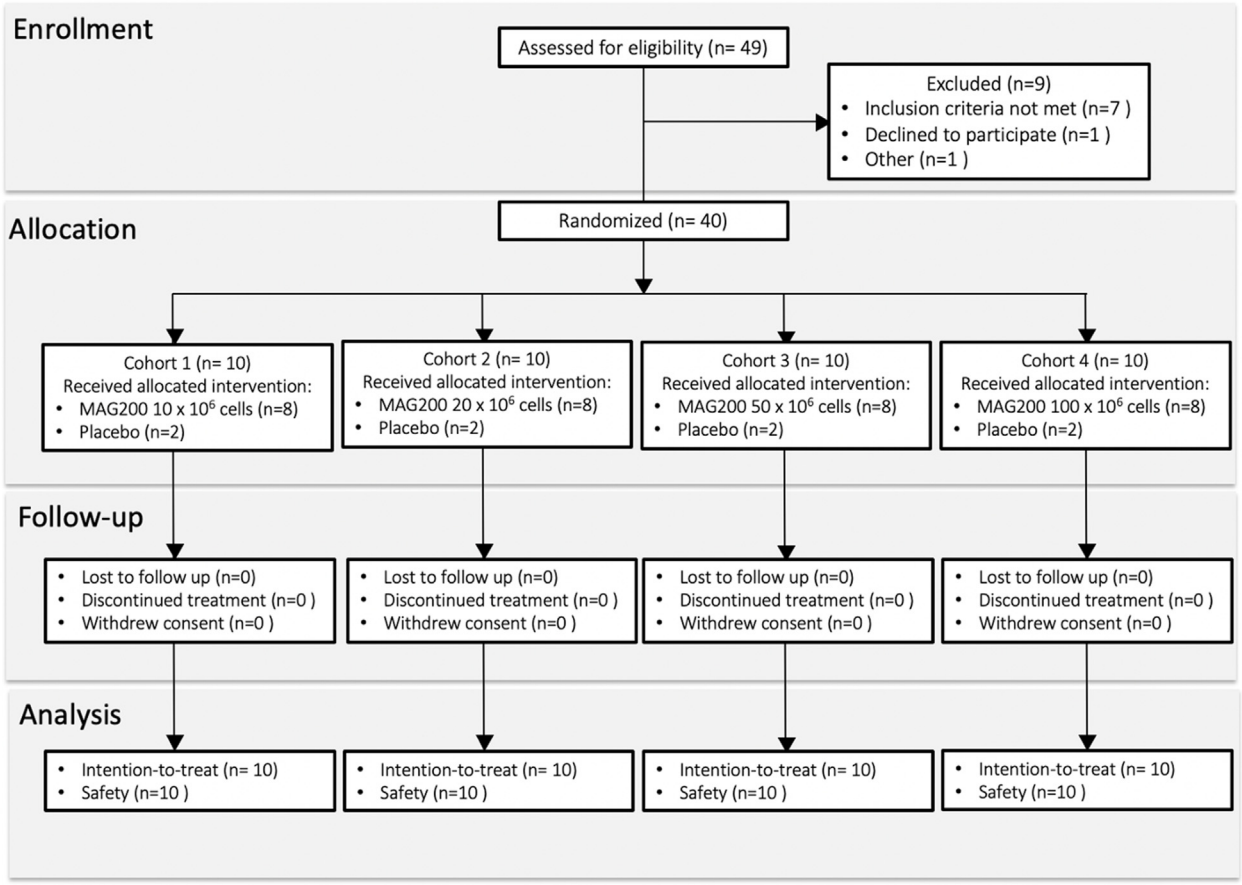

Fig. 1. Participant flow chart (CONSORT).

recognised as a validated non-invasive assessment of cartilage quality [45], with increased superficial zone T2-values associated with reduced cartilage quality and progression in OA [46]. T2-values >80 ms were excluded as they represent tissue other than cartilage or result from chemical shift artefact [47,48]. To reduce bias and ensure reproducibility of the MRI measurements, a trained observer, who was blinded to participant characteristics, timing of MRI and group allocation, read each MRI.

Table 2
Demographics and baseline characteristics.

	MAG200 10×10^6 cells (N = 8)	MAG200 20×10^6 cells (N = 8)	MAG200 50×10^6 cells (N = 8)	MAG200 100×10^6 cells (N = 8)	Placebo 0 cells (N = 8)
Demographics					
Age (Years)	57.0 (6.7)	45.5 (12.0)	49.0 (9.6)	47.6 (5.9)	39.1 (10.8)
Sex					
Female	3 (38%)	2 (25%)	3 (38%)	3 (38%)	1 (13%)
Male	5 (63%)	6 (75%)	5 (63%)	5 (63%)	7 (88%)
Race					
Asian	1 (13%)	1 (13%)			
Caucasian	7 (88%)	7 (88%)	8 (100%)	8 (100%)	8 (100%)
Weight (kg)	78.84 (14.6)	87.62 (17.89)	80.10 (15.24)	85.38 (16.53)	81.73 (15.62)
Height (cm)	172.8 (7.8)	180.9 (14.2)	173.3 (8.6)	175.6 (9.6)	170.9 (10.6)
BMI (kg/m^2)	26.30 (3.81)	26.76 (4.66)	26.47 (3.12)	27.59 (4.28)	27.81 (3.86)
OA Characteristics					
Prior knee surgery	8 (100%)	6 (75%)	5 (63%)	6 (75%)	5 (63%)
KL OA Grade 2	3 (38%)	5 (63%)	4 (50%)	3 (38%)	6 (75%)
KL OA Grade 3	5 (63%)	3 (38%)	4 (50%)	5 (63%)	2 (25%)
Patient reported outcomes					
NPRS score	6.75 (1.04)	6.25 (1.04)	6.63 (1.31)	6.5 (1.20)	6.5 (0.53)
OMSPQ-Short score	54.9 (17.39)	46.0 (12.21)	43.9 (8.06)	47.4 (9.93)	42.9 (12.67)
Proportion at risk of long-term pain[a]	5 (63%)	3 (38%)	2 (25%)	3 (38%)	3 (38%)

Data presented are mean (SD) or n (%); BMI = Body Mass Index, KL = Kellgren-Lawrence Grade, NPRS = numeric pain rating scale; OMSPQ-Short = short version of Orebro Musculoskeletal Pain Questionnaire, SD = Standard deviation.

[a] Proportion of participants with a Baseline OMSPQ-Short score of >50.

Table 3
Post-injection treatment emergent adverse events (TEAEs).

	MAG200 10×10^6 cells (N = 8)	MAG200 20×10^6 cells (N = 8)	MAG200 50×10^6 cells (N = 8)	MAG200 100×10^6 cells (N = 8)	Placebo 0 cells (N = 8)
Any TEAE	7 (88%) [9]	6 (75%) [9]	6 (75%) [9]	8 (100%) [22]	5 (63%) [8]
Severity:					
Mild	4 (50%) [6]	2 (25%) [3]	3 (38%) [6]	6 (75%) [19]	4 (50%) [7]
Moderate	3 (38%) [3]	4 (50%) [6]	3 (38%) [3]	2 (25%) [3]	1 (13%) [1]
Severe	–	–	–	–	–
Most common TEAEs[a]:					
Arthralgia	2 (25%) [2]	–	1 (13%) [2]	–	1 (13%) [1]
Joint effusion[b]	–	–	1 (13%) [1]	2 (25%) [2]	–
Joint swelling[b]	1 (13%) [1]	2 (25%) [3]	–	3 (38%) [4]	–
Injection site joint effusion[b]	1 (13%) [1]		3 (38%) [3]	4 (50%) [4]	–
Injection site joint swelling[b]	–	1 (13%) [1]	3 (38%) [3]	3 (38%) [3]	–
Injection site pain	4 (50%) [4]	–	–	1 (13%) [1]	2 (25%) [2]
Blood creatine phosphokinase increased	–	1 (13%) [1]	–	2 (25%) [2]	–
Laboratory test abnormal	–	1 (13%) [1]	–	1 (13%) [1]	1 (13%) [1]
Treatment Related TEAEs:	1 (13%) [1]	3 (38%) [3]	6 (75%) [8]	8 (100%) [11]	–
Arthralgia	–	–	1 (13%) [1]	–	–
Joint effusion[b]	–	–	1 (13%) [1]	1 (13%) [1]	–
Joint swelling[b]	–	2 (25%) [2]	–	2 (25%) [2]	–
Muscle tightness	–	–	–	1 (13%) [1]	–
Injection site joint effusion[b]	1 (13%) [1]	–	3 (38%) [3]	4 (50%) [4]	–
Injection site joint swelling[b]	–	1 (13%) [1]	2 (25%) [2]	3 (38%) [3]	–
Treatment Related TEAEs of moderate severity	–	2 (25%) [3]	3 (38%) [3]	1 (13%) [1]	–

Data presented are: number of participants (%) [number of events]. TEAE = treatment emergent adverse event.
[a] TEAEs occurring in at least 5% (>2) participants across the trial.
[b] TEAEs of injection site swelling and injection site effusion occurred ≤24 h of injection (MedDRA system organ class: General disorders and administration site conditions), whereas joint swelling and joint effusion occurred >24 h after injection (MedDRA system organ class: Musculoskeletal and connective tissue disorders).

2.7. Statistical analyses

The sample size for this study was based on clinical and regulatory considerations for first-in-human studies [49]. All participants who underwent randomisation and received study treatment, were included in the safety and efficacy analysis (intention-to-treat analysis).

Responder analysis was performed using a stratified (by timepoint) Cochrane Mantel Haenszel approach for each treatment dose, providing estimates of the risk difference (active dose – placebo) and relative risk with exact 95% confidence limits and an exact chi-square test to determine whether the responder rate in the active dose group was different from (2-sided test) the placebo group at each timepoint.

To assess the effect of active treatment compared with placebo on pain and function a mixed model was fitted with change in NPRS or $KOOS_{subscale}$ as the outcome variable and dose and timepoint (and the dose × timepoint interaction) as factors. In addition, a customised estimate was obtained for the difference between active and placebo for all active doses combined. The effect of treatment on MRI data (cartilage

Table 4
Adjusted mean percent change by dose at 12 months: NPRS and KOOS subscales.

		MAG200 10×10^6 cells (N = 8)	MAG200 20×10^6 cells (N = 8)	MAG200 50×10^6 cells (N = 8)	MAG200 100×10^6 cells (N = 8)	Placebo 0 cells (N = 8)
NPRS	Mean change[a]	−3.80	−2.62	−2.78	−3.25	−1.55
	95% CI	[-5.29, −2.31]	[-3.89, −1.36]	[-4.44, −1.13]	[-4.86, −1.64]	[-3.27, 0.18]
	P value	<0.0001	0.0004	0.0022	0.0006	0.0767
	MCID	Yes	Yes	Yes	Yes	No
KOOS ADL	Mean change[a]	16.47	20.12	8.87	20.8	9.99
	95% CI	[6.44, 26.50]	[11.11, 29.12]	[-2.42, 20.15]	[10.47, 31.14]	[2.48, 17.50]
	P value	0.0036	0.0001	0.1138	0.0005	0.0135
	MCID	Yes	Yes	Yes	Yes	Yes
KOOS Sport	Mean change[a]	24.12	31.1	16.79	34.2	16.66
	95% CI	[5.27, 42.98]	[18.21, 43.99]	[4.43, 29.15]	[17.96, 50.45]	[0.16, 33.16]
	P value	0.0168	<0.0001	0.0107	0.003	0.0482
	MCID	Yes	Yes	Yes	Yes	Yes
KOOS QoL	Mean change[a]	28.1	20.43	12.12	35.82	11.52
	95% CI	[16.25, 39.96]	[7.79, 33.07]	[-1.39, 25.64]	[23.63, 48.02]	[-2.26, 25.30]
	P value	0.0002	0.004	0.0746	<0.0001	0.0935
	MCID	Yes	Yes	Yes	Yes	Yes
KOOS Symptoms	Mean change[a]	19.36	16.03	12.12	22.47	5.15
	95% CI	[10.13, 28.59]	[9.85, 22.20]	[2.11, 22.12]	[11.11, 33.82]	[-6.24, 16.55]
	P value	0.0006	<0.0001	0.0216	0.0009	0.3441
	MCID	Yes	Yes	Yes	Yes	No
KOOS pain	Mean change[a]	17.4	20.11	10.75	24.63	12.23
	95% CI	[5.35, 29.45]	[12.17, 28.04]	[-0.31, 21.82]	[13.89, 35.38]	[2.17, 22.29]
	P value	0.0092	<0.0001	0.0558	0.0002	0.0206
	MCID	Yes	Yes	Yes	Yes	Yes

CI = confidence interval; KOOS = Knee Injury and Osteoarthritis Outcome Score, MCID = minimum clinically important difference (Yes/No); NPRS = numeric pain rating scale, ADL = function in daily living, Sport = function in sport and recreation, QoL = knee related quality of life.
[a] Adjusted mean change from baseline.

volume, cartilage quality) was analysed using a general linear model with change from baseline as the outcome, dose as a factor and baseline value as a covariate. Estimates of treatment effect (with 95% confidence limits) were obtained for each assessment. The adjusted mean change from baseline was tested within the model for each dose (including placebo).

As this was an early-stage exploratory ascending dose trial the level of statistical significance was set at $p < 0.05$. A Bonferroni adjustment for multiple comparisons was not made due to the potential risk of increasing Type II errors and failing to detect real differences.

Safety data were summarised descriptively.

All statistical analyses were generated using SAS (Ver25.09.4, SAS Institute Inc, Cary, NC).

3. Results

3.1. Baseline characteristics and study participants

A total of 49 participants were screened, of whom 40 met the inclusion criteria and were enrolled, and completed the study as per the protocol (Fig. 1). All cohorts had a mean BMI within the 'overweight' range, included both male and female participants and included participants who had undergone previous knee surgery (Table 2). The MAG200 10×10^6 dose cohort had a greater mean age than other cohorts and recorded a higher mean OMSPQ-Short score suggesting an increased risk of long-term pain/disability. In contrast, the placebo group was comprised of a higher proportion of males (7:1), and younger participants with less severe OA and lower OMPSQ-Short scores compared with other cohorts.

3.2. Safety outcomes

In the initial 0–3-month post-treatment period, 32 (80%) participants reported 57 treatment emergent adverse events (TEAEs), the majority of which were mild (41, 72%). The most commonly occurring TEAEs were arthralgia, injection-site related swelling and effusion (occurring ≤24 h after injection), injection site pain, and joint swelling and effusion (occurring >24 h after injection). Treatment-related TEAEs were observed only in the MAG200 groups (23, 40%), the majority of which were mild (17, 74%). The most common TEAE was injection site related effusion (8 participants) and swelling (6 participants). A dose-related increase in the proportion of participants reporting treatment-related TEAEs was observed (13% in the lowest dose [MAG200 10×10^6] group and 100% in the highest dose [MAG200 100×10^6] group). There was no observed dose-dependent relationship on severity of TEAEs and

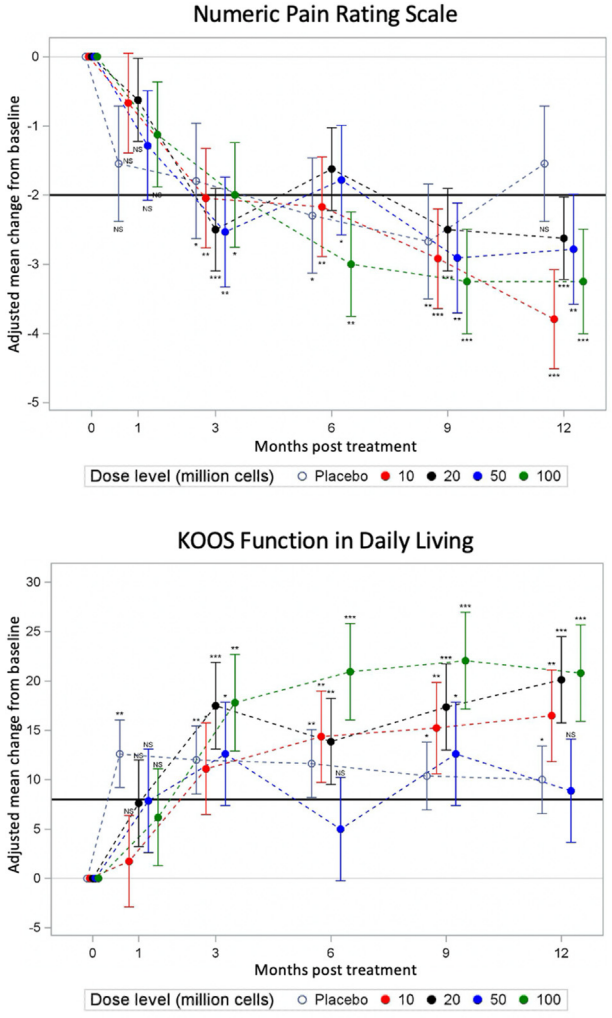

Fig. 2. Key Secondary Endpoints – Change from baseline in pain (NPRS) and in KOOS Function in Daily Living ($KOOS_{ADL}$). Error bars represent ±1 times the standard error of the mean value. The horizontal black line represents the Minimum Clinically Important Difference (MCID) from baseline score. Values below this line for NPRS are considered clinically meaningful. Values above this line for KOOS are considered clinically meaningful. NS = change from baseline is not statistically significant ($p > 0.05$). * = change from baseline is statistically significant ($p \leq 0.05$ but $p > 0.01$). ** = change from baseline is statistically significant ($p \leq 0.01$ but $p > 0.001$). *** = change from baseline is statistically significant ($p \leq 0.001$).

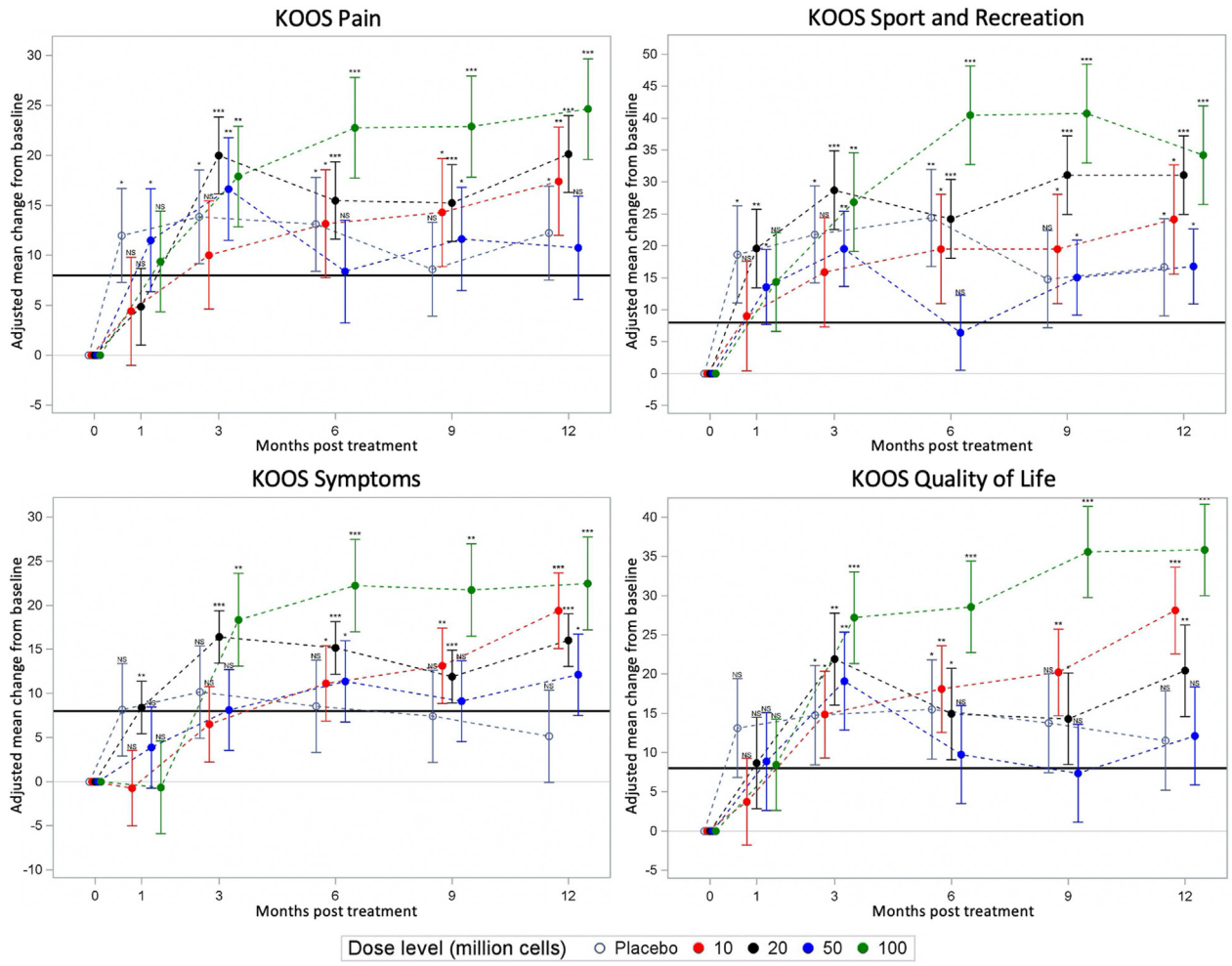

Fig. 3. Change from baseline in all other KOOS subscales. Error bars represent ±1 times the standard error of the mean value. The horizontal black line represents the Minimum Clinically Important Difference (MCID) from baseline score. Values above this line are considered clinically meaningful. NS = change from baseline is not statistically significant ($p > 0.05$). * = change from baseline is statistically significant ($p \leq 0.05$ but $p > 0.01$). ** = change from baseline is statistically significant ($p \leq 0.01$ but $p > 0.001$). *** = change from baseline is statistically significant ($p \leq 0.001$).

there were no treatment-related serious TEAEs (Table 3). No treatment-related changes in vital signs, laboratory tests or electrocardiograms were observed.

Use of concomitant medications was more frequent in the initial 0-3-month post treatment period than during longer-term follow-up (22 participants [18 MAG200, 3 placebo] vs. 4 participants [3 MAG200, 1 placebo], respectively).

3.3. *Efficacy outcomes*

At month 12, all MAG200 dose cohorts exhibited a greater number of responders than placebo (50% placebo group, 62.5% MAG200 10×10^6, 100% MAG200 20×10^6, 62.5% MAG200 50×10^6, and 75% MAG200 100×10^6) (Supplementary Fig. S2). The MAG200 20×10^6 dose group demonstrated a doubling of response rate compared with placebo (relative risk = 2.0).

A clinically relevant (≥2 point decrease) and statistically significant improvement in pain from baseline at month 12 was observed in all MAG200 cohorts, but not in the placebo group which failed to achieve statistically significant or clinically relevant improvement (Table 4, Fig. 2). A clinically relevant (≥8 point increase) and statistically significant improvement from baseline to month 12 was observed in $KOOS_{ADL}$ for MAG200 10, 20, and 100×10^6 dose groups and in all other KOOS subscales for all MAG200 cohorts with most subscales indicating clinically relevant improvement as early as 3 months post treatment (Table 4, Figs. 2 and 3).

At month 12, MAG200 therapy was associated with a positive treatment effect against placebo with greater pain reduction, irrespective of the dose received (Fig. 4). The greatest treatment effect was seen in the MAG200 10×10^6 dose cohort, which was both statistically significant ($p = 0.0468$) and clinically relevant. Further, estimates of treatment effect showed improvements beyond placebo in all five KOOS subscales for participants in the MAG200 10, 20 and 100×10^6 dose groups with the MAG200 100×10^6 dose group showing clinically relevant improvement against placebo in all subscales (Fig. 5).

Estimates of the treatment effects of MAG200 on pain reduction (NPRS) and functional improvement ($KOOS_{ADL}$) at all time points show treatment effect against placebo as early as 3 months with sustained treatment effect out to month 12 (Supplementary Figs. S3,S4).

At month 12, based on GPE, more patients who had received MAG200 treatment reported improvement or complete recovery from symptoms of knee OA compared with placebo (75% vs 37.5%) (Supplementary Fig. S5).

3.4. *Effect of MAG200 on joint structures of the study knee*

qMRI assessment indicated progression in OA in the placebo group as measured by mean percentage cartilage volume loss (-0.59 [95%CI:-

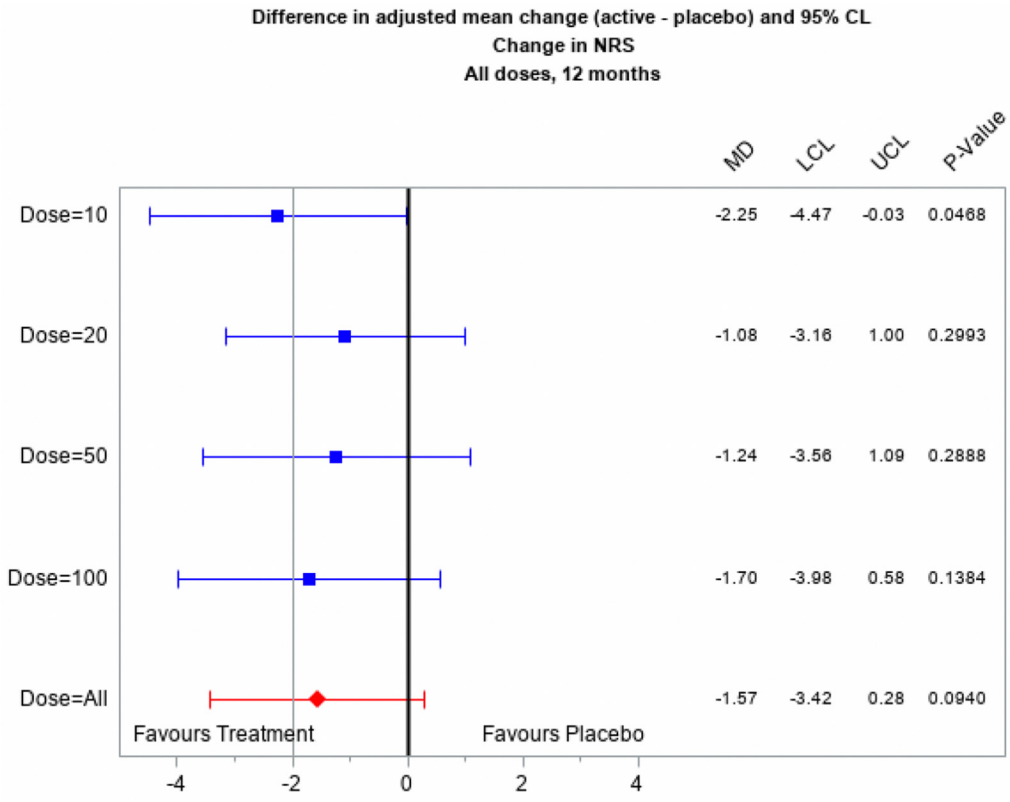

Fig. 4. Estimates of treatment effect (MAG200 minus placebo) on pain reduction (NPRS) at month 12. Mean Difference = estimate of treatment effect and represents change from baseline on active treatment minus change from baseline on placebo. Pain as measured by NPRS. Values further to the left support a greater reduction in pain from baseline in MAG200 cohorts compared to placebo. Vertical dotted line represents the Minimum Clinically Important Difference (MCID) from placebo. MD = Mean Difference, LCL/UCL = Lower/Upper 95% Confidence Limit.

1.79,0.61]), with observed mean percentage improvement in total knee cartilage volume in MAG200 10 × 10^6 (0.18 [95%CI:-1.04,1.39]), 20 × 10^6 (0.32 [95%CI:-0.90,1.54]) and 100 × 10^6 (0.33 [95%CI:-0.86,1.51]) dose cohorts, though these changes did not reach statistical significance (Supplementary Fig. S6). Assessment of treatment effect indicated most significant change in lateral femoral condyle cartilage volume, which was statistically significant in the MAG200 20 × 10^6 dose cohort ($p = 0.032$) and MAG200 at all doses ($p = 0.037$) (Supplementary Fig. S7). Although no results reached statistical significance, the observed treatment effects on cartilage quality, as measured by change in superficial zone T2-mapping values, favoured the MAG200 100 × 10^6 dose group with improvement in the medial (−0.46 [95%CI:-3.74,2.82]), lateral (−0.07 [95%CI:-2.70,2.57]), patellofemoral compartments (−0.03 [95% CI:-2.92,2.86]) and total knee average (−0.30 [95%CI:-2.44,1.84]) when compared against placebo (Supplementary Fig. S8). These results were in contrast to change in femoral trochlea (1.67 [95%CI:-1.70,5.04] and medial femoral condyle (0.53 [95%CI:-3.76,4.74] T2-values which favoured placebo. Indicative qMRI images are displayed in Fig. 6.

4. Discussion

This first-in-human double-blind, randomised controlled trial assessing an allogeneic ADMSC preparation (MAG200), administered as a single IA injection to the knee achieved its primary safety and efficacy outcomes. MAG200 therapy was observed to be well tolerated and safe with the proportion of clinical responders being higher in all active treatment groups than in placebo at 12 months.

The observed safety of IA MAG200 is consistent with other early-phase trials evaluating allogeneic [50–52] or autologous [29,53,54] ADMSC preparations [55]. Our results suggested a potential dose related trend in treatment-related TEAE incidence, though there was no observed dose relationship in severity of TEAEs.

Efficacy endpoints were met as assessed by pain and functional improvements and observed treatment effect over placebo at 12 months. All active treatment cohorts exhibited both clinically relevant and statistically significant improvement with 75% of patients receiving MAG200 reporting improvement or complete recovery. The observed response following MAG200 therapy reflects previous early-phase trials using allogeneic ADMSCs and supports the efficacy of allogeneic ADMSCs in the treatment of knee OA [50–52].

Quantitative disease-modification assessment indicated positive treatment effects in favour of MAG200 in assessments of cartilage volume at 12 months, with the most promising results seen in the 20 and 100 × 10^6 dose groups. qMRI T2-mapping indicated a dose response association in disease-modification with improved total knee cartilage quality against placebo observed in the MAG200 100 × 10^6 dose group, though improved T2-values against placebo were not observed across all regions. In comparison, outcomes of MRI-assessed structural changes after injection of other allogeneic ADMSCs have been variable. Chen et al. reported no improvements at 24 months of follow-up [52], while Kuah et al. showed statistically significant greater cartilage loss with placebo compared to active after 12 months of follow-up [50], and Lu et al. showed improvements in cartilage volume only in a low dose group after 12 months [53]. Jo et al. in assessment of autologous ADMSC therapy observed consistent radiological improvement after high dose therapy (100 × 10^6 cells) in comparison to lower dose preparations which may reflect a dose response disease-modification effect which is supported by our results [56].

A focal interest of MSCs in the management of OA is their potential to delay, defer and/or prevent TKR surgery through sustained pain and functional improvement in addition to disease-modification. Unanswered questions remain as to the optimal cell tissue source, donor type (allogeneic/autologous) and dose. Consistent with past meta-analysis which report larger treatment effect benefits for pain relief and cartilage repair with ADMSC than with bone-marrow derived MSCs (BM-MSCs) [57], MAG200 therapy was associated with greater pain (NPRS) improvement over placebo in direct comparison to studies involving BM-MSCs [58]. This was additionally reflected in pain and functional

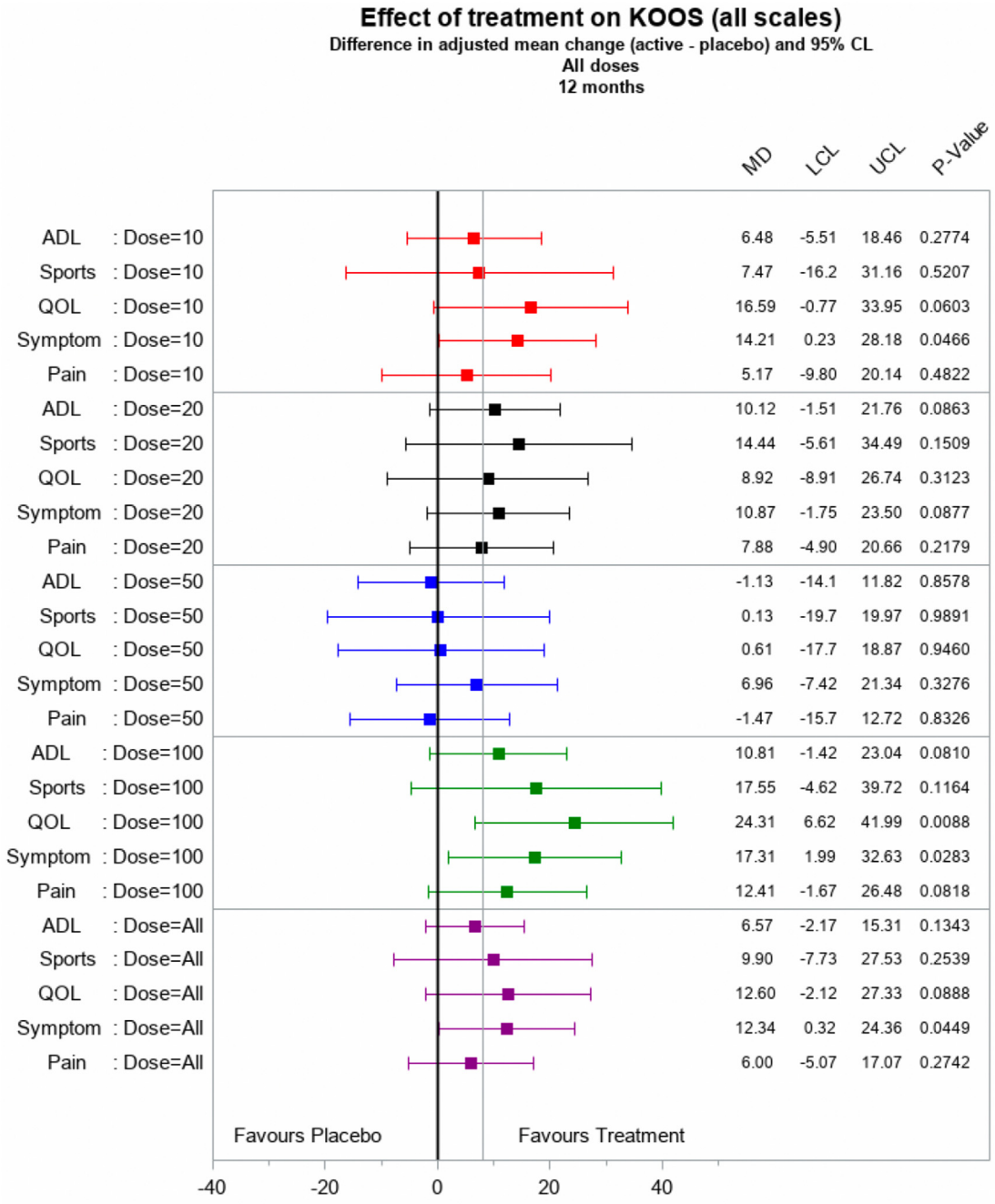

Fig. 5. Estimates of treatment effect (MAG200 minus placebo) on pain and function as measured by KOOS subscales at month 12. Mean Difference = estimate of treatment effect and represents change from baseline on active treatment minus change from baseline on placebo. Values further to the right support a greater improvement in KOOS subscale scores in MAG200 cohorts in comparison to placebo. Vertical dotted line represents the Minimum Clinically Important Difference (MCID) from placebo. MD = Mean Difference, LCL/UCL = Lower/Upper 95% Confidence Limit.

outcomes as measured by KOOS subscales where the MAG200 100×10^6 dose group exhibited a reproducible treatment effect and improvement from baseline typically greater than that seen with BM-MSCs [59].

While 12-month qMRI results from our trial provide a promising signal for potential disease-modification with MAG200, additional analyses may have provided supportive data. Importantly, T2-mapping which has been validated as a non-invasive assessment of cartilage quality remains an experimental endpoint as it has not been validated for assessment of OA progression. Accordingly, future research may benefit from analysis of disease-modification surrogate endpoints including serum, synovial and urinary biomarkers (e.g. COMP, CTX-I/II, C2C) which are less time dependent and serve as suitable supportive measures of disease-modification [60].

Despite an ascending dose exploratory protocol, the results were unable to provide clear direction as to the optimal dose of MAG200. Key limitations which may have impacted this were the small sample size and discrepancies in baseline demographic characteristics between cohorts. Lack of clear intergroup differences between active treatment cohorts may however be an indication of the efficacy of MAG200 as a defined allogeneic cell line in the treatment of OA. Whilst variability may be expected due to cohort sample size, the consistent statistically significant and clinically relevant improvement from baseline and observed

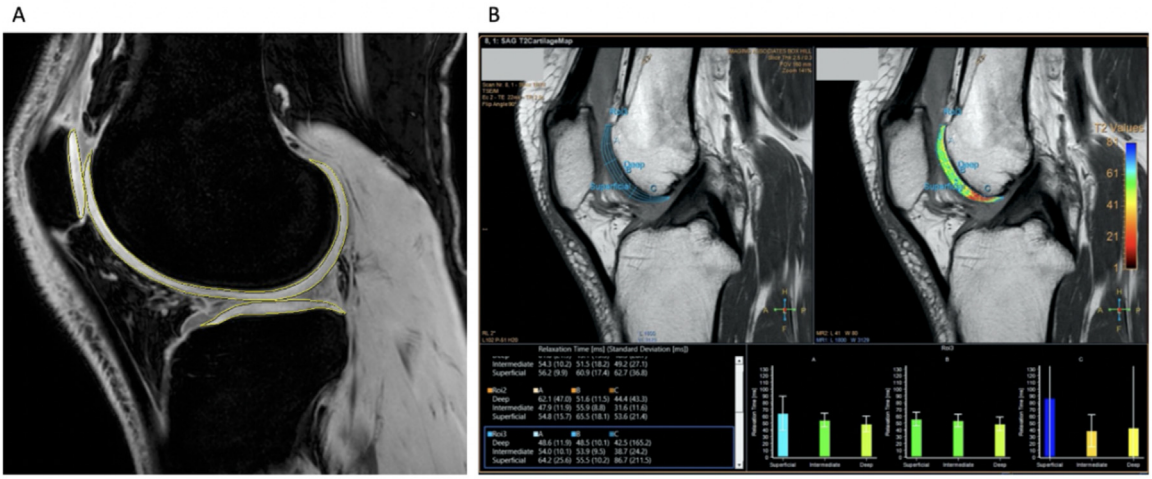

Fig. 6. Quantitative MRI analysis. (A) Single sagittal T1-weighted fat saturated image of a participant's knee with outline used to calculate segmental cartilage volume. (B) Single sagittal T2 mapping image of a participant's knee showing calculated segmental cartilage T2-value assessment.

treatment effect support the efficacy of MAG200 in the treatment of OA.

There are no current disease-modifying therapies for OA. With the growing incidence of OA and increasing rate of total joint replacement the orthopaedic workforce may be insufficient to meet demand with recent research suggesting a need to increase the number of orthopaedic surgeons by 10% every five years [61]. For an OA therapy to be considered disease-modifying and therefore delay and/or prevent TJR, it should demonstrate both symptomatic (pain, function) and structural benefits [62]. The pain, functional and structural benefits observed with MAG200 suggests that MSC therapy may be an effective disease-modifying treatment that promises to delay or prevent the need for total joint replacement and thus reduce the growing clinical and economic burden of OA.

5. Conclusion

OA is a major unmet clinical need and public health burden for which preventative and reparative therapies are urgently needed. Allogeneic MSC-based therapies offer an exciting possibility in the treatment of OA, providing a scalable "off-the-shelf" solution. The results of this Phase I/IIa study indicate that MAG200 has significant promise in the treatment of knee OA and provide sufficient evidence to progress its clinical development to later-stage trials.

Data availability statement

Extra data are available upon reasonable request and with permission of Magellan Biologicals Pty Ltd by emailing drjulienfreitag@magellanstemcells.com.au. There are no plans to disseminate the results to the study participants.

Ethics statement

This study involved human participants and was approved by Charles Sturt University Human Research Ethics Committee, Boorooma Street, Wagga Wagga NSW 2678, Australia. Approval Number H18167. All participants provided written informed consent for data collection and publication. Trial registration: ACTRN12617001095358 / ACTRN12621000622808.

JF (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author contributions

Julien Freitag (JF): conception and design, financial support, administrative support, provision of study material or participants, collection and/or assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Matthew Chamberlain (MC): conception and design, provision of study material or participants, collection and/or assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

James Wickham (JW): conception and design, provision of study material or participants, collection and/or assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Kiran Shah (KS): conception and design, provision of study material or participants, collection and/or assembly of data, data analysis and interpretation and final approval of manuscript.

Flavia M Cicuttini (FMC): collection and/or assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Yuanyuan Wang (YW): collection and/or assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Ann Solterbeck (AS): data analysis and interpretation, final approval of manuscript.

Role of the funding source

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Declaration of competing interest

JF is the Chief Medical Officer of Magellan Stem Cells Pty Ltd, holds stocks or options in Magellan Stem Cells Pty Ltd and is the Current Chair of the Magellan Stem Cells Medical and Scientific Advisory Board.

MC declares no conflicts of interest.

JW declares no conflicts of interest.

KS is an employee of Magellan Stem Cells Pty Ltd.

YW is the recipient of National Health and Medical Research Council of Australia Translating Research into Practice Fellowship (APP1168185).

AS declares no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2024.100500.

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