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Osteoarthritis and Cartilage

Intra-articular MM-II for the treatment of knee osteoarthritis pain: Efficacy and safety results from a 26-week, phase 2b, placebo-controlled, double-blind, randomized dose-ranging trial

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SUMMARY

Objective: Determine optimal dose, efficacy, and safety of MM-II, a suspension of large empty liposomes, for knee osteoarthritis (OA) pain.
Method: A double-blind phase 2b study (NCT04506463) randomized participants 3:3:3:1:3:1 to one intra-articular injection of 1, 3, or 6 mL MM-II or 1, 3, or 6 mL placebo, respectively. Inclusion criteria included age ≥40 years and radiographic and symptomatic knee OA. The primary endpoint was change from baseline in Western Ontario and McMaster Universities OA Index (WOMAC) pain (range, 0–4) 12 weeks post-injection (multiplicity-adjusted). Secondary endpoints included weekly average of daily knee pain (WADP), WOMAC pain at other visits, WOMAC function, patient global assessment (PtGA), and rescue medication use. Safety was assessed by treatment-emergent adverse events (TEAEs).
Results: Overall, 396 participants received treatment. In the 3 mL MM-II vs placebo group, WOMAC pain numerically improved at week 12 (least squares mean difference [95% confidence interval], −0.24 [−0.48, 0.00]; unadjusted $P = 0.047$; multiplicity-adjusted $P = 0.085$ [primary endpoint not met]). In the same 3 mL group, WADP showed improvements at week 12 (−10.9 [−18.9, −2.8]) lasting through week 26 (−11.8 [−20.4, −3.3]; unadjusted $P < 0.01$ at both time points). Numeric improvements were also seen in WOMAC function from week 8–26, and PtGA at weeks 16 and 26. Rescue medication use with 3 mL MM-II was consistent with reduced pain. Results were numerically superior with 3 mL MM-II vs 1 mL MM-II; 6 mL MM-II was the least efficacious dose. MM-II was well tolerated, with low TEAE incidence.
Conclusion: MM-II was safe, and the optimal effective dose for the treatment of knee OA pain was 3 mL.

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Introduction

Osteoarthritis (OA) can cause chronic pain and loss of function in patients, contributing to a significant burden of disease.[1,2] The most frequent large joint affected by OA is the knee, with a prevalence of approximately 4307 cases per 100,000 globally.[1] Global prevalence of knee OA is projected to continue increasing due to population growth and population aging.[1]

There is a substantial unmet need in managing pain and improving function for people with knee OA, as currently available pharmacological treatments have limited efficacy and durability of effect. For example, the efficacy of oral nonsteroidal anti-inflammatory drugs (NSAIDs) can be short-lived, and continued use increases the risk of adverse events, including serious gastrointestinal effects.[3–5] Although intra-articular glucocorticoid injections are effective short-term, the long-term benefits for pain and function are not fully established and concerns have been raised about deleterious effects on joint cartilage.[3,4,6–8] Another treatment option, intra-articular hyaluronic acid injection, is controversial and not recommended by the American College of Rheumatology or the American Academy of Orthopedic Surgeons based on conflicting evidence of its efficacy.[4,6,9–11]

MM-II is a first-in-class investigational treatment for knee OA that consists of empty liposomes (3–4 μm in diameter) comprised of the phospholipids dipalmitoylphosphatidylcholine (DPPC) and 1,2-dimyristoyl-phosphatidylcholine at a predesignated molar ratio.[12] This ratio, which has a direct impact on the membrane fluidity of the liposomes, enables the liposomes to adhere to the cartilage surface and provide a lubricative layer.[13] Based on *ex vivo* and *in vivo* preclinical studies, intra-articular MM-II injection has been proposed to replenish the lipid component of the natural cartilage boundary lubrication system to provide effective protection from cartilage wear.[12–16] A first-in-human exploratory study with descriptive statistics found that 3 mL MM-II reduced knee pain up to 90 days post-injection.[17] Here, we report the results of a phase 2b dose-finding trial evaluating the efficacy and safety of a single intra-articular administration of MM-II for painful knee OA.

Method

Study design and participants

This was a phase 2b, 26-week, randomized, double-blind, dose-ranging, placebo-controlled, single-administration trial (NCT04506463). The primary objectives were to determine the optimal dose, safety, and tolerability of a single intra-articular injection of MM-II to treat knee pain in people with knee OA 12 weeks after injection. Participants were randomized 1:3:3:1:3:1 to 1, 3, or 6 mL MM-II or 1, 3, or 6 mL placebo, respectively, for the first 168 participants and 7:3:3:1:3:1 for the remaining participants, for an approximate final allocation ratio of 3:3:3:1:3:1 and a planned total sample size of 348 participants (Fig. 1). Randomization was coordinated centrally, and participants were allocated to treatment arms using an interactive web response system. Key inclusion criteria included age ≥40 years, radiographic Kellgren-Lawrence grades 2 or 3 in the index knee, American College of Rheumatology criteria for OA, Western Ontario and McMaster Universities OA Index (WOMAC) pain score ≥2 (0–4 range; calculated as the mean of the subscales) for the last 24 h before screening and baseline, index knee visual analog scale (VAS) pain score of ≥50 to ≤90 mm for at least 5 of the 7 days before baseline, and intolerance or inadequate response to NSAIDs or acetaminophen. Patients with moderate to large effusions as determined by the treating physician in the index knee or moderate to severe pain in another joint were excluded. Randomization was stratified by body mass index (BMI; < 30 kg/m^2, ≥30 kg/m^2 to < 35 kg/m^2, and ≥35 kg/m^2; participants with BMI ≥40 kg/m^2 were capped at 10% of the total number of participants) and index knee pain (VAS ≤74 and VAS ≥75). Screening took place within 28 days of baseline and treatment.

Ethics

The study was conducted in compliance with the International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use Good Clinical Practice. All participants provided written informed consent, and the protocol was

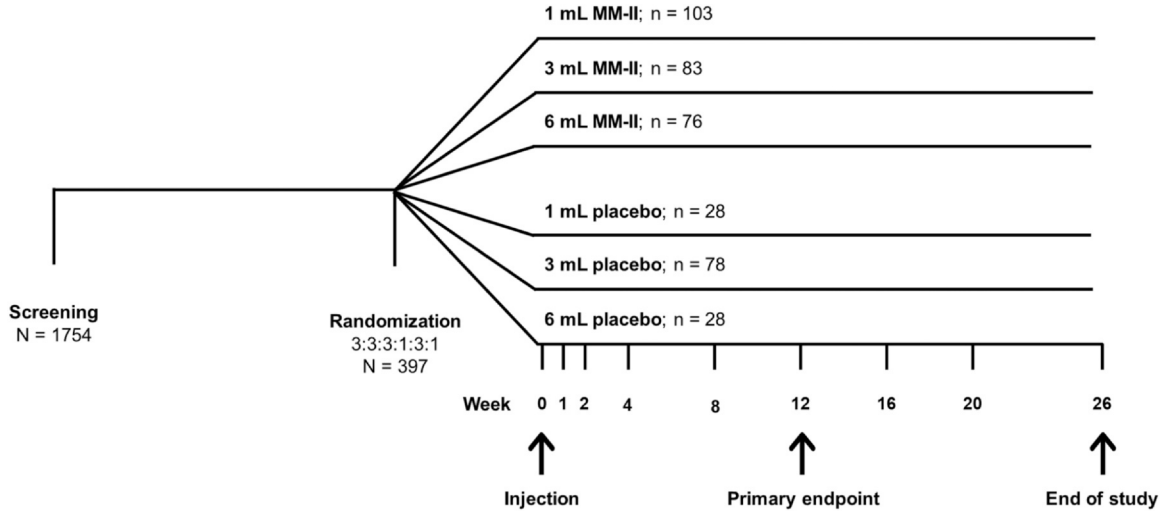

Fig. 1

Osteoarthritis and Cartilage

Study design.

approved by the independent ethics committee or institutional review boards of all participating study sites.

Interventions

MM-II was provided as an injectable suspension of liposomes (150 mM lipids); placebo was a solution containing the same excipients as MM-II with no active ingredients. MM-II or placebo was administered as a single intra-articular injection of 1 mL, 3 mL, or 6 mL into the index knee joint using a syringe; ultrasound guidance was used at the discretion of the investigator. Study visits took place 1, 2, 4, 8, 12, 16, 20, and 26 weeks after injection. The study was double-blind, with all participants and investigators remaining blind to the identity of the treatment from randomization until database lock. Study site staff were blinded except for those who prepared the syringes or performed injections; such staff were not involved in the study beyond these tasks. The primary comparator was 3 mL placebo; the 1 and 6 mL placebo groups were included to maintain study blinding and to evaluate potential placebo volume effects.

Concomitant topical analgesics (including NSAIDs), except for use on the index knee, and inhaled corticosteroids were allowed if the dosage was stable at least 2 months before enrollment and throughout the study. Acetaminophen use was allowed up to a maximum of 4 g per day as rescue medication for breakthrough pain in the index knee but had to be discontinued within 24 h of a scheduled efficacy evaluation. No other concomitant analgesics or NSAIDs were allowed. Nonpharmacological therapies were allowed if the intensity and frequency of the therapy were stable for 4 weeks before injection and throughout the study.

Endpoints

The primary efficacy endpoint was change from baseline in WOMAC pain score at week 12 for each MM-II dose compared with 3 mL placebo. Secondary endpoints were WOMAC pain scores at other time points as well as WOMAC function scores, WOMAC stiffness scores, weekly average of daily knee pain (WADP) scores, cumulative weekly rescue medication use (acetaminophen/paracetamol), and patient global assessment (PtGA) of disease activity over time. The proportion of participants who achieved 30% and 50% improvement from baseline in WOMAC pain at each post-baseline visit was an exploratory endpoint. Participants reported daily knee pain in an eDiary by marking a VAS scale of 0 to 100 mm (lower values indicated less pain). Weekly cumulative rescue medication use for a given visit was calculated by summing daily doses in the period, dividing by the number of days in the period, and multiplying by 7. Participants reported PtGA by responding to the question, “Considering all the ways your knee OA affects you, please indicate by tapping on the line, on average, how have you been doing during the last 24 h?” on a VAS scale (0–100). The safety and tolerability of a single intra-articular injection of MM-II was assessed by documenting treatment-emergent adverse events (TEAEs).

Statistical analysis

The sample size was based on the ability to detect a minimum clinically meaningful difference in average WOMAC pain between placebo and MM-II of 0.28 out of 4 and a standard deviation of 0.59 with a 2-sided $\alpha = 0.05$ and 80% power. The full analysis set (FAS) was a modified intention-to-treat population that included all randomized participants who received a dose of MM-II or placebo and was analyzed based on the treatment to which they were randomized irrespective of the actual treatment received. The safety analysis set included all FAS participants but was analyzed based on treatment received.

The primary efficacy endpoint (change from baseline in WOMAC pain score) was analyzed using a mixed model repeated measures, with treatment, visit, and treatment-visit interaction as fixed effects and site, baseline WOMAC pain score, baseline BMI group (< 30 kg/m^2, ≥30 kg/m^2 to < 35 kg/m^2, and ≥35 kg/m^2), and baseline VAS group (≤74, ≥75) as covariates. An unstructured covariance matrix was used to model the within-participant, between-visit variances. Week 12 treatment differences were estimated for all MM-II groups against the 3 mL placebo group using least squares means (LSMs), 2-sided 95% confidence intervals (CIs), and *P*-values. CIs were not adjusted for multiplicity. *P*-values were adjusted for multiplicity using step-down Dunnett testing for comparison of the active doses to 3 mL placebo ($\alpha = 0.05$). Secondary endpoints were analyzed using the same model as the primary efficacy endpoint, but *P*-values were not adjusted for multiplicity. Pairwise comparisons of MM-II dose levels vs 3 mL placebo for 30% and 50% improvement in WOMAC pain score from baseline were analyzed using a Cochran–Mantel–Haenszel test stratified by region. *P*-values for analyses other than the primary analysis were not adjusted and are provided for descriptive purposes. Post hoc effect sizes for pain outcomes were calculated using the observed LSM differences and standard deviations between the 3 mL MM-II and 3 mL placebo arms. No imputation of missing values was performed. All calculations and statistical analyses were performed in SAS® Version 9.4. Safety endpoints were analyzed with summary statistics.

Results

Participants

Between December 21, 2020, and August 10, 2022, 1754 patients were screened at 25 study centers in the United States, Denmark, and Hong Kong, and 397 participants were randomized at 22 centers (Fig. 2). The number of randomized participants exceeded the planned sample size of 348 participants due to rapid recruitment toward the end of the study, resulting in a higher number of participants randomized to 1 mL MM-II than planned. The FAS included 396 participants, and 369 participants completed the study. By the end of the study at week 26, 28 (7.1%) participants discontinued, most commonly due to withdrawn consent (3.3%). One participant randomized to 3 mL placebo did not receive any treatment, 1 participant randomized to 1 mL MM-II received 3 mL MM-II, and 2 participants randomized to 6 mL MM-II received 3 mL MM-II; these participants were included in the FAS and safety analysis set based on the group they were randomized to and based on the treatment actually received, respectively. The majority of participants were female, White, and not Hispanic or Latino; participant demographics and baseline characteristics were comparable among treatment groups (Table I). An approximately equal number of participants were from sites in the United States and Denmark; slightly fewer participants were from sites in Hong Kong.

Knee pain

The change from baseline to week 12 in WOMAC pain score was numerically greater for the 3 mL MM-II group compared with 3 mL placebo but did not reach statistical significance when adjusted for multiplicity (LSM difference [95% CI], −0.24 [−0.48, 0.00]; multiplicity-adjusted $P = 0.085$; multiplicity-unadjusted $P = 0.047$; Fig. 3A, Fig. S1; Table S1). This endpoint was the only one adjusted for multiplicity. The calculated post hoc WOMAC pain effect size for 3 mL MM-II compared with 3 mL placebo was 0.33 at week 12. WOMAC pain was reduced with 3 mL MM-II compared with 3 mL placebo at week 16 (LSM difference [95% CI], −0.27 [−0.49, −0.04]; $P = 0.022$) and week 20 (LSM difference [95% CI], −0.23 [−0.45, −0.01]; $P = 0.041$), and

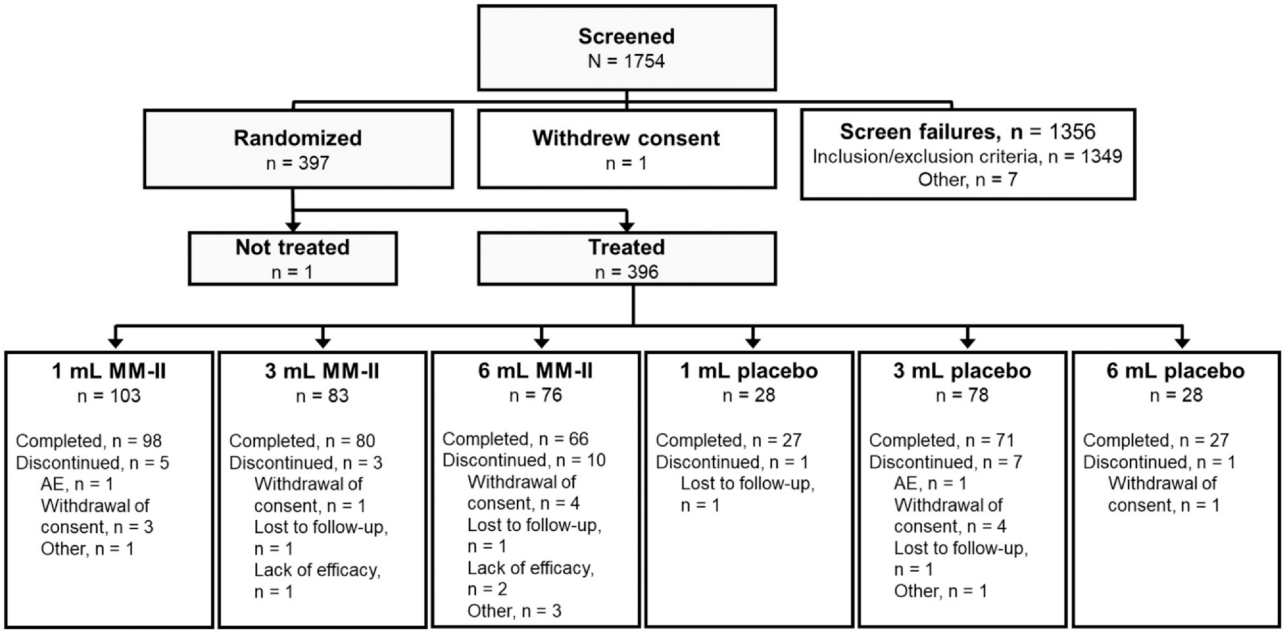

Fig. 2 Osteoarthritis and Cartilage

Participant flow diagram. AE, adverse event.

Parameter	1 mL MM-II (n = 102)	3 mL MM-II (n = 86)	6 mL MM-II (n = 74)	1 mL placebo (n = 28)	3 mL placebo (n = 78)	6 mL placebo (n = 28)
Age (years)	62.7 (8.2)	64.2 (8.5)	61.6 (7.2)	62.1 (8.2)	62.3 (7.9)	62.8 (8.4)
Sex, n (%)						
Male	32 (31.4)	27 (31.4)	35 (47.3)	8 (28.6)	27 (34.6)	9 (32.1)
Female	70 (68.6)	59 (68.6)	39 (52.7)	20 (71.4)	51 (65.4)	19 (67.9)
Race, n (%)						
Asian	29 (28.4)	19 (22.1)	17 (23.0)	5 (17.9)	21 (26.9)	5 (17.9)
Black or African American	3 (2.9)	10 (11.6)	11 (14.9)	3 (10.7)	3 (3.8)	4 (14.3)
White	70 (68.6)	57 (66.3)	46 (62.2)	20 (71.4)	54 (69.2)	19 (67.9)
Ethnicity, n (%)						
Hispanic or Latino	14 (13.7)	13 (15.1)	16 (21.6)	3 (10.7)	8 (10.3)	5 (17.9)
Not Hispanic or Latino	88 (86.3)	73 (84.9)	58 (78.4)	25 (89.3)	70 (89.7)	23 (82.1)
Region, n (%)						
US	26 (25.5)	38 (44.2)	32 (43.2)	10 (35.7)	26 (33.3)	14 (50.0)
Denmark	47 (46.1)	29 (33.7)	25 (33.8)	13 (46.4)	31 (39.7)	9 (32.1)
Hong Kong	29 (28.4)	19 (22.1)	17 (23.0)	5 (17.9)	21 (26.9)	5 (17.9)
Weight (kg)	86.2 (21.7)	85.7 (20.2)	87.5 (18.9)	83.5 (16.6)	85.1 (20.8)	85.8 (20.2)
Height (cm)	166.7 (10.8)	166.5 (9.3)	167.8 (12.3)	168.0 (7.2)	165.9 (10.3)	167.3 (7.7)
BMI (kg/m^2)	30.9 (6.4)	30.7 (6.0)	31.0 (5.7)	29.5 (5.6)	30.7 (6.4)	30.5 (6.4)
WOMAC pain score (0–4)	2.5 (0.4)	2.4 (0.3)	2.5 (0.4)	2.5 (0.4)	2.3 (0.4)	2.5 (0.4)
Min, max	2.0, 3.8	2.0, 3.8	2.0, 3.6	2.0, 3.4	1.8, 3.4	2.0, 3.4
WOMAC stiffness score (0–4)	2.4 (0.6)	2.3 (0.7)	2.3 (0.8)	2.4 (0.6)	2.3 (0.7)	2.4 (0.7)
Min, max	0.0, 4.0	0.5, 4.0	0.0, 4.0	1.0, 3.0	0.0, 4.0	1.0, 4.0
WOMAC function score (0–4)	2.3 (0.5)	2.2 (0.6)	2.3 (0.6)	2.3 (0.4)	2.2 (0.5)	2.4 (0.5)
Min, max	0.8, 3.5	0.4, 3.9	1.4, 3.5	1.4, 3.5	0.3, 3.7	1.4, 3.5
VAS index knee pain (0–100)	70.6 (9.7)	69.0 (9.6)	69.0 (10.9)	67.5 (9.6)	68.0 (10.4)	68.0 (10.0)
Min, max	53, 90	51, 90	51, 92	50, 81	52, 88	53, 87

Data are presented as mean (SD) unless otherwise noted.
BMI = body mass index; SD = standard deviation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table I Osteoarthritis and Cartilage

Participant demographics and baseline characteristics (safety analysis set).

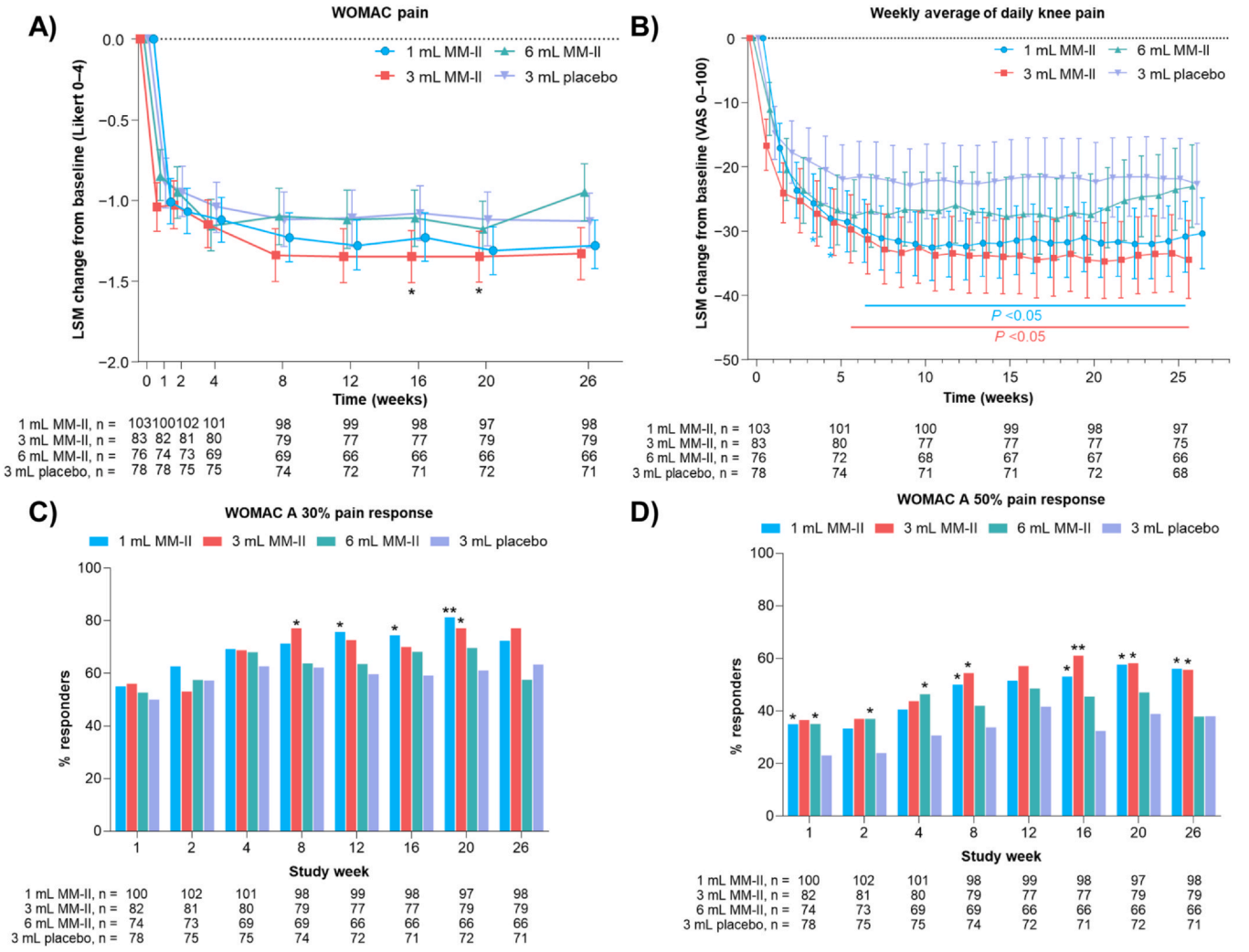

Fig. 3 Osteoarthritis and Cartilage

A) Change from baseline in WOMAC pain over time. B) Change from baseline in WADP VAS score over time. C) 30% and D) 50% reduction in WOMAC pain score by study week (full analysis set). Only the comparison for change from baseline in WOMAC pain at week 12 in panel A was adjusted for multiplicity. *$P < 0.05$, **$P < 0.01$ compared with 3 mL placebo unadjusted for multiplicity. Error bars represent 95% confidence intervals, which were not adjusted for multiplicity.
LSM, least squares mean; VAS, visual analog scale; WADP, weekly average of daily knee pain; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

sustained numeric differences of WOMAC pain in favor of 3 mL MM-II were observed from week 8 through week 26. Consistent improvements in WOMAC pain were also observed in the 1 mL MM-II group at weeks 8 through 26, but the magnitudes of the improvements were lower than in the 3 mL MM-II group. The 6 mL MM-II dose provided the lowest WOMAC pain response throughout the study.

The sustained efficacy of MM-II was most notable when WADP was used to evaluate knee pain. WADP scores were reduced from baseline for the majority of the study in the 3 mL MM-II group from weeks 6 to 26, with LSM differences (95% CIs) ranging from −13.0 (−21.28, −4.67) to −8.2 (−15.57, −0.74; $P < 0.05$ compared with 3 mL placebo), and in the 1 mL MM-II group from weeks 6 to 25, with LSM differences (95% CIs) ranging from −10.5 (−18.50, −2.49) to −8.4 (−15.49, −1.39; $P < 0.05$ compared with 3 mL placebo; Fig. 3B; Table S1). *P*-values for this endpoint were not adjusted for multiplicity. At week 12, the calculated post hoc WADP effect size for 3 mL MM-II compared with 3 mL placebo was 0.44 at week 12. Similar to observations with WOMAC pain, the magnitude of the reduction in WADP was higher for 3 mL MM-II than for 1 mL MM-II. No significant differences were observed in WADP for the 6 mL MM-II group compared with 3 mL placebo group at any time point ($P > 0.05$).

Results from the exploratory endpoints of rates of 30% and 50% improvement in WOMAC pain support the durability of pain reduction mediated by MM-II. A higher proportion of participants achieved a 30% reduction from baseline in WOMAC pain than the 3 mL placebo group at weeks 8 and 20 in the 3 mL MM-II group and at weeks 12, 16, and 20 for the 1 mL MM-II group ($P < 0.05$; Fig. 3C). *P*-values for this endpoint were not adjusted for multiplicity. Furthermore, a 50% improvement in WOMAC pain was achieved by a larger proportion of participants in the 3 mL MM-II group than in the 3 mL placebo group at weeks 8, 16, 20, and 26 ($P < 0.05$; Fig. 3D). This proportion was also higher compared with the 3 mL placebo group

at weeks 1, 8, 16, 20, and 26 ($P < 0.05$) in the 1 mL MM-II group, but only at the earlier time points of weeks 1, 2, and 4 ($P < 0.05$) in the 6 mL MM-II group.

Function and stiffness

The 3 mL MM-II group had consistently higher numerical improvements from baseline WOMAC function score compared with the 3 mL placebo group starting at week 8, when LSM differences (95% CIs) ranged from −0.22 (−0.45, 0.01) at week 16 to −0.14 (−0.37, 0.09) at week 26 (Fig. 4A; Fig. S2). The magnitude of change from baseline was similar between the 3 mL MM-II and the 1 mL MM-II groups (LSM [95% CI] between −0.22 [−0.44, −0.01] and −0.15 [−0.37, 0.07] for 1 mL MM-II vs 3 mL placebo). Conversely, the 6 mL MM-II dose provided negligible improvements in WOMAC function compared with placebo at all time points. WOMAC stiffness scores were not consistently improved with any MM-II dose compared with 3 mL placebo across the trial (Fig. 4B; Fig. S3).

Patient global assessment of disease activity

PtGA scores were improved with 3 mL MM-II compared with 3 mL placebo at week 16 (LSM difference [95% CI], −9.4 [−17.72, −1.08]; $P = 0.027$) and week 26 (LSM difference [95% CI], −9.1 [−17.63, −0.57]; $P = 0.037$), with numeric differences starting at week 8 and extending through the end of the study (Fig. 5; Fig. S4). *P*-values for this endpoint were not adjusted for multiplicity. Numeric improvements in PtGA scores were also evident for the 1 mL MM-II group compared with 3 mL placebo at weeks 8 through 26 (LSM differences [95% CI] between −7.7 [−15.48, 0.11] and −4.8 [−12.25, 2.55]). Congruent with measures of knee pain and WOMAC function, PtGA scores for the 6 mL MM-II group were not improved compared with the 3 mL placebo group.

Rescue medication

Weekly exposure to rescue medication for breakthrough index knee pain was also tracked. Acetaminophen use was low in all treatment arms. At week 26, LSM differences (95% CIs) were −1109.4 (−1855.37, −363.48) mg, −686.2 (−1468.58, 96.23) mg, and −526.7 (−1339.96, 286.66) mg in the 1 mL, 3 mL, and 6 mL MM-II groups, respectively (Fig. S5). Exposure stayed consistent in the 3 mL placebo group, with an LSM (95% CI) of 1932.5 (1241.5, 2623.5) mg at week 1 and 1976.6 (1387.7, 2565.5) mg at week 26.

Safety

A total of 526 TEAEs occurred in 253 (63.9%) participants (Table II). There were no differences in the proportions of participants who experienced a TEAE between MM-II doses, nor were there notable differences in the incidence of TEAEs between MM-II and placebo groups. Serious TEAEs, none of which were related to the study treatment, occurred in 11 (2.8%) participants, 2 of which resulted in study discontinuation (1 participant in the 1 mL MM-II group and 1 participant in the 3 mL placebo group). Of 36 cases of arthralgia, which occurred in ≥5% of participants in at least 1 treatment arm, 5 were determined to be related to the study treatment (1, 3, and 1 cases in the 1 mL MM-II, 6 mL MM-II, and 6 mL placebo groups, respectively), and 9 were assessed as related to the study procedure (1, 3, 4, and 1 in the 1 mL MM-II, 3 mL MM-II, 6 mL MM-II, and 1 mL placebo groups, respectively). All TEAEs related to the study medication and study procedure were mild or moderate. No clinically relevant changes in vital signs or laboratory tests were observed (data not shown).

Discussion

This dose-finding phase 2b study investigated the efficacy and safety of MM-II, a novel suspension of large, empty liposomes, compared with placebo in participants with painful knee OA. The primary efficacy endpoint of change from baseline in WOMAC pain at week 12, the only comparison adjusted for multiplicity, was not met by any MM-II group. However, the 3 mL dose provided sustained reduction in the secondary endpoint of WADP based on descriptive statistics and exploratory analyses starting 6 weeks after injection to the end of the study 26 weeks post-injection, and provided numerical improvements in WOMAC pain score relative to placebo for roughly the same period during which WADP was reduced, suggesting that MM-II may reduce knee pain. The week 12 effect sizes for both pain endpoints were comparable to those reported for existing intra-articular therapies, suggesting that the reduction in knee pain may be clinically relevant.[18,19] Moreover, improved WOMAC function and PtGA scores compared with placebo were observed up to 26 weeks post-injection with 3 mL MM-II. Based on these observations, a single intra-articular injection of 3 mL MM-II may be expected to provide durable pain relief in people with knee OA. While 1 mL MM-II also provided improvements in the WOMAC pain, WADP, WOMAC function, and PtGA endpoints, the magnitudes of improvement from baseline in the measures of knee pain were lower than those observed for 3 mL MM-II. Treatment with 6 mL MM-II provided minimal improvements for each of the efficacy endpoints. Therefore, we conclude that 3 mL MM-II is the optimal effective dose. Importantly, MM-II was safe and well tolerated, with no serious TEAEs related to the study medication or study procedure, and overall safety profiles were consistent between placebo and MM-II.

This study used 2 different measures of knee pain, both of which provided evidence that MM-II may provide relief from knee OA pain. However, based on *P*-values and effect sizes, measurement of pain using WADP allowed for greater distinction from placebo than using the WOMAC questionnaire. The WOMAC was completed by participants at each study visit, which required retrospective assessment of pain. Recall bias may influence self-reported pain due to knee OA, with participants reporting greater pain in retrospective assessments compared with daily reporting.[20] In contrast to WOMAC, daily pain eDiary recordings were used to derive WADP, which may be a more reliable method of measuring the trajectory of pain outcomes or possibly captures different aspects of knee pain. It has also been suggested that the VAS for OA pain is more sensitive than WOMAC pain.[21] Despite this, both WADP and WOMAC pain effect sizes were comparable to those reported for existing intra-articular therapies at 12 weeks after injection and other secondary efficacy measures also showed improvement with 3 mL MM-II through week 26.[18,19] Therefore, the totality of the results of this study, including descriptive statistics and exploratory analyses of secondary endpoints, suggests that MM-II may provide clinically relevant pain relief at 3 months post-injection; follow-up studies designed and powered to conclusively evaluate efficacy may find clinically relevant effects at additional time points.

There is a need for effective and safe treatments that can be used long term to manage pain and improve function in people with knee OA. The currently used approaches all have significant limitations. In a meta-analysis, acetaminophen for the treatment of knee OA did not provide clinically meaningful pain relief and may have increased the risk of liver toxicity.[22] Oral NSAIDs are effective in reducing pain and improving function, but dose and duration of use are limited by tolerability and the risk of serious adverse events.[3–6] Additionally, NSAIDs are contraindicated for many people with OA (eg, people on anticoagulants, with renal insufficiency, or with gastrointestinal or cardiovascular comorbidities). Opioid use is discouraged due to

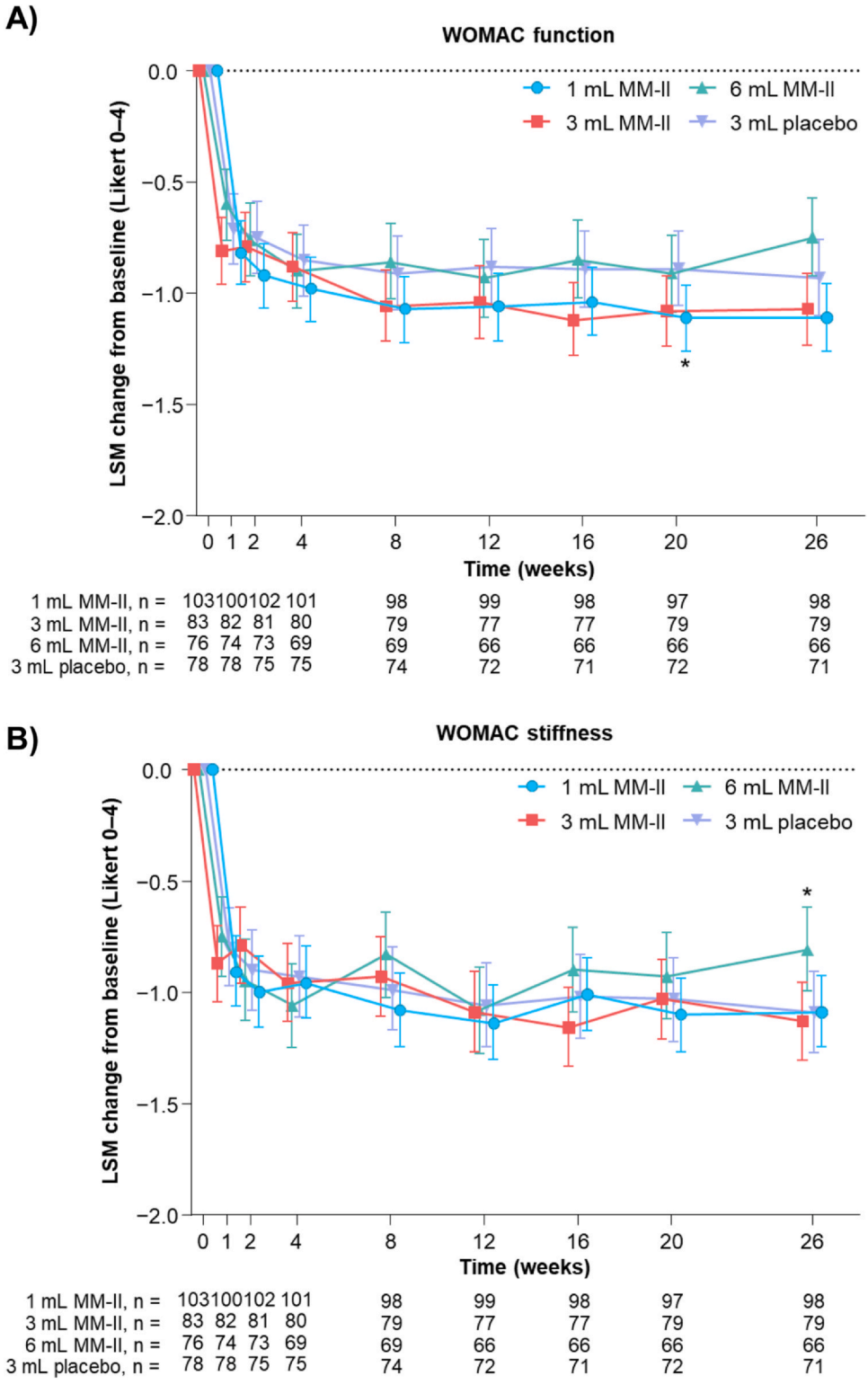

Fig. 4

Osteoarthritis and Cartilage

Change from baseline in A) WOMAC function and B) WOMAC stiffness score over time (full analysis set). *$P < 0.05$ compared with 3 mL placebo unadjusted for multiplicity. Error bars represent 95% confidence intervals, which were not adjusted for multiplicity.
LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

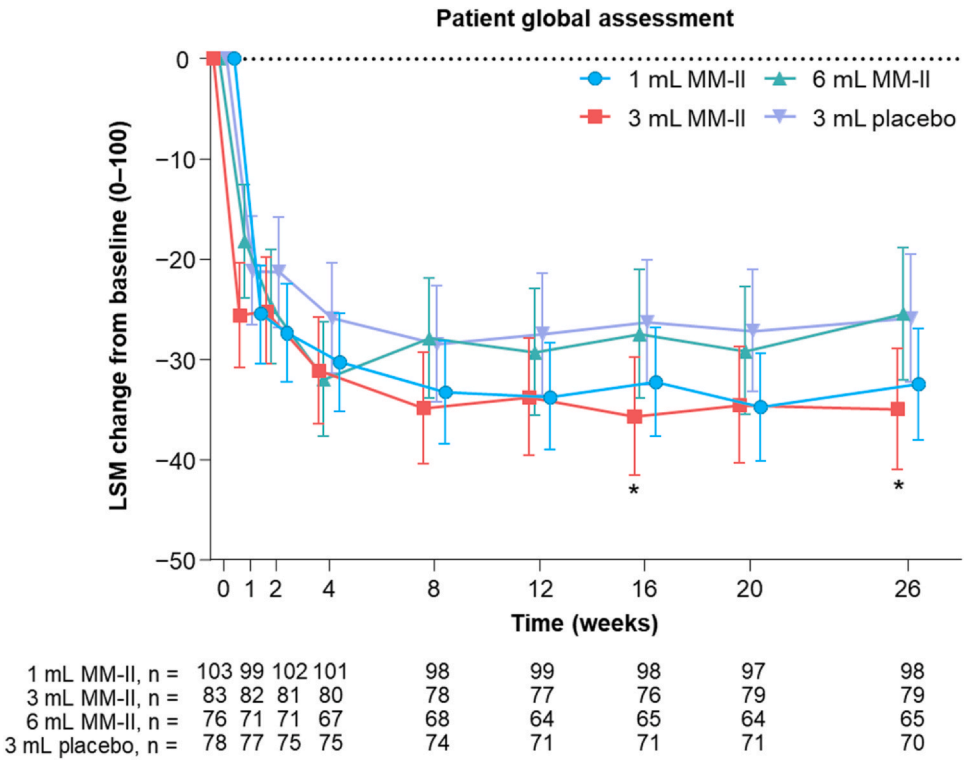

Fig. 5

Osteoarthritis and Cartilage

Change from baseline in patient global assessment of disease activity score over time (full analysis set). *$P < 0.05$ compared with 3 mL placebo unadjusted for multiplicity. Error bars represent 95% confidence intervals, which were not adjusted for multiplicity.
LSM, least squares mean.

safety concerns and the risk of dependence; furthermore, longer-term efficacy in OA has not been confirmed.[3,4,6,23] The serotonin-norepinephrine reuptake inhibitor duloxetine may reduce pain due to knee OA but is not well tolerated.[24] In contrast, MM-II was well tolerated in this study with a low incidence of treatment-related TEAEs, supporting the possibility of a more favorable safety profile than current systemic therapies.

Among intra-articular injectable treatments, the durability of effect remains a concern. Current guidelines recommend intra-articular glucocorticoids for short-term reduction in knee pain due to OA.[3,4,6] Long-acting intra-articular glucocorticoid preparations that are potentially efficacious up to 16 weeks post-injection are available, although safety and efficacy evaluations for repeat dosing have not yet been completed.[19,25,26] Furthermore, safety concerns have been raised with respect to repeated intra-articular glucocorticoid injections, with such use being associated with potential detrimental effects on joint cartilage.[7] Recent meta-analyses and guidance from professional societies have questioned the clinical efficacy of another intra-articular injectable, hyaluronic acid.[4,6,11,27] In contrast, although the primary efficacy endpoint was not met, MM-II was associated with potentially clinically relevant improvements in WOMAC pain and WADP at week 12 and reduced WADP through week 26 post-injection; additional studies powered for conclusive efficacy assessments are planned to substantiate these results. Additionally, MM-II is not expected to adversely affect joint tissue because it is based on a surface active phospholipid, DPPC, which is a major component of synovial fluid.[16,28,29] The promising durability of MM-II efficacy is planned to be investigated further.

Among the MM-II doses evaluated here, 6 mL MM-II consistently provided the lowest numerical magnitudes of change in most efficacy endpoints. The mechanisms underlying the lack of efficacy observed with 6 mL MM-II treatment are currently unknown. Based on previous analyses of this trial that found no effect of placebo volume on knee pain, WOMAC stiffness, WOMAC function, PtGA, or the incidence of adverse events, it is unlikely that the lack of efficacy was due to the volume of the intra-articular injection.[30] Existing literature suggests that exceeding the optimal local concentration of phospholipids may diminish the synergistic relationship with hyaluronic acid found in synovial fluid for lubrication.[31,32] Further work will be required to test this hypothesis.

This study had some limitations. The study assessed a single intra-articular injection of MM-II, whereas a repeat-dosing regimen may yield additional benefit; however, the observed benefit of MM-II was already demonstrated to be at least 26 weeks. Patients with moderate to large effusions were excluded in this study to prevent dilution effects, potentially limiting interpretation in patients with more marked inflammation. Finally, the study population was predominantly White, which may limit the generalizability of these results.

We conclude that 3 mL MM-II is the optimal effective dose and that a single intra-articular injection of 3 mL MM-II may provide pain relief as well as improvements in function and self-assessments of disease state for people with knee OA. MM-II was well tolerated with an acceptable safety profile. Based on these results, phase 3 clinical investigations of MM-II are planned to definitively assess the efficacy of MM-II.

Parameter, n (%)	1 mL MM-II (n = 102)	3 mL MM-II (n = 86)	6 mL MM-II (n = 74)	1 mL placebo (n = 28)	3 mL placebo (n = 78)	6 mL placebo (n = 28)
AEs	75 (73.5)	49 (57.0)	49 (66.2)	15 (53.6)	46 (59.0)	19 (67.9)
SAEs	4 (3.9)	0	3 (4.1)	0	3 (3.8)	1 (3.6)
Treatment–related AEs[a]	3 (2.9)	2 (2.3)	4 (5.4)	1 (3.6)	1 (1.3)	2 (7.1)
Procedure-related AEs[b]	1 (1.0)	6 (7.0)	7 (9.5)	1 (3.6)	1 (1.3)	1 (3.6)
Severe AEs	4 (3.9)	0	2 (2.7)	0	2 (2.6)	1 (3.6)
Injection-site AEs[c]	0	2 (2.3)	1 (1.4)	1 (3.6)	0	0
AEs leading to discontinuation[d]	1 (1.0)	0	0	0	1 (1.3)	0
TEAEs occurring in ≥5% of participants in ≥1 treatment arm						
Preferred term, n (%)						
Anemia	7 (6.9)	3 (3.5)	2 (2.7)	0	4 (5.1)	0
Arthralgia	7 (6.9)	5 (5.8)	10 (13.5)	1 (3.6)	6 (7.7)	3 (10.7)
Back pain	3 (2.9)	5 (5.8)	3 (4.1)	0	2 (2.6)	0
Contusion	0	0	0	2 (7.1)	1 (1.3)	0
COVID-19	18 (17.6)	7 (8.1)	7 (9.5)	4 (14.3)	8 (10.3)	3 (10.7)
Fall	0	0	1 (1.4)	0	0	2 (7.1)
Hyperlipidemia	2 (2.0)	0	2 (2.7)	0	4 (5.1)	0
Hypertension	8 (7.8)	3 (3.5)	3 (4.1)	0	3 (3.8)	0
Influenza-like illness	5 (4.9)	1 (1.2)	2 (2.7)	3 (10.7)	3 (3.8)	1 (3.6)
Joint swelling	1 (1.0)	0	1 (1.4)	0	1 (1.3)	2 (7.1)
Leukopenia	4 (3.9)	6 (7.0)	3 (4.1)	1 (3.6)	2 (2.6)	3 (10.7)
Nasopharyngitis	8 (7.8)	3 (3.5)	6 (8.1)	1 (3.6)	3 (3.8)	2 (7.1)
Pain in extremity	3 (2.9)	1 (1.2)	2 (2.7)	0	4 (5.1)	1 (3.6)
Pneumonia	1 (1.0)	2 (2.3)	0	0	1 (1.3)	2 (7.1)
Urinary tract infection	5 (4.9)	0	2 (2.7)	0	4 (5.1)	2 (7.1)
Vaccination complication	0	0	4 (5.4)	3 (10.7)	1 (1.3)	1 (3.6)

Safety analysis set. One participant randomized to 3 mL placebo did not receive any treatment, 1 participant randomized to 1 mL MM-II received 3 mL MM-II, and 2 participants randomized to 6 mL MM-II received 3 mL MM-II. No AEs of special interest or fatal AEs were observed. Participants may have had more than 1 AE.
AE = adverse event; COVID-19 = coronavirus disease 2019; SAE = serious AE; TEAE = treatment-emergent AE.
[a] Includes AEs possibly, probably, and certainly related to the study treatment.
[b] Includes AEs possibly, probably, and certainly related to the study procedure.
[c] A total of 5 AEs from the same study site were reported inaccurately as injection-site AEs and excluded.
[d] As reported on the study completion/early discontinuation page of the electronic case report form.

Table II

Osteoarthritis and Cartilage

Treatment-emergent adverse events (safety analysis set).

Role of the funding source

Sun Pharmaceutical Industries, Inc and Moebius Medical Ltd funded the study and contributed to study design, data interpretation, manuscript preparation, and manuscript approval for submission.

Author contributions

All authors critically reviewed the manuscript and approved its contents. TJS, BB, RCC, PGC, TJ, S-LY, SW, MK, and RW contributed to data analysis, data management, data interpretation, study management, and study monitoring. XC, HR, EL, and SLB were investigators who carried out study procedures. ARB oversaw study management and monitoring and contributed to data management, analysis, and interpretation.

Competing interest statement

TJS has received consulting fees or served on advisory boards for AstraZeneca, Eli Lilly, GSK, Horizon, IBSA Group, Merck, Moebius Medical, Orion, Pfizer, Regeneron Pharmaceuticals, and Xalud. XC has received consulting fees and honoraria from IBSA Group and KiOmed. BB and TJ are employees and/or shareholders of Sun Pharmaceutical Industries Limited, India. RCC has received consultation fees from Sun Pharma. SW is an employee and/or shareholder of Sun Pharma Advanced Research Company Limited, USA. MK is an employee and/or shareholder of Sun Pharma Advanced Research Company, India. ARB is an employee and shareholder of NBCD A/S. RW is an employee and shareholder of Moebius Medical. S-LY was an employee and/or shareholder of Sun Pharma Advanced Research Company Limited, USA, when this work was conducted. MK is an employee and/or shareholder of Sun Pharma Advanced Research Company Limited, India. PGC has received speaker fees from AbbVie, Eli Lilly, Novartis, and Sandoz and consultancies from AbbVie, Diffusion, Eli Lilly, Galapagos, Genascence, GSK, Grunenthal, Janssen, Levicept, Moebius Medical, Novartis, Stryker, Takeda, and TrialSpark. HR, EL, and SLB have no conflicts to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2025.04.006.

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