

Three-year follow-up from a randomised controlled trial of a single intra-articular polyacrylamide hydrogel injection in subjects with knee osteoarthritis

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Abstract

Objective

A randomised controlled trial demonstrated comparable efficacy and safety of a single 6 mL intra-articular (IA) injection of 2.5% polyacrylamide hydrogel (2.5% iPAAG) versus hyaluronic acid (HA) over one year in adults with moderate-to-severe knee osteoarthritis (OA). This study evaluated the long-term effectiveness and safety of 2.5% iPAAG.

Methods

This 3-year extension of a randomised controlled trial (RCT) (ClinicalTrials.gov Identifier: NCT04045431) followed participants who received a single 6 mL IA injection of 2.5% iPAAG. Outcomes included changes from baseline to year 3 in WOMAC pain, stiffness, and physical function subscales (0–100 scale) and patient global assessment (PGA) of OA impact. Safety was assessed up to year 3.

Results

A total of 119 participants received IA 2.5% iPAAG. After one year, 91 participants (44 females) entered the extension study, and 75 completed 3-years of follow-up. At year 3, the mean change in WOMAC pain was -13.1 (95% CI: -17.9 to -8.4; $p < 0.0001$). Between the 1-year and 3-year visits, fifty adverse events (AEs) were reported by 36 participants (29.8%), none of which were assessed as related to 2.5% iPAAG.

Conclusion

A single 6 mL IA injection of 2.5% iPAAG appears to be safe and effective in providing sustained symptom relief for up to 3 years in individuals with knee OA.

Key words

osteoarthritis, polyacrylamide hydrogels, hyaluronic acid, intra-articular injections

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Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder, affecting over 595 million people globally, with projections exceeding 1.1 billion by 2050 (1) with the knee being the most commonly affected joint (2-3). OA is characterised by chronic pain, stiffness, and functional impairment, driven by cartilage degradation, subchondral bone remodeling, osteophyte formation, and synovial inflammation (1,4) Aging is the primary non-modifiable risk factor, while obesity, joint injury, increased mechanical loading, and muscle weakness contribute to disease progression (1). Current OA management remains symptomatic, emphasising pain relief, functional improvement, and lifestyle modifications. Standard treatments such as exercise, weight management, non-steroidal anti-inflammatory drugs (NSAIDs), and intra-articular (IA) corticosteroids provide limited relief, and no disease-modifying osteoarthritis drugs have been demonstrated. While IA injections such as glucocorticoids and hyaluronic acid (HA) offer short-term pain relief, their long-term efficacy remains controversial, necessitating repeated administration with uncertain benefits over placebo (1, 5-6).

Injectable polyacrylamide hydrogel (2.5% iPAAG, Contura Ltd) is a biocompatible, non-degradable hydrogel, recently approved in the European Union for knee OA. Animal experiments indicate that 2.5% iPAAG is a self-integrating synovial implant, which incorporates into the synovial tissue, forming a stable, long-lasting gel matrix (7). Comprising 2.5% polyacrylamide and 97.5% non-pyrogenic water, it integrates into soft tissue, maintaining its volume through continuous water exchange (8-10). It has been used for soft tissue augmentation (11) and stress urinary incontinence (12) for over 20 years.

A randomised controlled trial by Bliddal *et al.* (2024), demonstrated comparable efficacy and safety of 6 mL 2.5% iPAAG *versus* HA over one year. Given the chronic nature of OA, evaluating long-term outcomes is crucial. This study aimed to evaluate the safety and sustained efficacy of 2.5% iPAAG up to 3 years after initial IA injection.

Materials and methods

Study design and regulatory approvals

The original study was a one year blinded randomised controlled trial (RCT) evaluating the efficacy and safety of a single IA injection of 6 mL 2.5% iPAAG in knee OA. This RCT was conducted at three sites in Denmark and enrolled 239 participants, who were randomised 1:1 to receive either 2.5% iPAAG (Arthrosamid, n=119) or HA (Synvisc-One; n=120) (9). The trial remained blinded for one year, after which it was unblinded, and an extension phase was initiated, primarily for safety reasons, to follow participants in the 2.5% iPAAG arm for up to five years.

Additionally, a subgroup analysis was conducted to assess the efficacy in patients aged <70 and ≥70 years. The choice of 70 years as the cut-off was guided by both clinical relevance and statistical considerations. Clinically, 70 years corresponds closely to the average age for primary total knee replacement in Europe (13), representing a threshold where patients are more likely to transition from conservative to surgical management of knee OA. Statistically, this cut-off provided two subgroups of sufficient and comparable size to preserve analytical power while enabling exploration of potential age-related differences in treatment response.

The original protocol and subsequent amendments were approved by the regional ethics committee (ref. no.: H 19003910) and the Danish Health Authority. The trial was conducted according to Good Clinical Practice (GCP) and registered at clinicaltrials.gov (NCT04045431). Participants provided written informed consent before enrolment and signed a new consent form to participate in the extension phase.

Inclusion and exclusion criteria for the main study

The inclusion and exclusion criteria have been previously described (9) and are summarised briefly here.

Inclusion criteria: Adults diagnosed with knee OA according to American College of Rheumatology (ACR) (14) criteria, radiographic evidence of Kellgren-Lawrence (KL) grade 2–4,

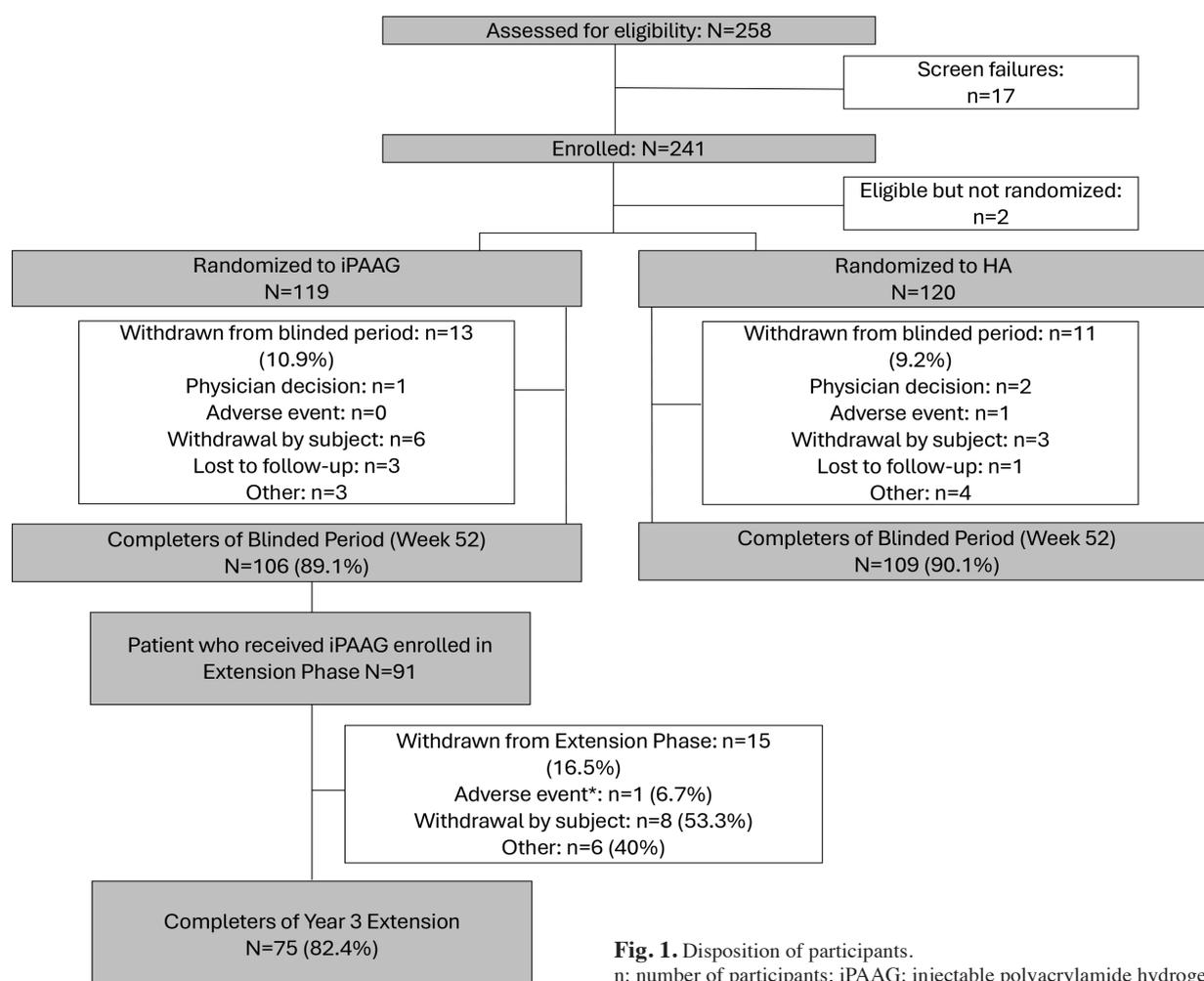


Fig. 1. Disposition of participants. n: number of participants; iPAAG: injectable polyacrylamide hydrogel.

pain intensity ≥ 4 (on a 0–10 numerical rating scale) when walking in the past week, BMI 20–35 kg/m², stable analgesic use (if any) for at least four weeks, and (for females of reproductive potential) adequate contraception throughout the study.

Exclusion criteria: History of other knee joint diseases, prior treatment with 2.5% iPAAG, HA, or its derivatives, surgery in the target knee within the past 6 months, IA corticosteroid injection within the past 3 months, or skin disease at the injection site.

Study procedures and treatment administration

All injections were administered by experienced investigators trained in IA injection techniques. Participants were allowed to continue analgesics (except 48 hours prior to study visits) and non-pharmacological therapies, but topical (on the target knee) and systemic

corticosteroids as well as additional IA injections were prohibited.

Outcomes

This long-term extension study evaluates changes from baseline to year 3 in WOMAC pain, stiffness, and physical function subscales (normalised to 0–100 scales, where higher scores indicate worse symptoms), as well as participants' global assessment (PGA) of knee OA impact, measured on a 0–100 mm visual analogue scale, with higher scores indicating greater perceived disease impact. Furthermore, a *post-hoc* subgroup analysis was conducted for participants aged ≤ 70 and >70 years on the WOMAC pain subscale. Additionally, the study reports the time to knee replacement.

Adverse events (AEs) and adverse device effects (ADEs) were meticulously recorded in the electronic case report form at each study visit following GCP

recommendations (ISO 14155:2020). Participants reported AEs at every visit, including unscheduled visits and telephone follow-ups.

Statistical analysis

The changes from baseline to year 3 for the WOMAC subscales were analysed using a mixed model for repeated measures (MMRM) with a restricted maximum likelihood (REML)-based approach. The model included fixed categorical effects of time (all timepoints from baseline; weeks 4, 12, 26, 52, 104, and 156), baseline value, and baseline value by time interaction as covariates. The estimated changes based on the least squares means at years 3 (week 156) are presented using 95% confidence intervals (CIs) using all available data from the 2.5% iPAAG population analysis set (*i.e.* all participants who received the study intervention). Missing data were not imputed but rather

Table I. Demographic and baseline characteristics.

	2.5% iPAAG population n=119	Included in extension study n=91	Not included in extension study n=28	Difference (95% CI)
Age (years), mean (SD)	67.2 (9.5)	67.5 (9.0)	66.1 (10.9)	1.40 (-2.66; 5.46)
Sex: female (n, %)	58 (48.7)	44 (48.4)	14 (50.0)	
Race: White (n, %)	118 (99.2)	90 (98.9)	28 (100.0)	
Height (cm), mean (SD)	172.9 (9.4)	172.7 (9.4)	173.6 (9.7)	-0.91 (-4.96; 3.15)
Weight (kg), mean (SD)	82.6 (13.5)	81.7 (12.7)	85.6 (15.5)	-3.87 (-9.61; 1.87)
BMI (kg/m ²), mean (SD)	27.58 (3.60)	27.37 (3.58)	28.26 (3.64)	-0.89 (-2.43; 0.65)
Baseline WOMAC pain, mean (SD)	45.1 (13.4)	44.1 (12.6)	48.4 (15.5)	-4.33 (-10.04; 1.39)
Baseline WOMAC stiffness, mean (SD)	52.7 (20.8)	53.6 (19.3)	50.0 (25.2)	3.57 (-5.34; 12.48)
Baseline WOMAC phys. function, mean (SD)	44.4 (15.1)	42.7 (14.7)	50.0 (15.2)	-7.30 (-13.64; -0.97)
Baseline PGA, mean (SD)	58.3 (18.3)	56.5 (17.4)	64.1 (20.0)	-7.55 (-15.28; 0.17)
Year 1 WOMAC pain, mean (SD)	n=107 26.3 (19.5)	n=91 24.0 (18.0)	n=16 39.1 (23.4)	-15.05 (-25.18; -4.92)
Year 1 WOMAC stiffness, mean (SD)	n=107 33.6 (24.9)	n=91 31.5 (23.7)	n=16 46.1 (28.4)	-14.64 (-27.79; -1.49)
Year 1 WOMAC phys. function, mean (SD)	n=107 24.5 (20.7)	n=91 21.9 (18.4)	n=16 39.0 (27.2)	-17.05 (-27.75; -6.36)
Year 1 PGA, mean (SD)	n=107 38.7 (27.1)	n=91 36.2 (25.4)	n=16 53.1 (32.1)	-16.95 (-31.19; -2.71)

iPAAG: injectable polyacrylamide hydrogel; CI: confidence interval; BMI: Body Mass Index; SD: standard deviation; PGA: Patient Global Assessment; n: number of participants contributing to the analysis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table II. Analyses of change from baseline in transformed WOMAC subscales (0–100) and Patient Global Assessment score.

	At 3 years		
	n.	LS mean (95% CI)	p-value
WOMAC pain subscale			
Population	75	-13.1 (-17.9; -8.4)	<0.0001
Extension participants	75	-15.3 (-19.9; 10.6)	<0.0001
BOCF	119	-10.8 (-14.3; -7.4)	<0.0001
WOMAC stiffness subscale			
Population	75	-14.4 (-19.7; -9.1)	<0.0001
Extension participants	75	-17.4 (-22.7; 12.1)	<0.0001
BOCF	119	-12.4 (-16.5; -8.3)	<0.0001
WOMAC phys. function subscale			
Population	75	-11.8 (-16.5; -7.2)	<0.0001
Extension participants	75	-14.3 (-18.8; -9.8)	<0.0001
BOCF	119	-10.4 (-13.8; -7.1)	<0.0001
Patient Global Assessment			
Population	74	-18.3 (-24.2; 12.4)	<0.0001
Extension participants	74	-20.0 (-25.8; 14.2)	<0.0001
BOCF	119	-14.0 (-18.4; -9.6)	<0.0001

n: number of subjects contributing to the analysis; CI, confidence interval; LS Mean: least squares mean; BOCF: Baseline Observation Carried Forward; participants' global assessment measures the impact of the subjects' knee osteoarthritis on their overall life using a 0–100 VAS. Here 0 is no impact at all and 100 is worst imaginable impact. The analysis is performed on change from baseline using a mixed model for repeated measures including fixed, categorical effects of treatment, week, treatment-by-week interaction and site, as well as the baseline value and baseline-by-week interaction as covariates.

handled using the maximum likelihood estimation. No adjustments for multiplicity were done.

Two sensitivity analyses were included to confirm the findings from the MMRM analyses:

1. An analysis of covariance model analysed the 3-year data of the entire 2.5% iPAAG population, with missing values replaced by the baseline values (*i.e.* Baseline Observation Carried Forward, BOCF).

2. The MMRM analysis was repeated using only the data from the study participants entering the extension year 3. The analysis of the change from baseline in the transformed WOMAC pain subscale for the age subgroup was performed using the same MMRM model as the main analysis. Differences between age groups were tested using an ANOVA model of change from baseline with age group as fixed effect.

Results

Extension phase and patient disposition

The participant flow is presented in Figure 1. Subject disposition in the main study has been previously reported (9). Of the 91 participants who entered the extension study, 75 completed the 3-year follow-up. One withdrawal was due to a non-treatment-related death. Among the six participants who withdrew for 'other' reasons, five underwent knee replacement, and one received a repeat 2.5% iPAAG injection.

Demographic and baseline characteristics of participants

Table I summarises the demographics and baseline characteristics of partici-

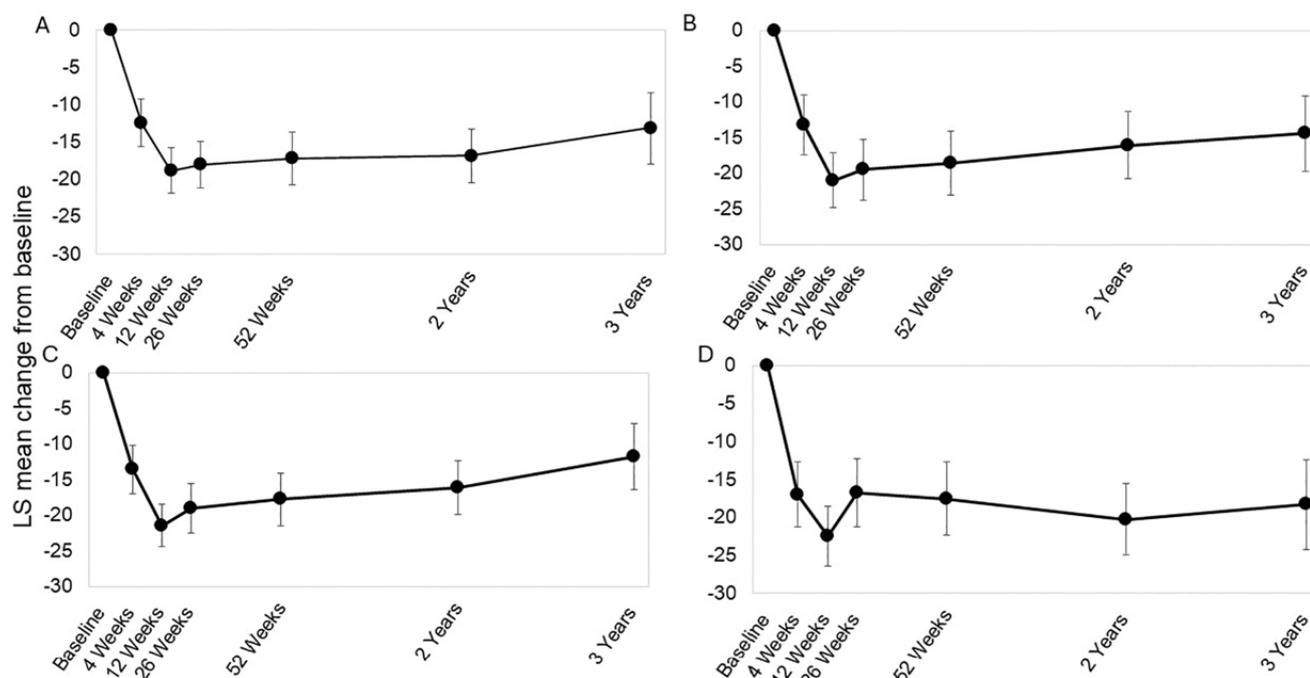


Fig. 2. Mean change from baseline to Year 3 in WOMAC Pain (A), Stiffness (B), Physical Function (C) subscales, and Participants' Global Assessment (PGA) (D). The analysis was performed on change from baseline using a mixed model for repeated measures, including fixed categorical effects of week and site, as well as the baseline value and baseline-by-week interaction as covariates. Error bars indicate confidence intervals.

LSMean: least squares mean; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

participants treated with 2.5% iPAAG, categorised by inclusion or non-inclusion in the extension phase. The baseline WOMAC physical function subscale score was lower in participants included in the extension phase compared to those not included ($p=0.0243$; 95% CI: -13.64 to -0.97), indicating less impairment in physical function at baseline among those who continued. Similarly, the lower mean baseline PGA score in participants included in the extension phase compared to those not included ($p=0.0553$; 95% CI: -15.28 to 0.17) suggests a lower perceived impact of knee OA at baseline among those who continued.

At year 1, the mean scores for WOMAC pain, WOMAC stiffness, WOMAC physical function subscales, and PGA were higher in participants not included in the extension study compared to those who continued (Table I), indicating worse symptoms and greater perceived disease impact in those who did not continue.

The participants included in the extension phase and those not included were comparable in terms of the remaining demographic and baseline characteristics.

Effectiveness endpoints

There were statistically significant reductions in all WOMAC subscales and the PGA from baseline to year 3 (Table II). These findings remained consistent across sensitivity analyses (Table II). Figure 2 illustrates the mean changes from baseline to year 3 in the transformed WOMAC pain, stiffness, and physical function subscales (0–100), as well as the PGA.

The analysis of changes from baseline in the transformed WOMAC pain subscale (0–100) showed statistically significant reductions at 2 years in both age groups (Fig. 3). At 3 years, the reduction remained significant for participants aged <70 years (18.3 points; 95% CI: -23.67 to 12.89, $p<0.0001$), while the reduction for those aged ≥ 70 years (3.90 points; 95% CI: -12.96 to 5.17, $p=0.3874$) was not statistically significant.

Concomitant treatments

Concomitant medication use was common, with paracetamol reported by 61 participants (51.3%) and ibuprofen by 23 participants (19.3%). Non-pharmacological therapies were also used, most notably physiotherapy in 19 par-

ticipants (16.0%). Procedural interventions during follow-up included joint aspiration in 8 participants (6.7%).

Time to knee replacement

Thirteen participants underwent knee replacement between the initiation of the extension study and their 3-year follow-up visit, with the median time to surgery being 728 days (Table III). Three of 119 (2.5%), had the procedure in the blinded study phase. The remaining 10 of 91 participants (11%) who continued into the extension study underwent knee replacement during the follow-up period. No follow-up data were available for the 15 participants who did not enter the extension study following completion of the main study.

Safety data

Between the 1-year and 3-year visits of this extension study, 36 participants (39.6%) reported a total of 50 AEs (Table IV). The most frequently reported AEs were arthralgia and joint swelling, with the majority classified as mild in intensity.

A total of six serious adverse events (SAEs) occurred in five participants (4.1%) during this period (Table IV),

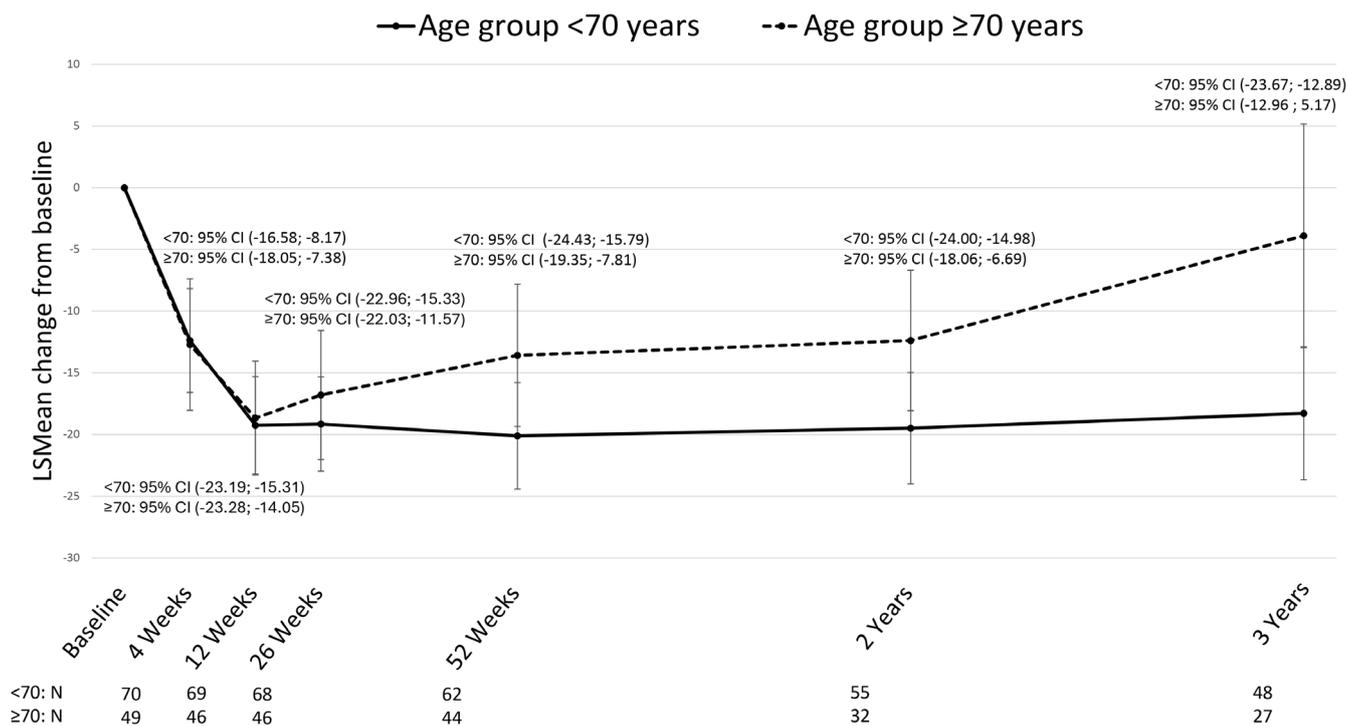


Fig. 3. Subgroup analysis of the WOMAC pain subscale by age from baseline to 3 years post-treatment. The analysis was performed on change from baseline using a mixed model for repeated measures including fixed, categorical effect of week, and baseline, and baseline by week interaction as covariates. LS Mean: least squares mean; N: number of subjects; CI: confidence interval.

including back pain, COVID-19 infection, death, two cases of myocardial infarction, and worsening of hip OA. None of these events were assessed as related to 2.5% iPAAG, and all, except for the death (Fatal AE, lead to withdrawal) (Table IV), resolved without sequelae.

Discussion

This study assessed the long-term effectiveness and safety of a single 6 mL IA injection of 2.5% iPAAG. At 3-years, improvements exceeded the minimal clinically important improvement (MCII) thresholds for WOMAC pain (9 points), function (6 points), and stiffness (7 points) on the 0–100 scale in patients with knee OA (15). These findings are consistent with previously reported outcomes at 1-year in both this trial and an open-label study (8, 9), suggesting that 2.5% iPAAG can provide long-term symptomatic relief. Participants under 70 years of age showed greater sustained benefit. The long-term follow-up strengthens this study, but several limitations remain. The absence of a comparator arm after year 1 prevents definitive attrib-

Table III. Summary of knee replacements for target knee OA from the initiation of the extension study and up to the 3-year extension safety analysis.

Time to knee replacement (days)	
n.	13*
mean (SD)	708.9 (312.1)
median	728.0
min-max	212-1063

n: number of subjects; SD: standard deviation.
 *No follow-up data are available for the 15 participants who did not continue from the main study into the extension study.

Table IV. Overview of adverse events between 1- and 3-year extension study visits.

	Extension participants, n=91
	N (%) E
Adverse events (AEs)	36 (39.6) 50
Serious AEs	5 (5.5) 6
Adverse device effects (ADEs)	0
Serious ADEs (SADEs)	0
Unanticipated serious ADEs	0
AEs leading to withdrawal from study	1 (1.1) 1
Fatal AEs	1 (1.1) 1

N: number of subjects experiencing the event at least once; %: percentage of subjects.
 E: total number of instances of reporting of the event.

tion of the observed benefits to 2.5% iPAAG. We cannot rule out placebo effects, regression to the mean, or other time-related factors. Nevertheless, the magnitude and consistency of im-

provements across sensitivity analyses support the potential for a true long-term treatment effect. Concomitant therapies present another limitation. At the 3-year visit, we re-

corded the number of participants using analgesics, physiotherapy, or procedural interventions; however, we did not record dosage, frequency, or duration. Concomitant treatments may have contributed, but the improvements remained clinically meaningful. Sensitivity analyses, including the conservative BOCF approach, support that these effects were not solely due to co-treatments

Selection bias may also have influenced the results. Participants who continued into the extension phase had better WOMAC and PGA scores at year 1 than those who did not, suggesting they experienced greater symptom control. A conservative BOCF analysis still demonstrated meaningful improvements, supporting the robustness of the findings, though the potential for overestimation of treatment effects remains.

The exact mechanism by which 2.5% iPAAG alleviates knee pain, stiffness, and functional impairment is unknown. Preclinical animal model studies show that following IA injection, 2.5% iPAAG is incorporated in the synovial subintima, likely as a combined action of the natural clearing mechanism of debris in the joint cavity and the general foreign body response on the synovial implant (7, 16). In these models, a stable, long-lasting sub-synovial gel layer has been observed to persist in both healthy and osteoarthritic joints (7). Additionally, post-mortem analyses in animal models suggest that 2.5% iPAAG has a positive impact on joint capsule elasticity (17).

The preclinical evidence of improved elasticity may help explain why WOMAC stiffness scores in particular showed long-term improvement in the 2.5% iPAAG treated participants.

Currently, only a limited number of established IA treatments are available for knee OA (1, 18-19). Corticosteroids, HA, and PRP are widely used but typically provide only short-term relief and may carry safety concerns (1, 6, 18-22). A recent phase 3 trial of IA locevicivint also failed to show meaningful improvements in pain, function, or structural outcomes over 56 weeks, despite a favourable safety profile (23). These challenges highlight the difficulty

of achieving long-term efficacy with injectable therapies and place the sustained 3-year improvements observed with 2.5% iPAAG into a broader clinical context.

Taken together, these results suggest that a single IA injection of 2.5% iPAAG may provide sustained symptomatic relief for knee OA for up to 3-years, with an acceptable safety profile.

Conclusion

In this long-term extension study, a single 6 mL IA injection of 2.5% iPAAG in individuals with knee OA demonstrated a favourable safety profile. Also, the study found indications of a long-term effect in a considerable number of participants.

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References

1. KLOPPENBURG M, NAMANE M, CICUTTINI F: Osteoarthritis. *Lancet* 2025; 405(10472): 71-85. [https://doi.org/10.1016/s0140-6736\(24\)02322-5](https://doi.org/10.1016/s0140-6736(24)02322-5)
2. KATZ JN, ARANT KR, LOESER RF: Diagnosis and treatment of hip and knee osteoarthritis: a review. *JAMA* 2021; 325(6): 568-78. <https://doi.org/10.1001/jama.2020.22171>
3. KRAUS VB, BLANCO FJ, ENGLUND M, KARSDAL MA, LOHMANDER LS: Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage* 2015; 23(8): 1233-41. <https://doi.org/10.1016/j.joca.2015.03.036>
4. MUKHERJEE A, DAS B: The role of inflammatory mediators and matrix metalloproteinases (MMPs) in the progression of osteoarthritis. *Biomater Biosyst* 2024; 13: 100090. <https://doi.org/10.1016/j.bbiosy.2024.100090>
5. SEN R, HURLEY J: Osteoarthritis. StatPearls [Internet] (2022): StatPearls Publishing, Treasure Island (FL).
6. KOLASINSKI SL, NEOGI T, HOCHBERG MC *et al.*: 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020; 72(2): 220-33. <https://doi.org/10.1002/art.41142>
7. CHRISTENSEN L, CAMITZ L, ILLIGEN KE, HANSEN M, SARVAA R, CONAGHAN PG: Synovial incorporation of polyacrylamide hydrogel after injection into normal and osteoarthritic animal joints. *Osteoarthritis Cartilage*

2016; 24(11): 1999-2002.

<https://doi.org/10.1016/j.joca.2016.07.007>

8. BLIDDAL H, BEIER J, HARTKOPP A, CONAGHAN PG, HENRIKSEN M: Effectiveness and safety of polyacrylamide hydrogel injection for knee osteoarthritis: results from a 12-month follow up of an open-label study. *J Orthop Surg Res* 2024; 19(1): 274. <https://doi.org/10.1186/s13018-024-04756-2>
9. BLIDDAL H, BEIER J, HARTKOPP A, CONAGHAN PG, HENRIKSEN M: Polyacrylamide gel versus hyaluronic acid for the treatment of knee osteoarthritis: a randomised controlled study. *Clin Exp Rheumatol* 2024; 42(9): 1729-35. <https://doi.org/10.55563/clinexprheumatol/i3fqqe>
10. HENRIKSEN M, OVERGAARD A, HARTKOPP A, BLIDDAL H: Intra-articular 2.5% polyacrylamide hydrogel for the treatment of knee osteoarthritis: an observational proof-of-concept cohort study. *Clin Exp Rheumatol* 2018; 36(6): 1082-85.
11. PALLUAN G, WOLTER TP: A 5-year assessment of safety and aesthetic results after facial soft-tissue augmentation with polyacrylamide hydrogel (Aquamid): a prospective multicenter study of 251 patients. *Plast Reconstr Surg* 2010; 125(6): 1797-804. <https://doi.org/10.1097/prs.0b013e3181d18158>
12. BROSCHE T, KUHN A, LOBODASCH K, SOKOLER: Seven-year efficacy and safety outcomes of Bulkamid for the treatment of stress urinary incontinence. *Neurourol Urodyn* 2021; 40(1): 502-8. <https://doi.org/10.1002/nau.24589>
13. LE STUM M, GICQUEL T, DARDENNE G, LE GOFF-PRONOST M, STINDEL E, CLAVÉ A: Total knee arthroplasty in France: male-driven rise in procedures in 2009-2019 and projections for 2050. *Orthop Traumatol Surg Res* 2023; 109(5): 103463. <https://doi.org/10.1016/j.otsr.2022.103463>
14. ALTMAN R, ASCH E, BLOCH D *et al.*: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; 29(8): 1039-49. <https://doi.org/10.1002/art.1780290816>
15. BELLAMY N, HOCHBERG M, TUBACH F *et al.*: Development of multinational definitions of minimal clinically important improvement and patient acceptable symptomatic state in osteoarthritis. *Arthritis Care Res (Hoboken)* 2015; 67(7): 972-80. <https://doi.org/10.1002/acr.22538>
16. TNIBAR A: Intra-articular 2.5% polyacrylamide hydrogel, a new concept in the medication of equine osteoarthritis: a review. *J Equine Vet Sci* 2022; 119: 104143. <https://doi.org/10.1016/j.jevs.2022.104143>
17. TNIBAR A, PERSSON A, JENSEN H: Mechanisms of action of an intraarticular 2.5% polyacrylamide hydrogel (Arthramid Vet) in a goat model of osteoarthritis: preliminary observations. *SM J Biomed Eng* 2017; 3(4): 1022.
18. FUSCO G, GAMBARO FM, DI MATTEO B, KON E: Injections in the osteoarthritic knee: a review of current treatment options. *EFORT Open Rev* 2021; 6(6): 501-9.

- <https://doi.org/10.1302/2058-5241.6.210026>
19. LIU SH, DUBÉ CE, EATON CB, DRIBAN JB, MCALINDON TE, LAPANE KL: Longterm effectiveness of intraarticular injections on patient-reported symptoms in knee osteoarthritis. *J Rheumatol* 2018; 45(9): 1316-24. <https://doi.org/10.3899/jrheum.171385>
20. PEREIRA TV, SAADAT P, BOBOS P *et al.*: Effectiveness and safety of intra-articular interventions for knee and hip osteoarthritis based on large randomized trials: A systematic review and network meta-analysis. *Osteoarthritis Cartilage* 2025; 33(2): 207-17. <http://doi.org/10.1016/j.joca.2024.08.014>
21. MILLER LE, BHATTACHARYYA S, PARRISH WR, FREDERICSON M, BISSON B, ALTMAN RD: Safety of intra-articular hyaluronic acid for knee osteoarthritis: systematic review and meta-analysis of randomized trials involving more than 8,000 patients. *Cartilage* 2021; 13(1_suppl): 351S-363S. <https://doi.org/10.1177/1947603519888783>
22. PEREIRA TV, JÜNI P, SAADAT P *et al.*: Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis. *BMJ* 2022; 378: e069722. <https://doi.org/10.1136/bmj-2022-069722>
23. YAZICI Y, TAMBIAH JRS, SWEARINGEN CJ *et al.*: A Phase 3, 56-week, randomised, double-blind, placebo-controlled study (OA-11) utilising patient-reported and radiographic outcomes evaluating the efficacy and safety of a loxecivint injection in patients with moderate to severe knee osteoarthritis. *Clin Exp Rheumatol* 2025; 43(5): 854-60. <https://doi.org/10.55563/clinexprheumatol/hjt118>