Polyacrylamide gel *versus* hyaluronic acid for the treatment of knee osteoarthritis: a randomised controlled study

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Abstract

Objective

To assess non-inferiority of intra-articular injectable polyacrylamide hydrogel (iPAAG) to hyaluronic acid (HA) on symptomatic benefit in individuals with knee osteoarthritis (OA).

Methods

This randomised, controlled, multi-centre trial recruited adults with symptomatic and radiographic knee OA from 3 clinical rheumatology sites in Denmark; two private clinics and one public hospital department. Participants were randomised 1:1 to receive a single intra-articular 6 mL injection of either HA or iPAAG on an outpatient basis. Primary outcome was change from baseline in WOMAC pain subscale after 26 weeks. Secondary outcomes were changes from baseline in WOMAC stiffness and physical function subscales, patients' global assessment of disease impact, EuroQoL-5D-5L, and proportion of positive OMERACT-OARSI responders after 26 and 52 weeks.

Results

239 adults were randomised: 120 to HA and 119 to iPAAG. For the primary outcome, the least squares mean changes in WOMAC pain were -14.8 (95% CI: -18.0 to -11.7) for HA and -18.5 (95% CI: -21.7 to -15.4) for iPAAG; group difference: 3.7 (95% CI: -0.7 to 8.1). The lower boundary of the 95% CI respected the pre-specified non-inferiority margin of 9 WOMAC pain points. No statistically significant differences were observed for the secondary outcomes. For HA, 9 participants (7.6%) reported 13 adverse device effects (ADEs). For iPAAG, 35 participants (28.9%) reported 41 ADEs. All ADEs were mild/moderate, with no serious ADEs reported.

Conclusion

iPAAG was found to be as effective and safe as HA for treatment of knee OA symptoms for at least 1 year after a single injection.

Key words

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

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Introduction

Knee osteoarthritis (OA) is a highly prevalent condition causing pain and physical disability (1). Globally, an estimated 248 million individuals were living with OA in 2019, a 113% increase since 1990, with knee OA accounting for approximately 61% of the OA cases (2). In recent years, synovial inflammation has gained increasing attention as a possible pathological key factor (3). Guidelines for OA treatment include injections of glucocorticosteroids, which may have an immediate effect on symptoms, but are variably recommended for repeated or long-term use due to potential side effects (4, 5). Another widely used non-surgical treatment option is intra-articular hyaluronic acid (HA), which is given as single or 3–5 injections spaced a week apart, for pain reduction and functional improvement in patients with knee OA (6). Studies have reported an effect of HA potentially lasting from 6 to 12 months after injection and a concomitant potential delay in the need for knee replacement (7, 8). However, with the expected increase in knee OA prevalence, alternative treatment options with long-lasting effects are warranted.

Injectable polyacrylamide hydrogel (iPAAG) was recently approved in the European Union for intra-articular use in patients with knee OA. iPAAG is non-toxic (9-11), non-biodegradable and non-absorbable and has been successfully used for over twenty years in clinical practice for soft tissue augmentation and treatment of stress urinary incontinence (12, 13). Histology of iPAAG-injected horse, rabbit and goat joints have shown persistent and stable integration of iPAAG into the synovial membrane (14, 15), and in horses treated with iPAAG for OA, significant reductions in lameness and joint effusion were observed for 24 months without adverse effects (16). In human studies, beneficial effects of 6 mL iPAAG, delivered in either one or two treatment sessions, on symptoms of knee OA up to 3 years, along with a favourable safety profile have been observed (17-19). However, comparisons of iPAAG to established treatment alternatives for knee OA are still lacking. The objectives of this study were to compare the efficacy and safety of one injection of 6 mL iPAAG with that of one injection of 6 mL HA in individuals with mild to severe knee OA.

Materials and methods

This was a multi-centre, randomised, clinical trial designed to assess the non-inferiority of iPAAG with respect to HA on symptomatic benefit in individuals with knee OA. The study consisted of 6 visits, where visits 1 (screening) and 2 (randomisation and treatment) could be held on the same day. Effectiveness and safety assessments were performed at 4 weeks (visit 3), 3 months (visit 4), 6 months (visit 5) and 12 months (visit 6). Treatments were performed on an outpatient basis at three clinical rheumatology sites in Denmark; two private clinics and one public hospital department. Data were collected from May 2019 to March 2021.

The protocol for this study was approved by the regional ethics committee (ref. no.: H19003910), the Danish Health Authority. The trial was initiated upon acceptance by the regional ethics committee, while registered at www.clinicaltrials.gov (NCT04045431) 3 months after study start. Participants gave informed consent prior to participation, and the study was conducted according to the principles of good clinical practice.

The study included both participants with unilateral and bilateral knee OA, but only the most symptomatic knee (target knee) was treated. Inclusion criteria were: adults with a clinical diagnosis of knee OA according to American College of Rheumatology criteria (20), definite radiographic OA in target knee (Kellgren-Lawrence 2–4 (21)), pain intensity ≥4 (0–10 numerical rating scale) in target knee during the past week when walking, a body mass index (BMI) between 20–35 kg/m^2, stable use of analgesics, if any, for the past four weeks, and for females of reproductive potential, adequate contraception had to be used throughout the trial.

Exclusion criteria included: other diseases than OA in the knee, previous treatment with iPAAG, HA or its derivatives, surgery in target knee within prior 6 months, intra-articular corticosteroids within 3 months, skin disease in

the injection area, and known allergic reactions to components of Synvisc-One, antibiotics (azithromycin and moxifloxacin) or local anaesthesia.

Randomisation and blinding

Before randomisation, all baseline measures were obtained. Participants were randomised 1:1 to receive a single 6 mL intra-articular injection of either iPAAG (Arthrosamid, Contura Ltd) or HA (Synvisc-One, Sanofi) at Visit 2. A computer-generated randomisation sequence produced by an independent statistician before participants were enrolled was used to allocate participants in permuted blocks of 2 to 6, stratified by participating site. The injections were administered by a health care practitioner experienced in administering intra-articular injections (unblinded injector) who was not otherwise involved in the management of the participant. The participant and all other study staff were blinded to treatment allocation.

Treatments

Injections were performed in accordance with usual practice for iPAAG. Thus, all participants were given a local anaesthetic prior to the injection according to local practice at the sites and received oral prophylactic antibacterial treatment with 500 mg azithromycin and 400 mg moxifloxacin 1-2 hours before treatment. Analgesic treatment with non-steroidal anti-inflammatory drugs and paracetamol was allowed during the trial period, but not exceeding the recommended dosage (*e.g.* paracetamol up to 4000 mg/day and ibuprofen 1200 mg/day), and not within 48 hours prior to a study visit. The number of participants receiving concomitant treatment was recorded, but daily dosages of concomitant medication were not.

Outcomes

The primary outcome measure was change from baseline in the 0–100 points normalised Western Ontario and McMaster Universities (WOMAC) (22) pain subscale at 26 weeks after treatment. Secondary outcome measures were change from baseline in the 0–100 points normalised WOMAC pain subscale at week 52, as well as changes from baseline at weeks 26 and 52 in the WOMAC stiffness and physical function subscales, patient's global assessment (PGA) of OA impact, and EuroQoL-5D-5L (EQ-5D-5L) health state (23, 24), and proportion of positive responders to the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI) criteria (25). PGA was based on patients' perceived impact of their knee OA on their overall life, where 0 = "No impact" and 100 = "Worst imaginable impact", indicated on a 100 mm visual analogue scale. Safety outcomes were incidence of adverse events (AEs) and incidence of adverse device effects (ADEs).

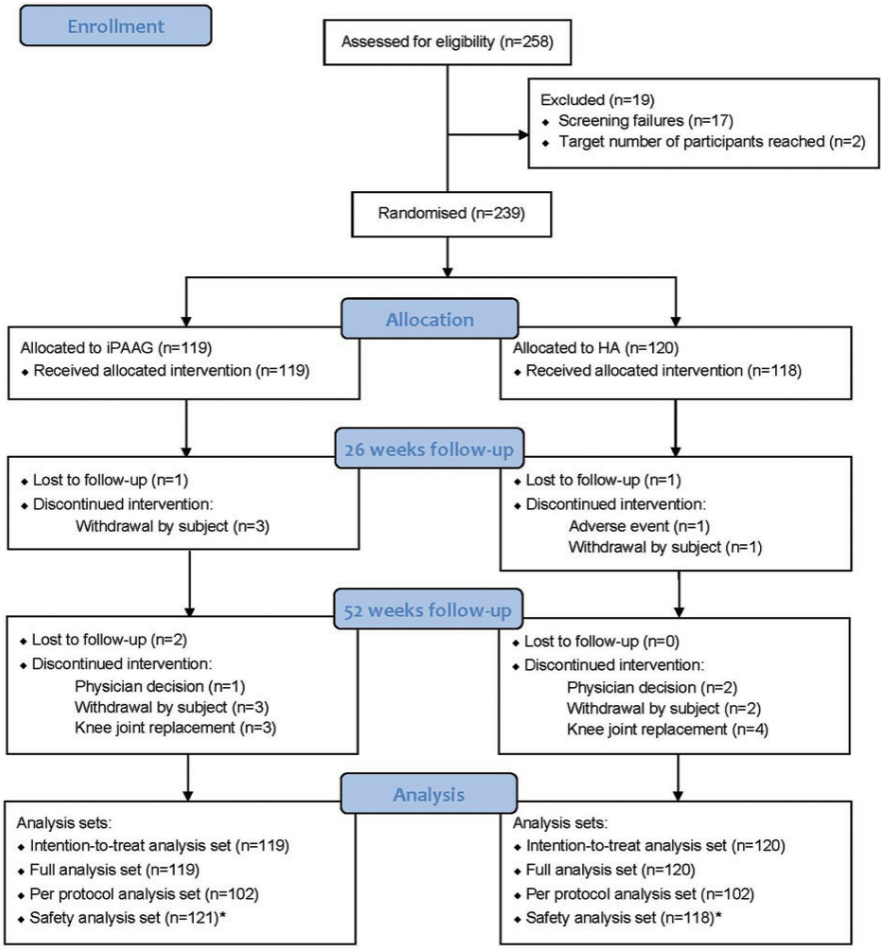

Fig. 1. Study flow chart.
*Two participants randomised to receive HA were mistakenly treated with iPAAG. Therefore, the safety analysis set consists of 121 participants in the iPAAG arm and 118 in the HA arm.

Statistical analysis

The sample size was calculated to test the non-inferiority of iPAAG *versus* HA in the change from baseline in the 0–100 points normalised WOMAC pain subscale. Using a two-sample t-test on the mean and a null mean difference of -9 (the non-inferiority margin) and a statistical significance level of 0.05, assuming a mean difference of 0 WOMAC pain subscale points (0–100 scale) and a common standard deviation of 22 WOMAC pain subscale points (0–100 scale), a total sample size of 190 was required to obtain a statistical power of 80% (assuming a balanced design). Assuming a dropout rate of 20%, a total of 238 participants were required.

The following analysis sets were used in the analysis of the data: The intention to treat (ITT) analysis set contains all randomised participants irrespective of whether they actually received study intervention or were in compliance with the study protocol. The full analysis set (FAS) contains all randomised participants who received study treatment (*i.e.*

iPAAG or HA) and who had WOMAC pain subscale assessed at baseline and at least one post-baseline assessment. The per protocol (PP) analysis set was defined as all participants in the FAS, meeting all inclusion criteria, and who did not have any major protocol deviations. The safety analysis set was defined as participants who received any study treatment.

The primary outcome was analysed using a mixed linear model for repeated measurement (MMRM) with a restricted maximum likelihood-based approach, 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. The primary comparisons were the differences between iPAAG and HA at week 26 based on the least squares means (LSMeans) for the treatment-by-week interaction effect. If the lower bound of the two-sided symmetric 95% confidence interval (CI) of the mean difference was > -9, the non-inferiority objective was met. The non-inferiority margin was based on the estimate of the minimal clinically important improvement (MCII) previously suggested for the 0–100 points normalised WOMAC pain subscale (26). If the lower bound of the 95% CI was >0 superiority was declared. The primary analysis was carried out using the FAS. Additionally, sensitivity analyses of the primary outcome were performed using the ITT and PP analysis sets (see Supplementary file.

The secondary analyses were performed using the ITT analysis set. Change from baseline in the WOMAC pain subscale at week 52, and in the WOMAC stiffness and physical function subscales, PGA and EQ-5D-5L health state at weeks 26 and 52 were estimated using an MMRM similar to the one described for the primary outcome. The safety analysis set was used for evaluation of safety. AEs and ADEs were presented using descriptive statistics.

Results

Disposition of participants

Between May 2019 and March 2020, 258 participants were screened and 239 randomised into the study (Fig. 1). A total of 215 participants (106 from the iPAAG arm and 109 from the HA arm) completed the study.

Table I. Demography and baseline characteristics.

	HA n=120	iPAAG n=119
Demographics		
Age (years)	66.6 (9.2)	67.2 (9.5)
Female sex, n (%)	68 (56.7)	58 (48.7)
Height (cm)	172.4 (9.0)	172.9 (9.4)
Body mass (kg)	81.4 (14.1)	82.6 (13.5)
Body mass index (kg/m^2)	27.3 (3.9)	27.6 (3.6)
Time since osteoarthritis diagnosis (years)	8.5 (7.5)	9.0 (7.9)
Relevant co-morbidities		
Musculoskeletal and connective tissue disorders (other than knee osteoarthritis)*, n (%)	33 (27.5)	19 (16.0)
Vascular and cardiac disorders, n (%)	51 (42.5)	58 (48.7)
Diabetes, n (%)	12 (10.0)	6 (5.0)
Other metabolism and nutrition disorders, n (%)	29 (24.2)	28 (23.5)
Musculoskeletal surgical procedures, n (%)	8 (6.7)	12 (10.1)
Nervous system disorders, n (%)	10 (8.3)	10 (8.4)
Psychiatric disorders, n (%)	11 (9.2)	7 (5.9)
Neoplasms benign, malignant and unspecified, n (%)	9 (7.5)	7 (5.9)
Relevant prior medication		
Non-steroidal anti-inflammatory drugs, n (%)	38 (31.7)	36 (30.3)
Paracetamol, n (%)	58 (48.3)	54 (45.4)
Steroids, n (%)	2 (1.7)	2 (1.7)
Opioids, n (%)	4 (3.3)	2 (1.7)
Relevant prior non-pharmacological treatment		
Physiotherapy, n (%)	16 (13.3)	17 (14.3)
Joint aspiration, n (%)	0 (0.0)	0 (0.0)
Exercise, n (%)	2 (1.7)	2 (1.7)
Baker's cyst draining, n (%)	0 (0.0)	0 (0.0)
Platelet-rich plasma therapy, n (%)	0 (0.0)	0 (0.0)
Radiographic disease severity (K-L grade)		
2, n (%)	58 (48.3)	67 (56.3)
3, n (%)	43 (35.8)	39 (32.8)
4, n (%)	19 (15.8)	13 (10.9)
WOMAC (0-100)		
Pain	46.5 (13.3)	45.1 (13.4)
Stiffness	51.1 (20.9)	52.7 (20.8)
Physical function	43.5 (16.2)	44.4 (15.1)
Other outcomes		
PGA (0-100)	57.9 (18.1)	58.3 (18.3)
EQ-5D-5L health state	0.67 (0.11)	0.68 (0.10)

*A large number of synovial cysts (Baker's cysts) were found in the HA arm compared to the iPAAG arm (22 *vs*. 5). Values are means (standard deviation) unless otherwise stated.
HA: hyaluronic acid; iPAAG: injectable polyacrylamide hydrogel; n: number of participants; %: percentage of participants; K-L grade: Kellgren-Lawrence grade; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PGA: Patient Global Assessment; EQ-5D-5L: EuroQoL-5D-5L.

The demography and baseline characteristics of the study population (ITT analysis set), as well as the number of participants using analgesic treatment at baseline, were similar between the iPAAG and HA arms (Table I).

Concomitant medication and non-pharmacological therapy

There were no significant differences in the number of participants using pain medication in the two treatment arms during the period of the study (Table I). A significantly larger number of participants received Baker's cyst excisions in the HA arm than in the iPAAG arm in the study period, but this can be attributed to the difference in number of participants having Baker's cysts at baseline (22 in the HA arm *vs*. 5 in the iPAAG arm). There were no significant differences in the number of participants receiving other relevant concomitant non-pharmacological treatments during the study period (Table II).

Primary and secondary analyses

For the primary endpoint of WOMAC pain (week 26), the least squares mean changes in WOMAC pain (0–100 scale)

Table II. Relevant concomitant medication and non-pharmacological therapy during the study.

	HA n=120	iPAAG n=119	*p*-value
Relevant concomitant medication			
Non-steroidal anti-inflammatory drugs, n (%)	48 (40.0)	42 (35.3)	0.4528
Paracetamol, n (%)	64 (53.3)	57 (47.9)	0.4008
Steroids, n (%)	13 (10.8)	12 (10.1)	0.8499
Opioids, n (%)	7 (5.8)	4 (3.4)	0.3618
Relevant concomitant non-pharmacological treatment			
Physiotherapy, n (%)	17 (14.2)	18 (15.1)	0.8339
Joint aspiration, n (%)	5 (4.2)	8 (6.7)	0.3834
Exercise, n (%)	2 (1.7)	2 (1.7)	0.9933
Baker's cyst draining*, n (%)	16 (13.3)	4 (3.4)	0.0054*
Platelet-rich plasma therapy, n (%)	1 (0.8)	0 (0.0)	0.3183

*The difference in number of Baker's cyst excisions performed in the two arms during the study can be attributed to the difference in number of Baker's cysts found at baseline (Table I).
The *p*-values for the categorical endpoints are calculated from Pearson's asymptotic chi-square test.
HA: hyaluronic acid; iPAAG: injectable polyacrylamide hydrogel; n: number of participants.

were -14.8 (95% CI: -18.0 to -11.7) for the HA arm and -18.5 (95% CI: -21.7 to -15.4) for the iPAAG arm, resulting in a group difference of 3.7 (95% CI: -0.8 to 8.1) WOMAC pain points (III). There was no statistical difference between the treatment groups, and the non-inferiority objective was met. The sensitivity analyses support the result of the primary efficacy analysis (see Suppl. file).
For the secondary efficacy endpoints, the difference in change from baseline in the normalised WOMAC pain subscale at week 52 also demonstrated no between group-difference (Table III). The mean (standard error) values of the normalised WOMAC pain subscale scores are plotted in Figure 2. for the ITT analysis set. For the other WOMAC subscales and PGA, treatment differences in favour of iPAAG were seen at weeks 26 and 52, but none of the differences were statistically significant (III). The analysis of the proportion of positive responders to the OMERACT-OARSI criteria showed treatment ratios (HA/ iPAAG odds ratios) indicating no difference between the 2 groups at weeks 26 and 52, and the analysis of change from baseline in the EQ-5D-5L health state also indicated no difference between the treatments (Table III).

Safety

Fifty-five participants (45.5%) in the iPAAG arm reported a total of 100 adverse events (AEs) compared to 78 AEs reported by 49 participants (41.5%) in the HA arm, the most frequently reported AEs being arthralgia and joint swelling in both groups. In general, HA and iPAAG were both well tolerated, and the AEs assessed as being at least possibly related to the devices (adverse device effects, ADEs) were of mild or moderate severity. An overview of the ADEs is presented in Table IV. Nine serious adverse events (SAEs), not related to the study devices, were reported: 6 events (arthritis infective, pneumonia, pulmonary

Table III. Primary and secondary outcomes at weeks 26 and 52.

Primary outcome – full analysis set	Week	HA n=117	iPAAG n=115	Treatment difference	Non-inferiority* (yes/no)
Change from baseline in normalised WOMAC pain subscale (0–100)	26	-14.8 (-18.0; -11.7)	-18.5 (-21.7; -15.4)	3.7 (-0.8; 8.1)	Yes
Secondary outcomes – intention to treat analysis set	Week	HA Week 26: n=117 Week 52: n=109	iPAAG Week 26: n=115 Week 52: n=106	Treatment difference	*p*-value
Change from baseline in normalised WOMAC pain subscale (0–100)	52	-13.3 (-16.6; -10.0)	-17.6 (-20.9; -14.2)	4.3 (-0.5; 9.0)	0.0775
Change from baseline in normalised WOMAC stiffness subscale (0–100)	26	-14.0 (-18.2 -9.8)	-18.4 (-22.6; -14.2)	4.4 (-1.5; 10.3)	0.1460
	52	-12.9 (-17.2; -8.6)	-17.5 (-21.9; -13.2)	4.6 (-1.5; 10.8)	0.1367
Change from baseline in normalised WOMAC physical function subscale (0–100)	26	-18.1 (-21.3; -15.0)	-18.9 (-22.1; -15.7)	0.7 (-3.8; 5.2)	0.7456
	52	-15.2 (-18.6; -11.8)	-17.5 (-20.9; -14.1)	2.3 (-2.5; 7.1)	0.3500
Change from baseline in PGA (0–100)	26	-14.5 (-18.9; -10.0)	-16.5 (-21.0; -12.0)	2.0 (-4.3; 8.4)	0.5289
	52	-13.5 (-18.1; -8.9)	-17.0 (-21.7; -12.4)	3.5 (-3.0; 10.1)	0.2900
Positive OMERACT-OARSI responders, n (%)	26	76 (65.0%)	76 (66.1%)	1.0 (0.6; 1.7)**	0.8929
	52	62 (56.9%)	59 (55.7%)	1.0 (0.6; 1.8)**	0.8849
Change from baseline in EQ-5D-5L health state	26	0.06 (0.04; 0.08)	0.06 (0.04; 0.08)	0.00 (-0.03; 0.04)	0.7678
	52	0.05 (0.03; 0.08)	0.06 (0.04; 0.09)	-0.01 (-0.04; 0.03)	0.6406

*If the lower bound of the 95% confidence interval (CI) > -9, the objective of non-inferiority is met. Superiority is declared if the lower bound of the 95% CI >0.
**HA / iPAAG odds ratio (95% confidence interval). Values are least squares means (95% confidence interval) unless otherwise stated.
HA: hyaluronic acid; iPAAG: injectable polyacrylamide hydrogel; n: number of participants contributing to analysis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PGA: Patient Global Assessment; OMERACT-OARSI: Outcome Measures in Rheumatology – Osteoarthritis Research Society International; EQ-5D-5L: EuroQoL-5D-5L.

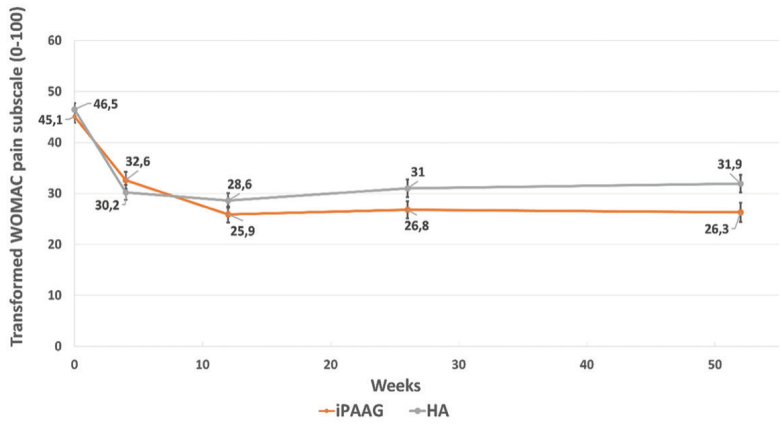

Fig. 2. Trajectories of the WOMAC pain subscale (0–100) in the ITT population. Higher values represent more pain. Data points represent mean values; error bars, standard error.

Table IV. Adverse device effects in the safety analysis set*.

	HA n (%) E	iPAAG n (%) E
Safety analysis set** n (%)	118 (100.0)	121 (100.0)
Any adverse device effects (ADEs)	9 (7.6) 13	35 (28.9) 41
Musculoskeletal and connective tissue disorders		
Arthralgia	7 (5.9) 8	19 (15.7) 21
Joint swelling	3 (2.5) 4	13 (10.7) 13
Synovitis		1 (0.8) 1
General disorders and administration site conditions		
Injection site pain		1 (0.8) 1
Peripheral swelling		1 (0.8) 1
Skin and subcutaneous tissue disorders		
Pruritus generalised		1 (0.8) 1
Rash	1 (0.8) 1	
Gastrointestinal disorders		
Constipation		1 (0.8) 1
Nervous system disorders		
Restless leg syndrome		1 (0.8) 1
Respiratory, thoracic and mediastinal disorders		
Cough		1 (0.8) 1

*The safety analysis set is the set of participants in the ITT population who have received a study treatment. **Two participants randomised to receive HA were mistakenly treated with iPAAG. Therefore, the safety analysis set consists of 121 participants in the iPAAG arm and 118 in the HA arm.

embolism, cardiac failure, erysipelas, endocarditis) in 3 participants in the iPAAG arm and 3 events (cardiac arrest, adenocarcinoma, appendicitis) in 3 participants in the HA arm.

Discussion

This randomised controlled study was the first to compare effectiveness and safety outcomes of iPAAG with a commonly used intra-articular therapy, HA, for the treatment of knee OA symptoms. The primary objective of demonstrating non-inferiority of iPAAG to HA with respect to change from baseline in the normalised WOMAC pain subscale at 26 weeks was met. Beneficial outcomes were found from injection with both iPAAG and HA at 26 and 52 weeks post-treatment, comparable to those found in previous studies on iPAAG (18, 19) or single-injection HA (27, 28) for treatment of knee OA. At 26 weeks after treatment, the effectiveness of iPAAG was non-inferior to HA. Similarly, no between group-differences were seen at week 52. The two treatments exhibited similar safety profiles with relatively few reported AEs, and all device-related AEs assessed to be mild or moderate. No infections of the injection site, related to the investigational devices, were experienced in any of the study arms. Demographic and baseline characteristics were similar between groups. Although the inclusion criteria imposed some limitations, the participants of the study are largely representative of patients with moderate to severe OA, and the results are therefore considered generalisable to these patients.

The impact of the individual participant activity level on the results was not assessed or accounted for in this study, which can be considered a limitation, along with the participant inclusion criterion of a BMI between 20–35 kg/m^2. Another limitation is the lack of recording of daily dosages of pain medication. Therefore, possible differences in the use of pain medication between the groups could not be quantified. The strengths of the study include the high retention (~90%) and the randomised controlled design. Furthermore, the similarity of the baseline characteristics of the iPAAG and HA arms validates the randomisation process.

As the complex pathophysiology of OA is not completely understood, efforts to identify the mechanisms of action of both HA and iPAAG are still ongoing. While intra-articular HA is believed to initially provide lubrication and shock absorption, its limited residence time in the joint (2–3 days) suggests that the prolonged effect of HA injection is caused by other mechanisms, such as enhancement of endogenous HA production (6, 8).

The mechanism of action of iPAAG on OA joints also has not been fully elucidated, but it has been speculated that iPAAG exerts its effects through an anti-inflammatory process in the synovium (18). Histopathological observations on joint tissue from horses, rabbits and goats (14, 15) have demonstrated that iPAAG becomes integrated in the synovial membrane after injection. Magnetic resonance imaging (MRI) studies on goat joints have shown reduction followed by stabilisation of surgically induced OA lesions (intra-articular bony and cartilaginous lesions) after iPAAG treatment (15), and reduced bone marrow lesions have also been observed by MRI in a human knee OA patient after treatment with iPAAG (29). Additionally, a signifi-

cant decrease in joint effusion has been observed in horse OA joints after treatment with iPAAG (16). Follow-up data from studies in which iPAAG implants have been used for other indications, including 10-year data from 104 patients who had correction of facial lipoatrophy (12), and 8-year data from 24 women who received urethral injection therapy for stress urinary incontinence (13), indicate that the risk of long-term side-effects is generally low. In these studies, efficacy evaluations and ultrasonography examinations further found the gel to be non-degradable and non-migratory (12, 13), making it an interesting and potentially long-term treatment alternative to current options for knee OA.

Based on this study, HA and iPAAG appear to have similar clinical performance at 1 year post-injection. The treatments also share similar safety profiles (types and numbers of AEs). Hence, from a patient perspective the main difference between the treatments is that iPAAG is expected to maintain this clinical performance for a longer time period than HA. Direct comparisons of the treatments beyond 1 year have not been performed, but efficacy and safety of iPAAG 3 years after injection has been evaluated in 49 patients with encouraging results (19), whereas the effect of HA is believed to last up to 12 months (7, 8).

In conclusion, this study finds iPAAG to be as effective and safe as HA for the treatment of knee OA symptoms for at least 1 year and supports iPAAG as a treatment option for knee OA.

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