Volume of intra-articular placebo injection has no effect on pain in knee osteoarthritic patients: Post hoc analyses from a phase 2b, double-blind, randomized trial

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Background

- Osteoarthritis (OA) is the most common form of arthritis, but current treatments are limited by efficacy and toxicity[1-3]
- The effect of injection volume of intra-articular (IA) therapies on pain outcomes is unclear, and relevant clinical data are scarce[4-6]
- In 2 previous studies evaluating IA injections of 2 or 20 mL of saline solution and 4 or 10 mL of saline solution, respectively, there was no clear volumetric effect on knee OA pain outcomes for these placebo solutions[4,5]
- The injection volume of IA solutions may affect the washout of inflammatory factors. It is therefore important to assess the volumetric effect of IA injections of placebo solutions
- In a recent phase 2b study evaluating efficacy and safety of MM-II—a novel suspension of empty, large, multilamellar liposomes—for pain reduction in knee OA, 3 different volumes of placebo (1, 3, and 6 mL) were tested

Objective

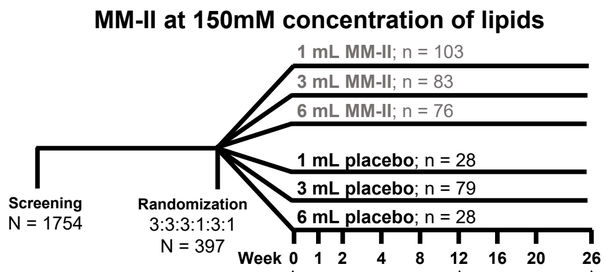
- To further explore the volumetric effect of placebo on OA pain outcomes and safety by analyzing results from the phase 2b trial assessing the use of MM-II for painful knee OA

Methods

Study design

- We performed a post hoc analysis of the 26-week, placebo-controlled, double-blind, randomized, phase 2b trial (NCT04506463) for a single IA injection of 1, 3, or 6 mL of MM-II (150mM lipids) vs 1, 3, or 6 mL of placebo (randomized 3:3:3:1:3:1) to evaluate the influence of placebo volume on study outcomes (**Figure 1**)
- Placebo consisted of a non-saline solution containing the same excipients as MM-II without active ingredients

Figure 1. Study design



Participants

- Key inclusion criteria were age ≥40 years, radiographic Kellgren-Lawrence grade 2 or 3 in the index knee, American College of Rheumatology criteria for OA, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A pain level >2 out of 4 in the index knee within 24 hours of baseline, index knee visual analog scale (VAS) pain score of ≥50 to ≤90 mm for ≥5 out of 7 days before baseline, and intolerance or inadequate response to nonsteroidal anti-inflammatory drugs or acetaminophen
- Key exclusion criteria were moderate-to-large effusions in the index knee or moderate-to-severe pain in another joint

Analyses

- Efficacy was assessed by change from baseline in WOMAC A pain, WOMAC B stiffness, and WOMAC C disability scores; weekly average of daily knee pain (WADP) assessed by VAS; and patient global assessment (PtGA) of disease activity
- Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs)
- Summary statistics and unadjusted *P*-values are provided for comparisons between placebo groups for descriptive purposes. The study was not powered for direct comparisons between placebo groups

Results

- Baseline demographics and clinical characteristics were generally well balanced across treatment arms (**Table 1**). Of 397 enrolled participants, 135 were assigned to a placebo group: 28 received 1 mL, 79 received 3 mL (1 participant excluded from analysis), and 28 received 6 mL

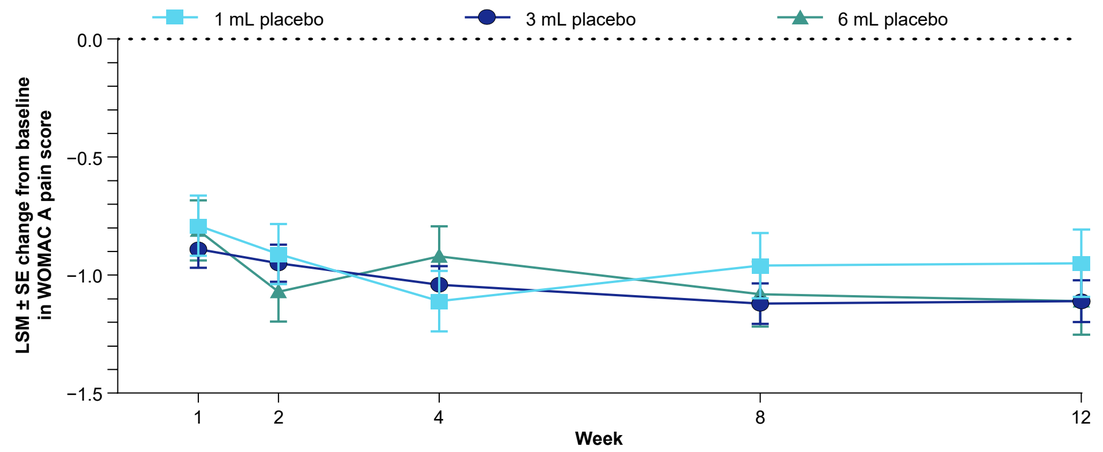
Table 1. Baseline demographics and clinical characteristics

	1 mL placebo (N = 28)	3 mL placebo (N = 79)	6 mL placebo (N = 28)
Age, mean (SD), years	62.1 (8.19)	62.1 (7.95)	62.8 (8.43)
Sex, n (%)			
Male	8 (28.6)	28 (35.4)	9 (32.1)
Female	20 (71.4)	51 (64.6)	19 (67.9)
Race, n (%)			
Asian	5 (17.9)	21 (26.6)	5 (17.9)
Black or African American	3 (10.7)	4 (5.1)	4 (14.3)
White	20 (71.4)	54 (68.4)	19 (67.9)
BMI, mean (SD), kg/m^2	29.5 (5.59)	30.9 (6.44)	30.5 (6.40)
Baseline WOMAC A pain score, mean (SD)	2.49 (0.355)	2.34 (0.353)	2.54 (0.369)
Baseline VAS index knee pain, mean (SD)	67.5 (9.61)	68.0 (10.37)	68.0 (10.03)

All-randomized analysis set.
BMI, body mass index; SD, standard deviation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

- Change from baseline in WOMAC A pain scores remained similar between placebo groups and did not decrease from week 1 to week 12 (*P* >0.15 for all comparisons; **Figure 2**)

Figure 2. Change from baseline in WOMAC A pain score over time

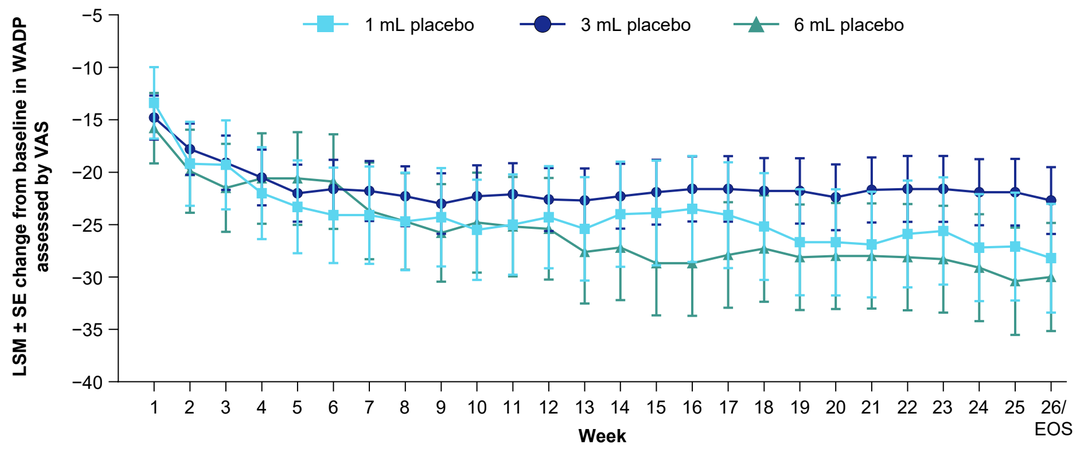


1 mL placebo, n =	28	28	28	28	28
3 mL placebo, n =	78	75	75	74	72
6 mL placebo, n =	27	28	28	28	28

LSMs are from a repeated-measures mixed model with fixed effects for treatment (1, 3, and 6 mL of MM-II and 1, 3, and 6 mL of placebo), visit, and treatment-by-visit interaction; random effect for participant; and covariates of site and baseline WOMAC A, BMI, and VAS group. WOMAC scores were assessed on a 0 to 4 Likert scale. Only placebo groups are presented. Error bars are ± SE.
BMI, body mass index; LSM, least squares mean; SE, standard error; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

- No differences in WADP scores were observed between the 1-, 3-, and 6-mL placebo groups at week 26 and throughout the study (*P* >0.15 for all comparisons; **Figure 3**). For all 3 placebo groups, a numeric reduction in WADP scores was observed from week 1 to week 5 after IA injection

Figure 3. Change from baseline in weekly average of daily knee pain over time

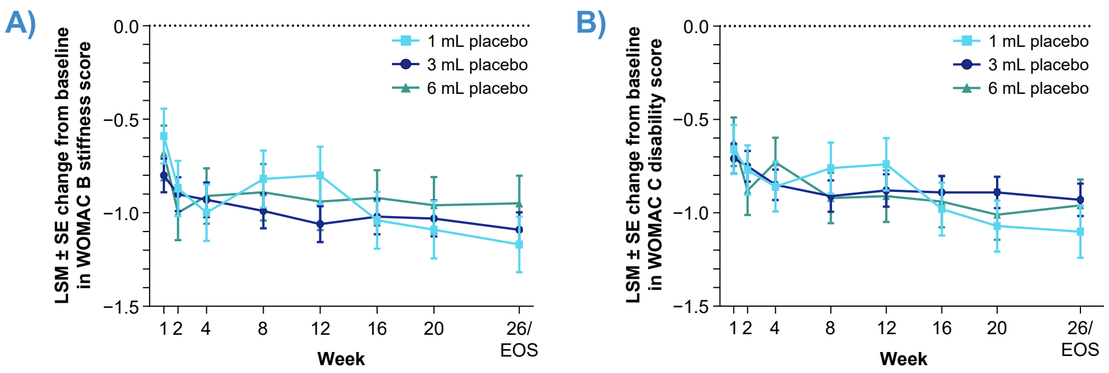


1 mL placebo, n =	28	28	27	28	28	28	28	28	28	27	27	28	28	28	28	28	27	26	26	26	26	25	23
3 mL placebo, n =	78	78	76	74	74	74	73	73	71	71	71	71	70	71	71	71	71	72	72	72	71	70	71	70	68	64
6 mL placebo, n =	28	28	28	28	28	28	27	28	28	28	27	28	27	28	27	27	27	27	27	27	27	27	27	27	27	26

LSMs are from a repeated-measures mixed model with fixed effects for treatment (1, 3, and 6 mL of MM-II and 1, 3, and 6 mL of placebo), visit, and treatment-by-visit interaction; random effect for participant; and covariates of site and baseline WADP assessed by VAS, BMI, and VAS group. Only placebo groups are presented. Error bars are ± SE.
BMI, body mass index; EOS, end of study; LSM, least squares mean; SE, standard error; VAS, visual analog scale, WADP, weekly average of daily knee pain.

- As was seen with the WOMAC A and WADP scores, the volume of placebo injected did not influence the change from baseline in WOMAC B stiffness or WOMAC C disability scores (**Figure 4**)

Figure 4. Change from baseline in A) WOMAC B stiffness score and B) WOMAC C disability score over time



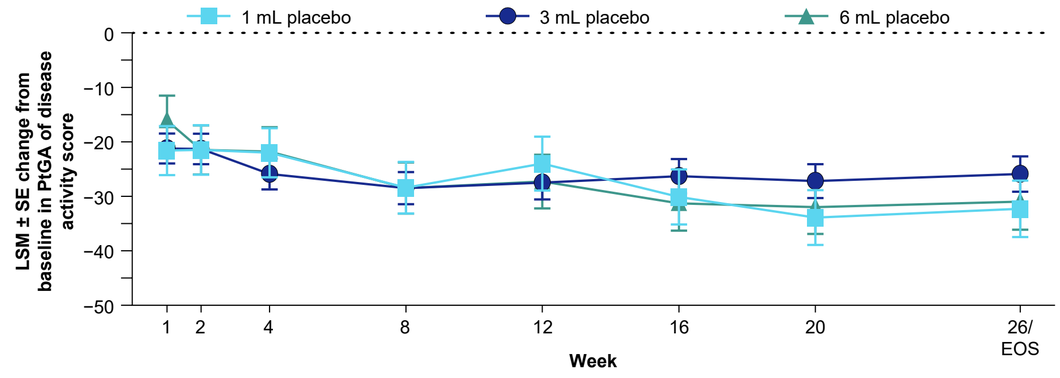
1 mL placebo, n =	28	28	28	28	28	27	27
3 mL placebo, n =	78	75	75	74	72	71	71
6 mL placebo, n =	27	28	28	28	28	28	27

1 mL placebo, n =	28	28	28	28	28	27	27
3 mL placebo, n =	78	75	75	74	72	71	71
6 mL placebo, n =	27	28	28	28	28	28	27

LSMs are from a repeated-measures mixed model with fixed effects for treatment (1, 3, and 6 mL of MM-II and 1, 3, and 6 mL of placebo), visit, and treatment-by-visit interaction; random effect for participant; and covariates of site and baseline WOMAC B stiffness score or WOMAC C disability score, BMI, and VAS group. WOMAC scores were assessed on a 0 to 4 Likert scale. Only placebo groups are presented. Error bars are ± SE.
BMI, body index; EOS, end of study; LSM, least squares mean; SE, standard error; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

- PtGA of disease activity scores displayed a modest numeric reduction from week 1 to week 26, and remained similar between all placebo volume groups throughout the study (**Figure 5**)

Figure 5. Change from baseline in patient global assessment of disease activity over time



1 mL placebo, n =	28	28	28	28	28	27	26	27
3 mL placebo, n =	77	75	75	74	71	71	71	70
6 mL placebo, n =	25	28	28	28	27	28	27	27

LSMs are from a repeated-measures mixed model with fixed effects for treatment (1, 3, and 6 mL of MM-II and 1, 3, and 6 mL of placebo), visit, and treatment-by-visit interaction; random effect for participant; and covariates of site and baseline PtGA of disease activity, BMI, and VAS group. Only placebo groups are presented. Error bars are ± SE.
BMI, body mass index; EOS, end of study; LSM, least squares mean; PtGA, patient global assessment; SE, standard error; VAS, visual analog scale.

- The incidence of TEAEs was not meaningfully different between the 1-, 3-, and 6-mL placebo groups

Table 2. Overall summary of treatment-emergent AEs

	1 mL placebo (N = 28)		3 mL placebo (N = 78)		6 mL placebo (N = 28)	
	n (%)	E	n (%)	E	n (%)	E
AEs	15 (53.6)	34	46 (59.0)	104	19 (67.9)	40
SAEs	0	0	3 (3.8)	6	1 (3.6)	2
Study medication–related AEs[a]	1 (3.6)	2	1 (1.3)	1	2 (7.1)	4
Study procedure–related AEs[a]	1 (3.6)	1	1 (1.3)	1	1 (3.6)	1
Severe AEs	0	0	2 (2.6)	5	1 (3.6)	2
AEs of special interest	0	0	0	0	0	0
Injection-site AEs	2 (7.1)	2	2 (2.6)	2	0	0
Fatal AEs	0	0	0	0	0	0
AEs leading to discontinuation	0	0	1 (1.3)	1	0	0

E indicates the number of events, n (%) indicates the number of participants.
[a]Includes possibly, probably, and certainly related AEs.
AE, adverse event; SAE, serious AE.

Conclusions

- These post hoc analyses suggest that the volume of placebo injected by the IA route has no impact on pain outcomes in patients with knee OA
  - Previous findings also support the lack of volumetric effect of a placebo saline solution on WOMAC A scores[5]
- All 3 volumes tested were generally well tolerated, without meaningful differences in incidence of TEAEs
- Limitations of this post hoc analysis include the small sample size and differences in patient numbers between groups. Further studies are warranted to confirm our findings

References

1) Chen D, et al. *Bone Res*. 2017;5:16044. **2)** Wallace IJ, et al. *Proc Natl Acad Sci USA*. 114(35):9332-6. **3)** Charlesworth J, et al. *BMC Musculoskelet Disord*. 2019;20(1):151. **4)** Lundsgaard C, et al. *Scand J Rheumatol*. 2008;37(2):142-50. **5)** Bar-Or D, et al. *PLoS One*. 2014;9(2):e87910. **6)** Wang Y, et al. *J Orthop Res*. 2022;40(9):2004-14.

Acknowledgments

We thank the participants and their families, investigators, and research staff at participating sites. We thank our collaborators and the staff at NBCD. Medical writing and editorial support were provided by Juliette Bouyssou, PhD, of AlphaBioCom, a Red Nucleus company, and funded by Moebius Medical.

Disclosures

BB, **SLY**, **RC**, **TJ**, **MK**, and **SW** are employees and shareholders of Sun Pharmaceutical Industries, Inc. **XC** has nothing to declare. **ARB** is an employee and shareholder of NBCD A/S. **RW** is an employee and shareholder of Moebius Medical. **TJS** has received consulting fees or served on advisory boards for AstraZeneca, Eli Lilly, GSK, Horizon Therapeutics, IBSA Group, Merck, Moebius Medical, Orion, Pfizer, Regeneron Pharmaceuticals, and Xalud Therapeutics. **PGC** has received speaker fees from AbbVie, Eli Lilly, and Novartis, and consultancies from AbbVie, Eli Lilly, Galapagos, Genascense, Grünenthal, GSK, Janssen, Levicept, Merck, Moebius Medical, Novartis, Stryker, Takeda, and TrialSpark.

Presented at the 2024 OARSI World Congress on Osteoarthritis, April 18–21, 2024, in Vienna, Austria