Sustained symptom relief and safety over five years following a single intra-articular injection of 2.5% polyacrylamide hydrogel in patients with knee osteoarthritis

H. Bliddal[1], J. Beier[2], A. Hartkopp[3], P.G. Conaghan[4], M. Henriksen[1]

[1]Department of Clinical Medicine, The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, University of Copenhagen, Denmark; [2]Gigtdoktor, Odense, Denmark; [3]A2 Rheumatology and Sports Medicine, Holte, Denmark; [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & NIHR Leeds Biomedical Research Centre, United Kingdom.

Abstract

Objective

A randomised controlled trial (RCT) demonstrated that a single 6 mL intra-articular (IA) injection of polyacrylamide hydrogel (iPAAG) provided comparable efficacy and safety to hyaluronic acid over one year in patients with moderate-to-severe knee osteoarthritis (OA). This study reports the longer-term outcomes of iPAAG.

Methods

In this long-term extension of the RCT (ClinicalTrials.gov Identifier: NCT04045431), participants treated with IA 2.5% iPAAG were followed for changes from the RCT baseline in WOMAC pain, stiffness, and physical function subscales (0–100), as well as patient global assessment (PGA) of OA impact. Safety was monitored throughout the extension study.

Results

Of 119 participants initially treated with iPAAG, 91 (47 men) entered the extension, and 58 completed 5 years of follow-up. At year 5, WOMAC pain improved by a mean of -16.2 points (95% CI: -20.0 to -12.4; p<0.0001). Similar improvements were observed across other WOMAC domains and PGA. Between years 1 and 5, 79 adverse events (AEs) were reported in 47 participants (51.6%), none considered related to iPAAG.

Conclusion

A single IA injection of iPAAG was associated with sustained improvements in pain and function, with a favourable safety profile maintained through 5 years. These observational data support iPAAG as a promising long-acting, non-surgical treatment option for knee OA.

Key words

knee osteoarthritis, implant, synovium, integrating, device

Henning Bliddal, DMSc
Jannie Beier, MD
Andreas Hartkopp, PhD
Philip G. Conaghan, MD, MBBS, PhD
Marius Henriksen, MD, PhD

Please address correspondence to:
Henning Bliddal
Bispebjerg Frederiksberg Hospital,
University of Copenhagen,
Nordre Fasanvej 57,
DK-2000 Frederiksberg, Denmark.
E-mail: henning.bliddal@regionh.dk

Received on October 15, 2025; accepted in revised form on December 23, 2025.

Funding: this study was sponsored by Contura International A/S, which was involved in the study design, data analysis, and interpretation.
The clinical investigation report was prepared by Contura International A/S, which also provided sponsorship for editorial and medical writing support for this manuscript and was responsible for the decision to submit it for publication. The authors retained full control over the interpretation of the study findings, the development of the manuscript, and the sponsor had no role in shaping the scientific conclusions beyond the acknowledged editorial support.
M. Henriksen and H. Bliddal receive partial funding from the OAK Foundation, which provides a core grant to The Parker Institute (OFIL-24-074).
P.G. Conaghan has received speaker's bureau/consultancy fees from AbbVie, Eli Lilly, Eupraxia, Formation Bio, Genascence, GSK, Grünenthal, Janssen, Kolon TissueGene, Levicept, Moebius, Novartis, Pacira, Stryker, and Takeda; and is partially funded by the National Institute for Health and Care Research (NIHR) Leeds Biomedica
The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Competing interests: none declared.

Introduction

Osteoarthritis (OA) remains the most challenging musculoskeletal condition worldwide with a high burden of disease, with the knee being the most affected joint and characterised by chronic pain (1-5). The pathological process in OA involves the whole joint, with progressive damage beginning in the articular cartilage and extending to the subchondral bone and synovial tissues (6). Symptoms of OA are pain, stiffness, swelling, and limited range of motion (6, 7). The most frequently associated risk factors for knee OA are aging, genetic predisposition, obesity, and muscle weakness (6, 8).

Currently, there is no curative treatment for OA. Management in routine clinical practice relies on a combination of pharmacological options, such as analgesics, topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular (IA) corticosteroid or hyaluronic acid (HA) injections, together with non-pharmacological measures, including therapeutic and aerobic exercise, and lifestyle modifications (7-9). These approaches offer short-term benefit, especially in moderate-to-severe knee OA, but long-term efficacy remains limited (6-7). Repeated IA corticosteroid injections raise safety concerns and have been linked to an increased degeneration of cartilage (10) and risk of subsequent knee arthroplasty (11), whereas HA injections demonstrate inconsistent efficacy and typically require multiple administrations (12-14).

Injectable polyacrylamide hydrogel (iPAAG; Arthrosamid®, Contura Ltd.) is a novel non-surgical option for knee OA. It contains 2.5% cross-linked polyacrylamide and 97.5% non-pyrogenic water. The material is non-degradable and maintains long-term integrity through synovial integration and continuous water exchange (15, 16). Unlike biodegradable agents, iPAAG is naturally integrated into the synovial membrane after IA injection where it forms a permanent, non-resorbable implant within the joint, with indications of sustained improvements in stiffness, pain and function of the knee (15-17). With over two decades of clinical use, iPAAG has shown biocompatibility in soft tissue augmentation (18) and treatment of stress urinary incontinence (19). Preclinical studies have demonstrated stable synovial integration and durable symptom relief in animal models without safety concerns, while *in vitro* investigations using human induced pluripotent stem cells confirmed that iPAAG does not exhibit neurotoxicity (20-22).

A randomised controlled trial (RCT) by Bliddal *et al*. compared a single 6 mL IA injection of iPAAG with 6 mL of HA in patients with knee OA, and demonstrated comparable efficacy and safety at one year (16) An observational extension was then conducted to assess durability of clinical outcomes. This manuscript presents the 5-year outcomes from the iPAAG arm, evaluating the long-term safety and sustained symptomatic benefit of a single IA injection in moderate to severe knee OA.

Materials and methods

Study design and regulatory approvals

This study was a long-term extension of a randomised controlled trial (RCT) evaluating the efficacy and safety of a single 6 mL intra-articular (IA) injection of iPAAG in knee OA. The original RCT was conducted at three sites in Denmark, enrolling 239 participants randomized 1:1 to iPAAG (n=119) or hyaluronic acid (HA; Synvisc-One® (Sanofi Genzyme), n=120). The trial remained blinded for one year, after which it was unblinded, and participants in the iPAAG arm were followed for up to 5 years.

The study protocol was approved by the regional ethics committee (ref. no.: H 19003910) and the Danish Health Authority. It was conducted in accordance with Good Clinical Practice (GCP) and registered at clinicaltrials.gov (NCT04045431). All participants provided written informed consent for the main study and signed a separate consent form for the extension phase.

Inclusion and exclusion criteria for the main study

The inclusion and exclusion criteria for the main trial have been published previously (17). In brief, adults with symp-

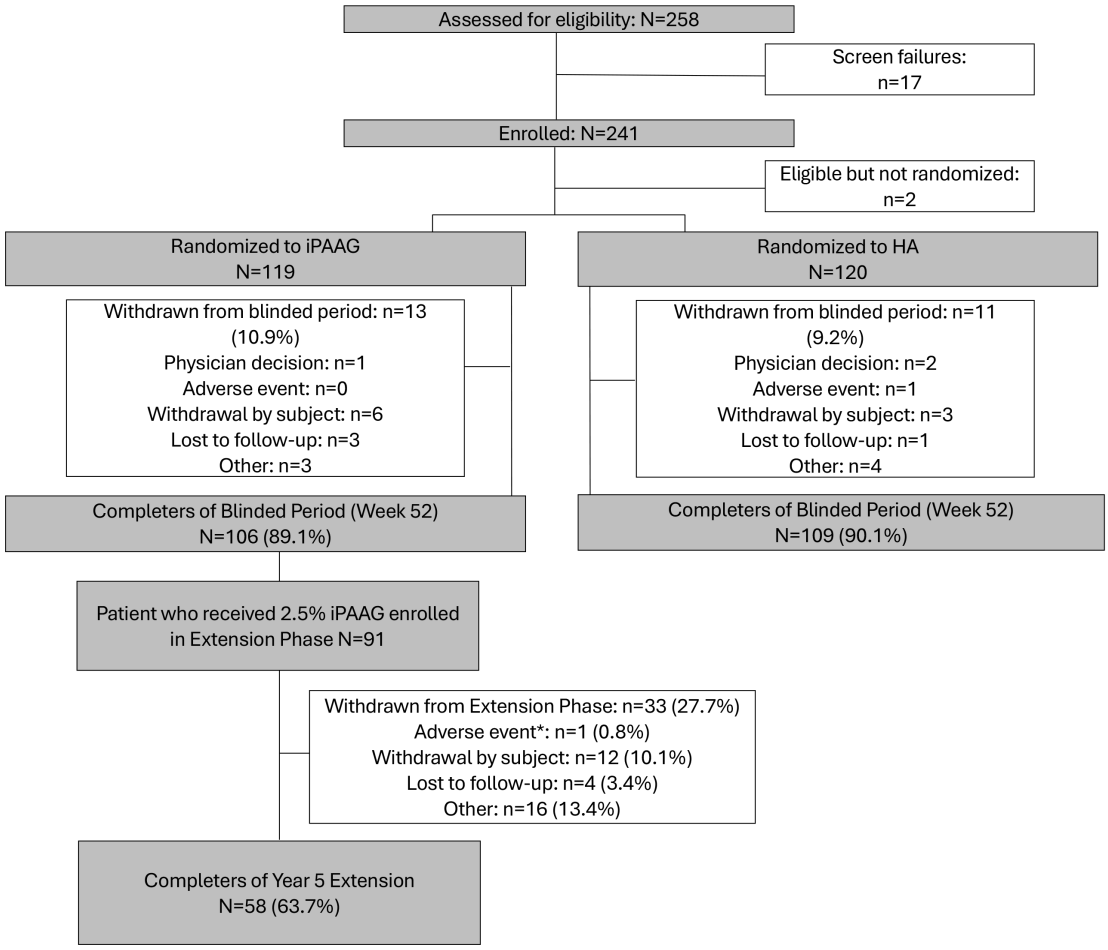

Fig. 1. Disposition of participants.
n: number of participants; iPAAG: injectable polyacrylamide hydrogel. * Non-treatment-related death. ** The 16 subjects that withdrew from study due to 'other' all received new therapy for their target knee: 15 had knee replacement while one subject was re-injected with 2.5% iPAAG.

tomatic knee OA fulfilling ACR criteria, radiographic KL grade 2–4, and pain on walking on flat surface ≥4/10 were eligible, provided they met BMI and analgesic stability requirements. Key exclusions included other knee pathology, recent surgery or intra-articular corticosteroid use, and previous exposure to iPAAG or hyaluronic acid.

Study procedures and treatment administration

Details of the injection procedure and permitted concomitant treatments have been reported previously (17). In summary, intra-articular injections were performed by experienced investigators, and participants could continue stable analgesics and non-pharmacological interventions, while systemic and topical corticosteroids or additional intra-articular treatments were not allowed.

Extension phase and patient disposition

A total of 91 participants from the iPAAG group entered the long-term extension phase, with 58 completing the 5-year follow-up visit.

Outcome measures

This long-term extension evaluated changes from the RCT baseline to year 5 in WOMAC pain, stiffness, and physical function subscales (normalised to 0–100, higher scores indicate worse symptoms), and participants' global assessment (PGA) of OA impact on a 0–100 mm visual analogue scale (higher scores indicate greater impact). A *post-hoc* subgroup analysis of WOMAC pain was performed by age (≤70 *vs.* >70 years), BMI (BMI normal: 18.5–24.9 kg/m^2, BMI overweight: 25–29.9 kg/m^2, BMI obese: above 30 kg/m^2) and Kellgren-Lawrence (KL) grade. Time to knee replacement was also recorded. Adverse events (AEs) and adverse device effects (ADEs) were recorded at each visit in accordance with GCP (ISO 14155:2020). Participants reported AEs at all scheduled and unscheduled visits, including telephone follow-ups.

Statistical analysis

Changes from RCT baseline to year 5 in WOMAC subscales were analysed using a mixed model for repeated measures (MMRM) with a restricted maximum likelihood (REML) approach. The model included fixed effects of time (baseline; weeks 4, 12, 26, 52, 104, 156, 260), baseline score, and baseline-by-time interaction. Least squares mean (LSM) changes with 95% confidence intervals (CIs) and *p*-values are reported at year 5 (week 260) based on the iPAAG population (all participants who received the intervention).

Table I. Demographic and baseline characteristics.

	iPAAG ITT population	Completers	Non-completers	Difference (95% CI)
	n=119	n=58	61 (100.0)	
Age (years), mean (SD)	67.2 (9.5)	67.2 (7.3)	67.1 (11.2)	0.1 (-3.4; 3.5)
Sex (n, %) Female	58 (48.7)	27 (46.6)	31 (50.8)	
Race (n, %) White	118 (99.2)	57 (98.3)	61 (100.0)	
Height (cm), mean (SD)	172.9 (9.4)	173.3 (9.0)	172.6 (10.0)	0.7 (-2.7; 4.2)
Weight (kg), mean (SD)	82.6 (13.5)	81.5 (12.8)	83.7 (14.1)	-2.1 (-7.0; 2.8)
BMI (kg/m^2), mean (SD)	27.58 (3.60)	27.12 (3.52)	28.03 (3.64)	-0.9 (-2.2; 0.4)
KL-grade (n, % of row)				
2	67 (100)	32 (47.8)	35 (52.2)	
3	39 (100)	22 (56.4)	17 (43.6)	
4	13 (100)	4 (37.8)	9 (62.2)	
Baseline WOMAC pain, mean (SD)	45.1 (13.4)	42.8 (13.7)	47.2 (12.9)	-4.4 (-9.2; 0.5)
Baseline WOMAC stiffness, mean (SD)	52.7 (20.8)	52.4 (19.1)	53.1 (22.4)	-0.7 (-8.3; 6.9)
Baseline WOMAC phys. function, mean (SD)	44.4 (15.1)	42.3 (16.0)	46.6 (14.0)	-4.3 (-9.7; 1.2)
Baseline PGA, mean (SD)	58.3 (18.3)	55.6 (16.8)	60.8 (19.3)	-5.2 (-11.8; 1.4)
	n=107			
Year 1 WOMAC pain, mean (SD)	26.3 (19.5)	20.3 (16.8)	33.3 (20.4)	-12.9 (-20.0; -5.8)
	n=107			
Year 1 WOMAC stiffness, mean (SD)	33.6 (24.9)	26.3 (21.9)	42.3 (25.6)	-16.1 (-25.2; -6.9)
	n=107			
Year 1 WOMAC phys. function, mean (SD)	24.5 (20.7)	18.5 (16.9)	31.5 (22.8)	-13.0 (-20.6; -5.4)
	n=107			
Year 1 PGA, mean (SD)	38.7 (27.1)	32.0 (24.1)	46.6 (28.5)	-14.6 (-24.7; -4.5)

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.
For categorical endpoints Pearsons asymptotic chi-square test is used.

All statistical tests were two-sided, and 95% CIs for LS mean changes were reported consistently across all WOMAC subscales. Missing data were handled using maximum likelihood estimation without imputation, and no multiplicity adjustments were applied.

Two sensitivity analyses were performed: 1. repeating the MMRM using only participants who completed the year 5 extension, and 2. an analysis of covariance (ANCOVA) of the full iPAAG population at year 5, with missing data replaced by baseline values (Baseline Observation Carried Forward, BOCF).

A *post-hoc* subgroup analysis of WOMAC pain was conducted using an age cut-off of ≤70 *versus* >70 years. This threshold was selected for both statistical and clinical reasons. Statistically, 70 years is close to the upper tertile of the cohort's age distribution (mean age 67.2 years), ensuring balanced subgroup sizes and sufficient power for comparison. Clinically, registry data from European populations show that the average age for primary total knee replacement is around 70 years (23), making this cut-off relevant to clinical decision-making, as patients above this age are more likely to undergo surgical intervention rather than continue with conservative management.

Results

Extension phase and patient disposition

The participant flow is presented in Figure 1. Subject disposition in the main study has been previously reported (17). Of the 91 participants who entered the extension study, 58 completed the 5-year follow-up. 16 participants were withdrawn because they initiated new treatments for their target knee: 15 underwent knee replacement surgery, and one received a repeat iPAAG injection. Twelve participants withdrew voluntarily, four were lost to follow-up and one participant died from a non–treatment-related death.

Demographic and baseline characteristics of participants

Table I presents the baseline characteristics of patients treated with iPAAG, stratified by completers and non-completers. At baseline, WOMAC pain, stiffness, physical function subscales, and PGA did not differ between groups, and overall demographics were comparable. By year 1, however, completers showed significantly lower scores in WOMAC pain, stiffness, physical function, and PGA compared with non-completers (p=0.0005, p=0.0007, p=0.0010,

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

	n	At 5 years LSMean (95% CI)	*p*-value
WOMAC pain subscale			
iPAAG ITT population	119	-16.2 (-20.0; 12.4)	<0.0001
Extension completers	58	-18.3 (-22.1; 14.5)	<0.0001
BOCF	119	-10.0 (-13.0; -7.0)	<0.0001
WOMAC stiffness subscale			
iPAAG ITT population	119	-12.7 (-18.7; -6.8)	<0.0001
Extension completers	58	-14.9 (-20.8; -8.9)	<0.0001
BOCF	119	-8.5 (-12.2; -4.8)	<0.0001
WOMAC phys. function subscale			
iPAAG ITT population	119	-11.4 (-15.9; -7.0)	<0.0001
Extension completers	58	-13.8 (-18.2; -9.5)	<0.0001
BOCF	119	-8.6 (-11.6; -5.7)	<0.0001
Patient Global Assessment			
iPAAG ITT population	119	-13.5 (-19.5; -7.4)	<0.0001
Extension completers	58	-16.7 (-22.9; -10.6)	<0.0001
BOCF	119	-10.2 (-13.9; -6.5)	<0.0001

n: number of subjects contributing to the analysis; CI: confidence interval; LSMean: Least squares mean; iPAAG: injectable polyacrylamide hydrogel; BOCF: Baseline Observation Carried Forward. Participants' global assessment measures the impact of the subject's 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.

Table III. Summary of knee replacements for target knee OA from the initiation of the extension study (1 year from RCT baseline) and up to the 5-year follow-up.

Time to knee replacement (years)	iPAAG
n	18*
mean (SD)	2.49 (1.17)
median	2.60
min-max	0.58 – 4.55

iPAAG: injectable polyacrylamide hydrogel; 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 5-year extension study visits.

	Extension participants - Safety analysis set n=91* n (%) E
Adverse events (AEs)	47 (51.6) 79
Serious AEs	10 (11.0) 11
Adverse device effects (ADEs)	0
Serious ADEs (SADEs)	0
Unanticipated Serious ADEs	0
AEs leading to withdrawal from study	1 (0.8) 1
Fatal AEs	1 (0.8) 1

N: Number of subjects experiencing the event at least once; %: Percentage of subjects; E: Total number of reporting of the event; *Safety analysis set.

and p=0.0050, respectively). This may indicate a poorer treatment effect in those who did not complete the extension study.

Effectiveness endpoints

Statistically significant improvements were observed across all WOMAC subscales and the PGA from baseline to year 5 (Table II). The results were robust, as confirmed by the sensitivity analyses (Table II). Figure 2 presents the mean changes from baseline to year 5 in the transformed WOMAC pain, stiffness, and physical function subscales (0–100), along with the PGA.

Evaluation of the transformed WOMAC pain subscale (0–100) revealed significant improvements from baseline at years 2, 4, and 5 across both age groups. At the 3-year assessment, participants <70 years demonstrated a significant reduction (18.3 points; 95% CI: –23.67 to –12.89, p<0.0001), whereas in those aged ≥70 years the reduction (3.90 points; 95% CI: –12.96 to 5.17, p=0.3874) did not reach statistical significance (Fig. 3A). The transformed WOMAC pain subscale (0–100) revealed significant improvements from baseline at all evaluated timepoints for all BMI subgroups (p<0.01) except for obese participants at year 3 (p=0.3330) (Fig. 3B). Furthermore, transformed WOMAC pain subscale (0–100) revealed significant improvements from baseline at all evaluated timepoints for all evaluated KL grade subgroups (p<0.0001 up to year 2 for all evaluated subgroups; year 5: p <0.0001 for KL grade 2, p=0.0003 for KL grade 3, p<0.0001 for KL grade 2+3) (Fig. 3C). No LS mean estimates were available for KL grade 4 due to sparse data.

Time to knee replacement

Between the initiation of the extension study and the 5-year follow-up, 18 participants underwent knee replacement, with a median time to surgery of about 2.6 years (Table III). No follow-up data were available for the 15 participants who did not enter the extension study after completing the main phase.

Safety data

Between the 1-year and 5-year follow-up visits of the extension phase, 47 participants (51.6%) experienced a total of 79 AEs (Table IV). Arthralgia and joint swelling were the most frequently observed AEs, with the majority described as mild in severity. None of the AEs were related to iPAAG.

During this interval, 11 serious adverse events (SAEs) were reported in 10 participants (11.0%) (Table IV). These included ankle fracture, arthralgia, back pain, chest pain, coronavirus infection, death, malignant lung neoplasm, two cases of myocardial infarction, patella

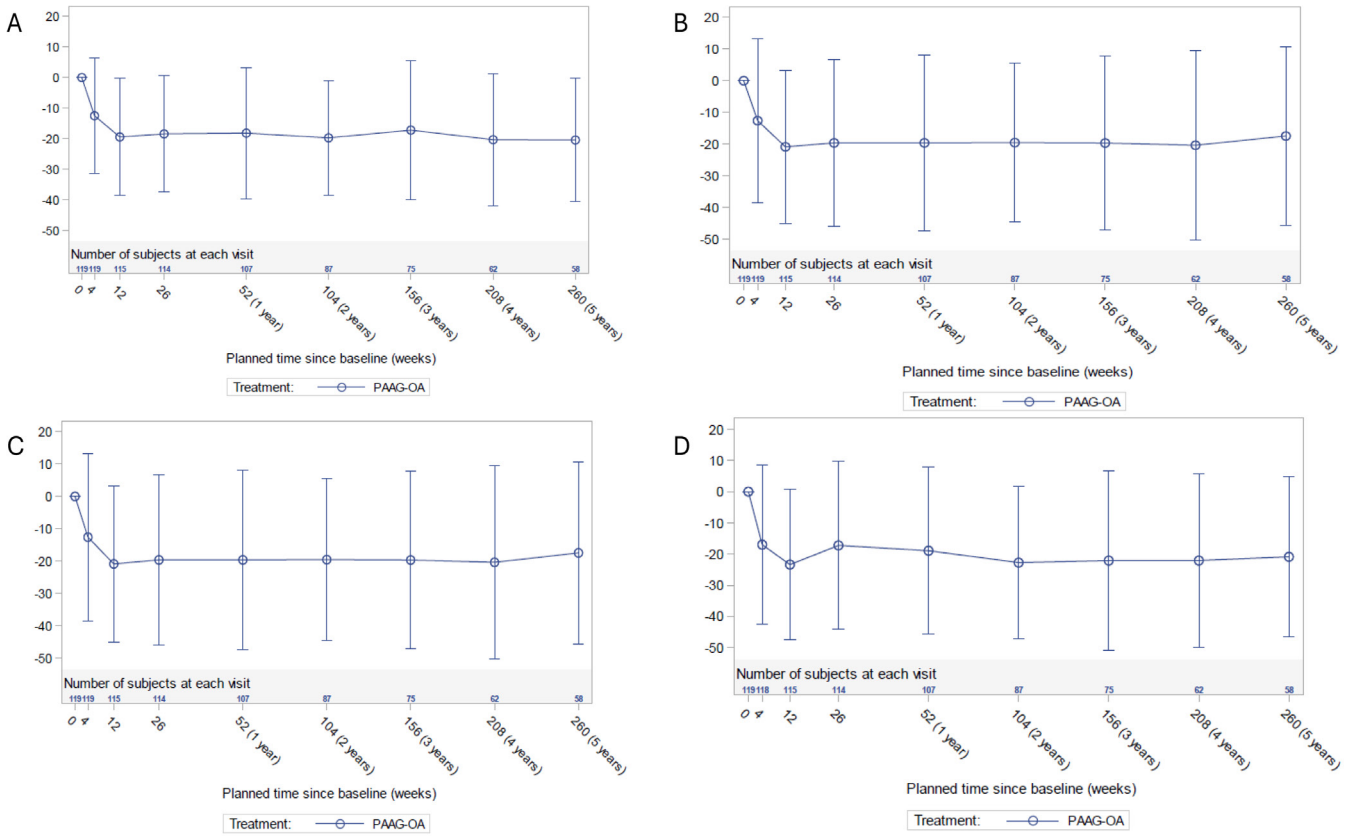

Fig. 2. Mean change from baseline to Year 5 in WOMAC Pain (**A**), Stiffness (**B**), Physical Function (**C**) subscales, and participants' global assessment (PGA) (**D**). The analysis was performed on change from baseline using a mixed model for repeated measures, including fixed categorical effects of week and site, as well as the baseline value and baseline-by-week interaction as covariates. Error bars indicate mean ± SD.

fracture, and progression of hip OA. None of these SAEs were considered related to iPAAG. All events resolved without persistent effects (Table IV), apart from the death, which led to study withdrawal and was assessed as unrelated to iPAAG.

Discussion

This study evaluated the long-term efficacy and safety of a single 6 mL intra-articular injection of iPAAG in patients with knee OA. In the 5-year completers, treatment with iPAAG resulted in sustained improvements throughout the extension phase, which were maintained at the 5-year follow-up. At this time point, reductions in WOMAC pain, function, and stiffness subscales, as well as improvements in PGA, exceeded the minimal clinically important improvement (MCII) thresholds (9 points for pain, 6 points for function, and 7 points for stiffness on the 0–100 scale) (24). These findings are consistent with previously reported outcomes at 1 year in this study (17) and in an independent prospective open-label trial of iPAAG (16). The persistence of these effects over 5 years supports the potential of iPAAG as a long-acting therapeutic intervention for knee OA.

A *post-hoc* analysis showed that, at the 3-year follow-up, participants <70 years reported higher response rates compared with those ≥70 years; however, no differences between the groups were observed at years 2, 4, or 5. This pattern could indicate that iPAAG is also effective in older patients, but it may equally reflect selective dropout in the age ≥70 subgroup. Specifically, participants who did not benefit may have been more likely to discontinue, leaving a remaining sample enriched with responders. Future studies should investigate treatment effects across more refined subgroups to better understand whether these findings reflect true differences or are influenced by attrition.

Given that the mean age for primary knee replacement in European registries is approximately 70 years (23), the chosen age cut-off may be clinically relevant. It is plausible that treatment with iPAAG could delay the need for surgical intervention beyond this age threshold. Nevertheless, this remains speculative and warrants further investigation in future studies.

The safety profile of iPAAG remained favourable throughout the study. A low incidence of AEs was observed, with 79 events reported between the 1-year and 5-year visits, none of which were considered related to treatment. One fatal event occurred, but this was not attributed to treatment. These findings are consistent with earlier studies and further support the long-term safety of iPAAG (15, 17).

The precise mechanism by which iPAAG reduces knee pain, stiffness, and functional impairment remains unclear. Preclinical studies indicate that, following IA injection, iPAAG becomes incorporated into the synovial subintima, likely through a combination of the joint's natural debris-clearing processes and the foreign body response to the synovial implant (15-17). Within the synovium, a

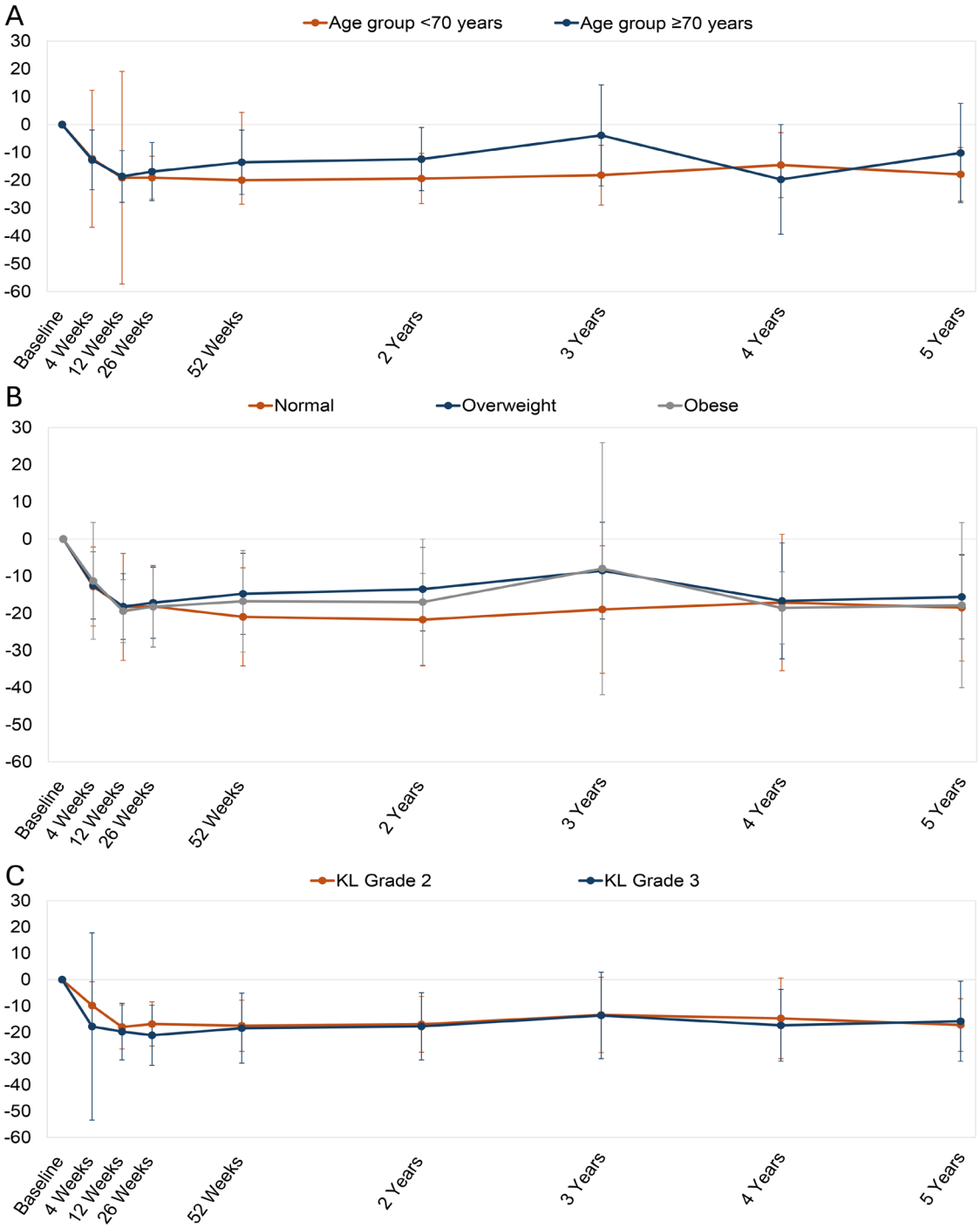

Fig. 3. Subgroup analysis of the WOMAC pain subscale by age (**A**), BMI (**B**), and Kellgren-Lawrence grade (**C**) from baseline to 5 years post-treatment. The analysis was performed on change from baseline using a mixed model for repeated measures including fixed, categorical effect of week, and baseline, and baseline by week interaction as covariates. Error bars represent 95% confidence intervals. LSMean: Least squares mean.

stable and long-lasting sub-synovial gel layer is established, which persists in both healthy and OA joints (20). Furthermore, preclinical post-mortem tissue analyses suggest that iPAAG may enhance joint capsule elasticity (25), a mechanism that could contribute to the improvements in patient-reported outcomes, particularly WOMAC stiffness scores.

Several limitations should be acknowledged. These include the lack of a control group, a small sample size further impacted by participant attrition. Additionally, data on concomitant non-surgical therapies administered during the study period are incomplete. The timing of the decision to enter the extension phase introduces a potential selection bias. Participants who chose to continue generally had more favourable early outcomes, suggesting that individuals experiencing better symptom control were more likely to remain in the study, while those with less improvement or symptom worsening may have been less inclined to participate. This differential retention may have

led to an imbalance in the study population over time. Although a conservative BOCF analysis still demonstrated clinically meaningful improvements, supporting the robustness of the overall findings, the possibility of overestimating treatment effects due to this attrition pattern cannot be excluded.

IA treatment options available today for knee OA remain limited (3, 13, 26). Commonly used injectables such as corticosteroids, HA, and PRP typically provide only short-term relief and may present safety concerns (2, 13-14, 26-27). A prospective cohort study reported that no evident effect of corticosteroid or HA injections was seen after use when compared with non-users (26).

The limited durability of these therapies underscores the challenge of achieving sustained symptom control and places the 5-year improvements seen with 2.5% iPAAG into a broader clinical context.

Conclusion

iPAAG remains safe and may be effective for its intended use 5 years after a single intra-articular injection. This study provides the first five-year data reporting both efficacy and safety outcomes following a single intra-articular injection, supporting the long-term therapeutic potential of iPAAG in the management of knee osteoarthritis. This investigation provides valid scientific evidence that iPAAG remains safe and appears effective for its intended use in OA, 5 years after injection.

References

1. GBD 2021 OSTEOARTHRITIS COLLABORATORS: Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol* 2023; 5(9): e508-e522. https://doi.org/10.1016/s2665-9913(23)00163-7
2. KLOPPENBURG M NM, CICUTTINI F: Osteoarthritis. *Lancet* 2025: 405(10472): 71-85. https://doi.org/10.1016/s0140-6736(24)02322-5
3. 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
4. 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
5. VANNESTE T, BELBA A, OEI G *et al*.: 9. Chronic knee pain. *Pain Pract* 2025; 25(1): e13408. https://doi.org/10.1111/papr.13408
6. GIORGINO R, ALBANO D, FUSCO S, PERETTI GM, MANGIAVINI L, MESSINA C: Knee osteoarthritis: epidemiology, pathogenesis, and mesenchymal stem cells: what else is new? An update. *Int J Mol Sci* 2023; 24(7): 6405. https://doi.org/10.3390/ijms24076405
7. SIDDIQ MAB, OO WM, HUNTER DJ: New therapeutic strategies in osteoarthritis. *Joint Bone Spine* 2024; 91(6): 105739. https://doi.org/10.1016/j.jbspin.2024.105739
8. BORTOLUZZI A, FURINI F, SCIRÈ CA: Osteoarthritis and its management - Epidemiology, nutritional aspects and environmental factors. *Autoimmun Rev* 2018; 17(11): 1097-104. https://doi.org/10.1016/j.autrev.2018.06.002
9. JÜNI P, HARI R, RUTJES AW *et al*.: Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev* 2015; 2015(10): CD005328. https://doi.org/10.1002/14651858.cd005328.pub3
10. MCALINDON TE, LAVALLEY MP, HARVEY WF *et al*.: Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA* 2017; 317(19): 1967-75. https://doi.org/10.1001/jama.2017.5283
11. WIJN SRW, ROVERS MM, VAN TIENEN TG, HANNINK G: Intra-articular corticosteroid injections increase the risk of requiring knee arthroplasty. *Bone Joint J* 2020; 102-b(5): 586-92. https://doi.org/10.1302/0301-620x.102b5.bjj-2019-1376.r1
12. BAGGA H, BURKHARDT D, SAMBROOK P, MARCH L: Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. *J Rheumatol* 2006; 33(5): 946-50.
13. 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
14. 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
15. BLIDDAL H BJ, 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: 274. https://doi.org/10.1186/s13018-024-04756-2
16. 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.
17. BLIDDAL H BJ, 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/i3fqee
18. PALLUA N, 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
19. 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
20. 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
21. TNIBAR A, SCHOUGAARD H, CAMITZ L *et al*.: An international multi-centre prospective study on the efficacy of an intraarticular polyacrylamide hydrogel in horses with osteoarthritis: a 24 months follow-up. *Acta Vet Scand* 2015; 57(1): 20. https://doi.org/10.1186/s13028-015-0110-6
22. WALMOD PS, KUSK P, JØHNK N, ANKORINA-STARK I, ESSEX A: An injectable 2.5% cross-linked polyacrylamide hydrogel (2.5 iPAAG) demonstrates no neurotoxicity in human induced pluripotent stem cells-derived iCell® GlutaNeurons *Front Toxicol* 2025; 7: 1585430. https://doi.org/10.3389/ftox.2025.1585430
23. 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
24. 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
25. 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
26. 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.
27. 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.