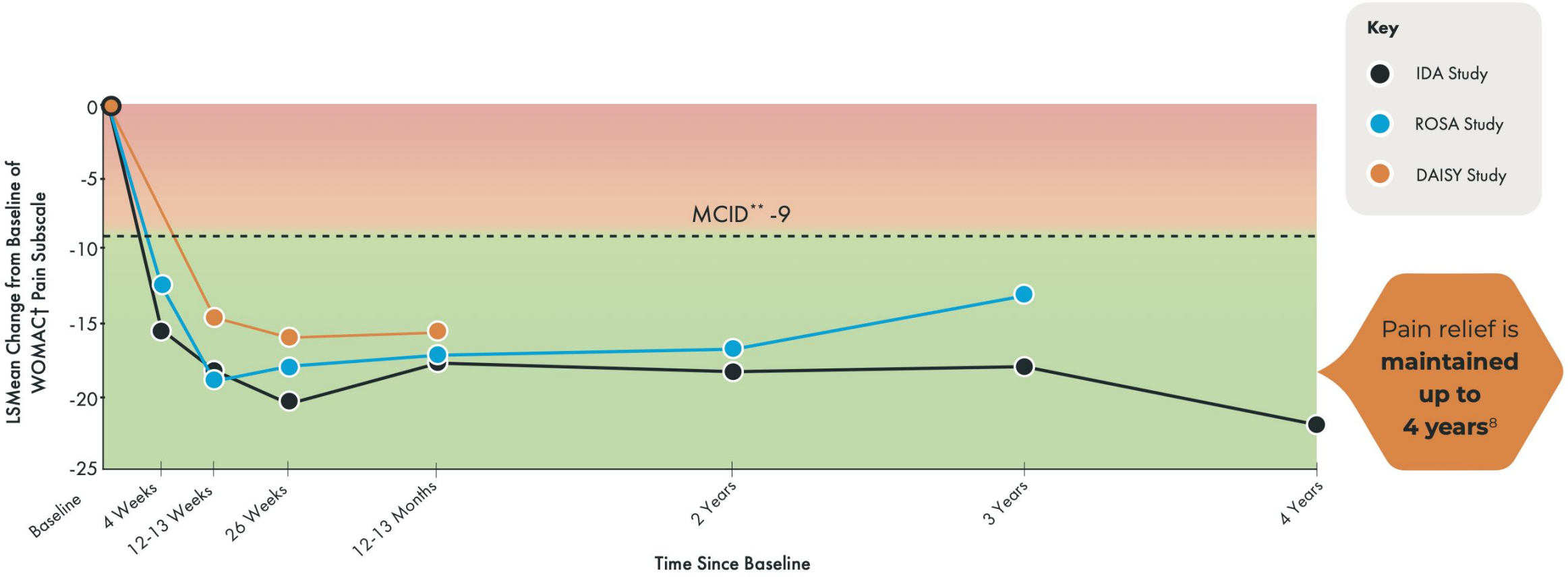
IDA study Arthrosamid®
4-years results

®

Reproducible pain reduction results[1-8]

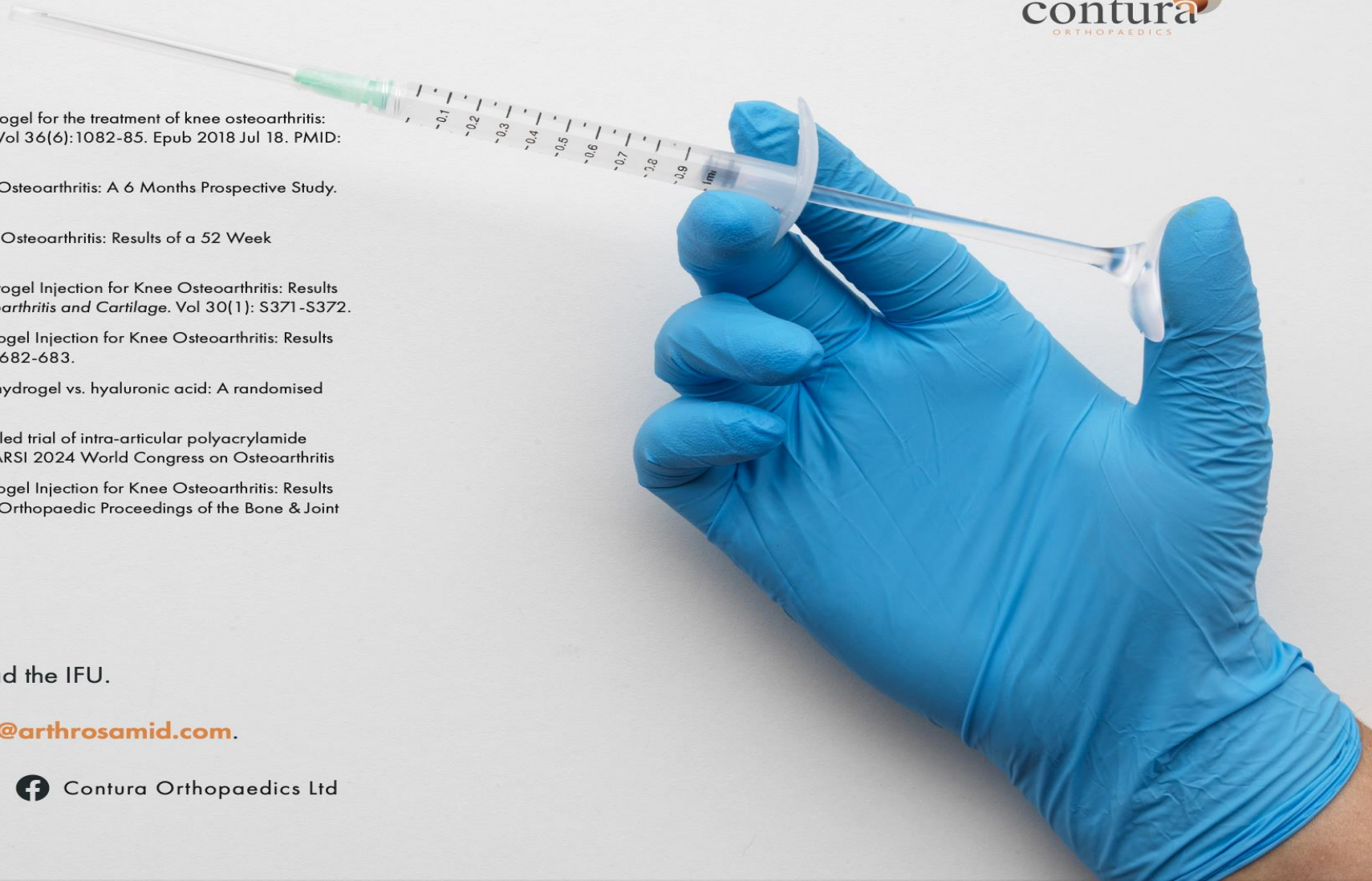
WOMAC pain subscale change from baseline across studies[1-8]

In all our studies[1-8], Arthrosamid® exceeds the MCID of 9 points[1,] and improvement is maintained up to 4 years after single injection.[8]



ARTHROSAMID®

by contura ORTHOPAEDICS



References:

1. Henriksen, M., *et al.* (2018). Intra-articular 2.5% polyacrylamide hydrogel for the treatment of knee osteoarthritis: an observational proof-of-concept cohort study. *Clin Exp Rheumatol.* Vol 36(6):1082-85. Epub 2018 Jul 18. PMID: 30148430.
2. Bliddal, H., *et al.* (2021) Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: A 6 Months Prospective Study. *J Orthop Res Ther.* Vol 6 (2): 1188. ISSN 2575-8241.
3. Bliddal, H., *et al.* (2021). Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: Results of a 52 Week Prospective Study. *Osteoarthritis and Cartilage.* Vol 29: S278.
4. Bliddal, H., *et al.* (2022). A Prospective Study of Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: Results From 2 Years After Treatment. Poster presented at OARSI 2022. *Osteoarthritis and Cartilage.* Vol 30(1): S371-S372.
5. Bliddal, H., *et al.* (2023) A Prospective Study of Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: Results From 3 Years After Treatment. *Osteoarthritis and Cartilage.* Vol 31(5): 682-683.
6. Bliddal, H., *et al.* (2022). One-year performance of polyacrylamide hydrogel vs. hyaluronic acid: A randomised controlled study. *Osteoarthritis and Cartilage.* Vol 30: S1, S371.
7. Bliddal, H., *et al.* (2024) 3 year follow-up from a randomized controlled trial of intra-articular polyacrylamide hydrogel injection in subjects with knee osteoarthritis. Poster LB-31, OARSI 2024 World Congress on Osteoarthritis
8. Bliddal, H., *et al.* (2024) A Prospective Study of Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: Results From 4 Years After Treatment. Presented at EORS 2024, Aalborg and Orthopaedic Proceedings of the Bone & Joint Journal.

OUS/ARTHRO/AUG2024/163

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4 yrs results as presented at the EORS in Copenhagen in 2024

POLYACRYLAMIDE HYDROGEL FOR KNEE OSTEOARTHRITIS: 4-YEAR RESULTS FROM A PROSPECTIVE STUDY

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Introduction

Polyacrylamide hydrogel (iPAAG[1]), is CE marked for treating symptomatic knee osteoarthritis (OA), meeting the need for an effective, long-lasting, and safe non-surgical option. This study evaluates the efficacy and safety of a single 6 ml intra-articular injection of iPAAG in participants with moderate to severe knee OA over a 5-year post-treatment period, presenting data from the 4-year follow up.

Method

This prospective multicentre study (3 sites in Denmark) involved 49 participants (31 females) with an average age of 70 (range 44 – 86 years). They received a single 6 mL iPAAG injection. All participants provided informed consent and re-consented to continue after 1 year. The study followed GCP principles and was approved by Danish health authorities and local Health Research Ethics committees. Twenty-seven participants completed the 4-year follow-up.

The study evaluated WOMAC pain, stiffness, function, and Patient Global Assessment (PGA) of disease impact. Changes from baseline were analysed using a mixed model for repeated measurement (MMRM). Sensitivity analyses were applied on the extension data, where the MMRM analysis was repeated only including patients in the extension phase and an ANCOVA model was used, replacing missing values at 4-years with baseline values (BOCF).

Results

The planned MMRM analysis (n=49) revealed a statistically significant decrease in WOMAC pain subscale scores (-22.0; 95%CI: -29.5; -14.4) from baseline to 4-years. Analysis of the extension phase (n=27) showed similar results (-21.8; 95%CI: -29.0; -14.6) compared to the initial analysis. Furthermore, BOCF analysis indicated a statistically significant reduction in WOMAC pain subscale scores from baseline (-13.0 units). Four new adverse events were reported between the 3-year and 4-year visits; none were related to treatment.

Conclusions

This study shows that single injections of 6 ml intra-articular iPAAG were well tolerated and continued to provide clinically important effectiveness at 4-years after treatment.

IDA Study

Study Overview for IDA-Study

- Prospective, one-armed, open-label study on the efficacy and safety of Arthrosamid® at 3 sites in Denmark (patients enrolled August-September 2019)
- Main study from screening to week 13 followed by extension study up to 1 year (since extended to up to 5 years). Data currently available up to 4 years after treatment
- Patients received a single intra-articular injection of 6 mL OA-PAAG (Arthrosamid®) and attended clinical follow-up visits after 4, 13, 26 weeks, and 1, 2, 3, 4 years (planned 5 years)

Main inclusion criteria:
Adults with a clinical diagnosis of knee OA according to the American College of Rheumatology, definite radiographic OA in the target knee (Kellgren-Lawrence grade 2-4) (locally read), score of ≥2 (on 0-4 scale) on the WOMAC question related to pain while walking on a flat surface, a BMI <35 kg/m^2, and, if patients were taking oral analgesics, they needed to have been on a stable dose for at least 4 weeks prior to inclusion

Main exclusion criteria:
Previous IA PAAG treatment, IA hyaluronic acid or its derivatives in target knee within prior 6 months, IA corticosteroids within 3 months, skin disease in the injection area, and surgery in the treatment knee within 6 months

BMI: body mass index; IA: intra-articular; OA: osteoarthritis; PAAG: polyacrylamide hydrogel; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Bliddal H, et al. J Orthop Res Ther 6. 2021; 1188
Bliddal H, et al. Osteoarthritis and Cartilage. 2021; 29: S278
Bliddal H, et al. Osteoarthritis and Cartilage. 2022; 30: 372
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Bliddal, H, et al. J Orthop Surg Res. 2024; 19:274
Data on file: Clinical Investigation Reports IDA Study

Objectives/Endpoints for IDA-Study

Main study

- **Primary endpoint**: change from baseline in the pain subscale of the WOMAC at 13 weeks
- **Secondary endpoints**: change from baseline at 4 weeks and 13 weeks in:
  - Physical function and stiffness subscales of WOMAC
  - PGA of OA impact
  - Proportion of positive responders to the OMERACT-OARSI response criteria
  - WOMAC pain-related subscale (4 weeks)

Extension study

- **Secondary endpoints**: change from baseline at 26 weeks, 1, 2, 3, 4 and 5 years in:
  - WOMAC pain, stiffness, and physical function-related subscales
  - PGA of impact of OA
  - OMERACT-OARSI response (only week 26 and 52)

Safety*

Incidence of AEs and ADEs

Exploratory analysis: by subgroups age and BMI

*Safety objectives for both main and extension study

AEs: adverse events; ADEs: adverse device effect; BMI: body mass index; OA: osteoarthritis; OMERACT-OARSI: Outcome Measures in Rheumatology - Osteoarthritis Research Society International; PGA: patient global assessment; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Objectives/Endpoints – Outcome Measures for IDA-Study

- The WOMAC is a self-reported questionnaire with a total of 24 items used to assess three knee OA related health concepts, pain (5 items), stiffness (2 items), and physical function (17 items). Items were rated on a 5-point Likert scale with scores ranging from 0 (no pain, stiffness, or difficulty) to 4 (extreme pain, stiffness, or difficulty). The 3 WOMAC subscales scores were normalised to a 0–100 scale with 0 indicating best and 100 worst
- Internationally applicable estimates of minimal clinically important improvements of the WOMAC scores on the 0–100 scale: WOMAC pain subscale: 9 points, WOMAC stiffness subscale: 7 points: WOMAC function subscale: 6 points[1]

- The PGA was based on responses to the question "How much does the knee osteoarthritis (treatment knee) as a whole affect your life at present?" indicated on a 100 mm VAS with anchors 0 "Not at all" and 100 "The worst imaginable"

- The OMERACT-OARSI response was defined as either (1) improvement in WOMAC pain or physical function ≥50% and an absolute change ≥ 20 normalised units (0-100); or (2) ≥20% improvement and an absolute change ≥10 points in 2 of the 3 categories: WOMAC pain, WOMAC physical function, and PGA

OA: osteoarthritis; OMERACT-OARSI: Outcome Measures in Rheumatology - Osteoarthritis Research Society International; PGA: patient global assessment; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

[1]Bellamy N, et al. Arthritis Care Res (Hoboken). 2015; 67 (7): 972-80
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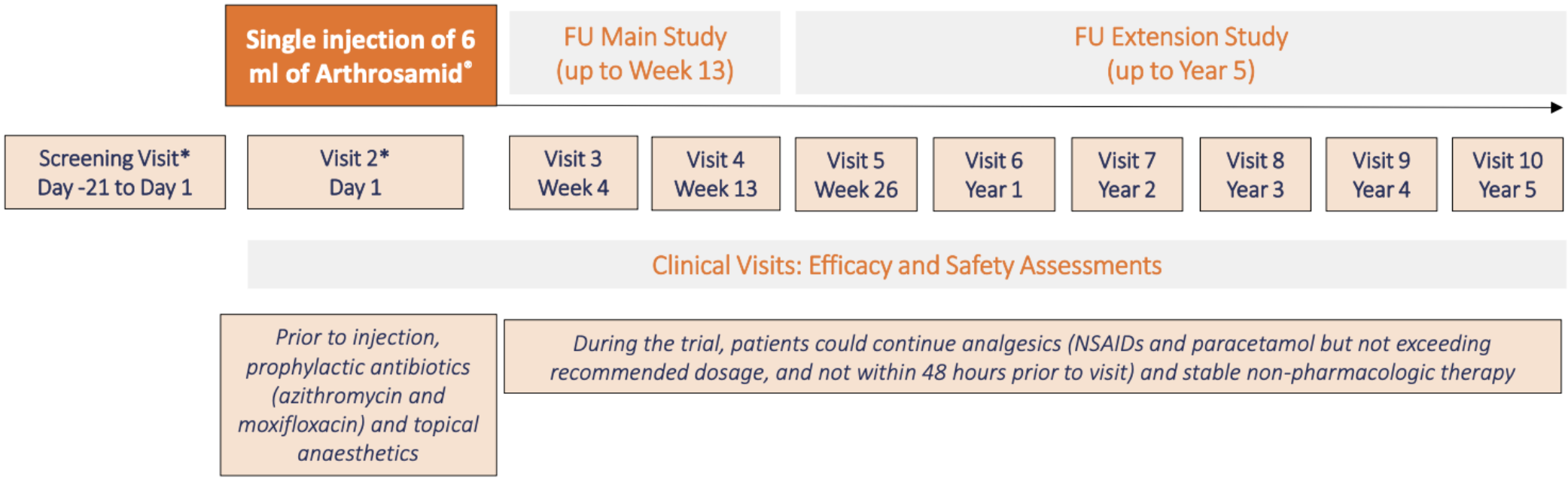
IDA - Study Design



Patients received a single intra-articular injection of 6 mL Arthrosamid® and attended clinical FU visits after 4 and 13 weeks (Main Study), and after 26 weeks and 1, 2, 3, 4 and 5 years (Extension Study)

*Screening visit and Visit 2 could be combined, if applicable
FU: follow-up; NSAIDs: non-steroidal anti-inflammatory drugs

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Study Analysis Populations for IDA-Study

Intent to Treat Analysis Set	49 (100%)
Full Analysis Set	48 (98.0%)
Per Protocol Analysis Set	41 (83.7%)

One subject received only approximately 5 ml of Arthrosamid® due to a user error; the full analysis set consisted of 48 patients

Intent to Treat Analysis Set: All subjects who received study intervention

Full Analysis Set: All subjects who received study treatment and who had a valid recording of the WOMAC pain subscale at baseline and at 3 months

Per Protocol Analysis Set: All patients in the Full Analysis Set, meeting all inclusion criteria, and who did not have any protocol deviations of clinical or statistical significance

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Baseline Characteristics (ITT) for IDA-Study

	N=49
Age, years, mean ± SD (range)	70.0 ± 8.6 (44–86)
Females, n (%)	31 (63.3%)
Race - White, n (%)	49 (100%)
Height, cm, mean ± SD (range)	171.6 ± 10.1 (150–191)
Weight, kg, mean ± SD (range)	81.3 ± 13.5 (55–125)
Body Mass Index, kg/m^2, mean ± SD (range)	27.5 ± 3.3 (21.0–34.6)
Baseline WOMAC Pain, mean ± SD (range)	50.3 ± 11.8 (20–75)
Baseline WOMAC Stiffness, mean ± SD (range)	55.6 ± 17.5 (0–88)
Baseline WOMAC Physical Function, mean ± SD (range)	46.6 ± 16.1 (9–87)
Baseline PGA, mean ± SD (range)	61.1 ± 18.3 (22–100)

ITT: intent to treat; PGA: patient global assessment; SD: standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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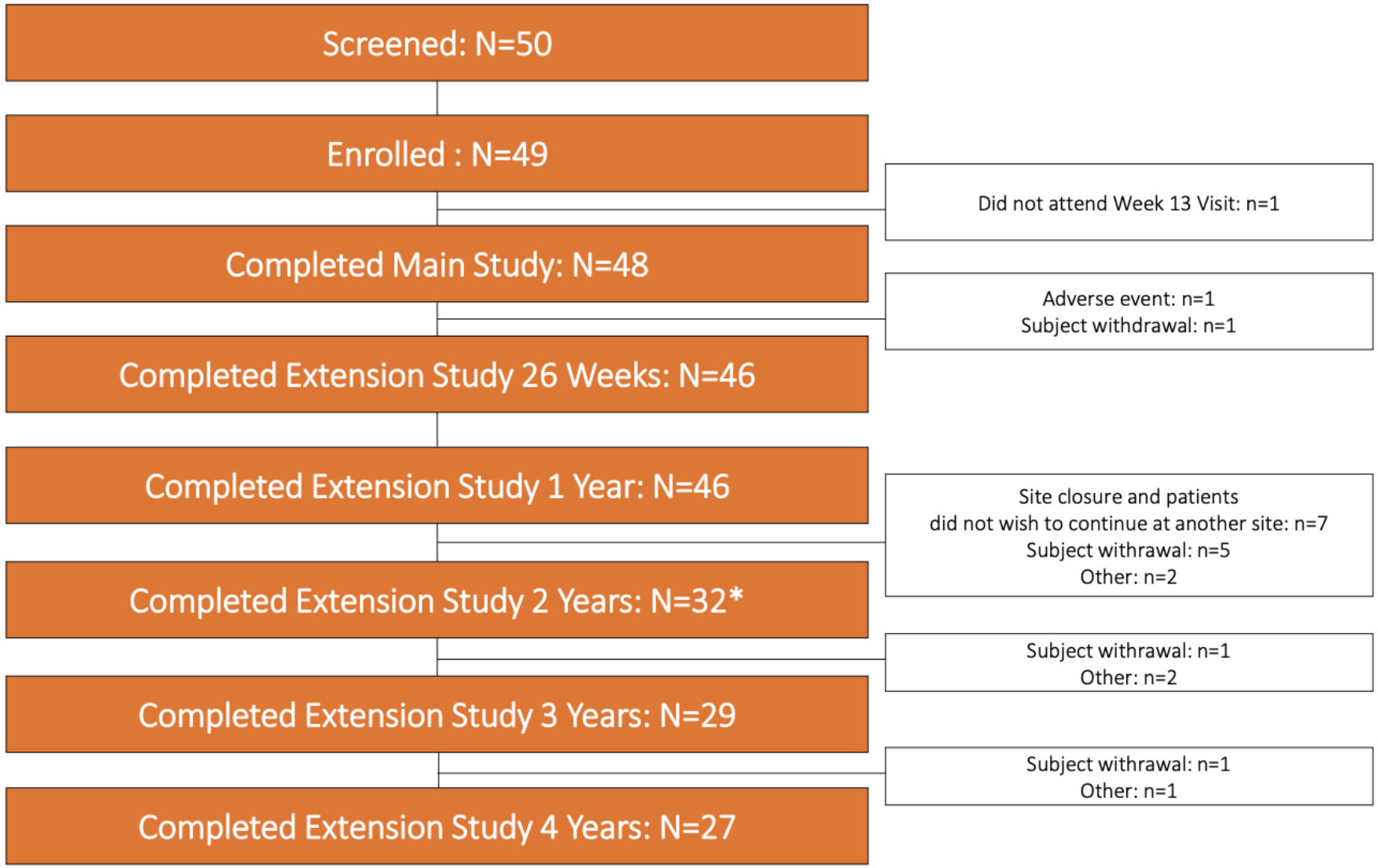
Flow Disposition for IDA-Study



*One of the investigator sites could not participate in the extension study (personal reasons) after the Year 1 Visit. Of 11 subjects completing Year 1 at this site, 4 continued at another investigator site, while 7 subjects did not sign consent to continue
Of the 35 subjects completing Year 1 at the other 2 sites, 4 did not sign consent to continue in the extension study
Three subjects withdrew from Year 2 of the extension (1 subject's withdrawal, 2 'other' reasons)
Two subjects withdrew from year 3 of the extension (1 subject withdrawn due to knee replacement, 1 other reason)

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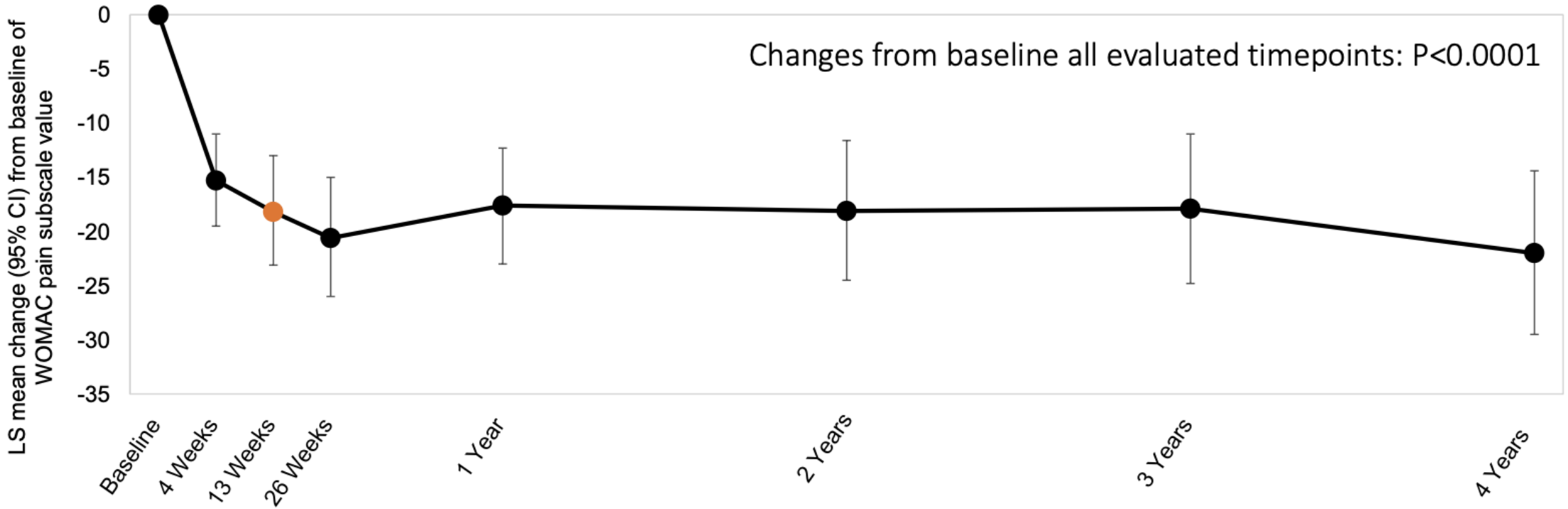
Results – Changes from Baseline WOMAC Pain Subscale (ITT) for IDA-Study

Clinically relevant and highly statistically significant reduction in WOMAC pain score at Week 13 (primary endpoint) (mean change -18.2 points; 95% CI: -23.1 to -13.0)[1], which was maintained up to 4 years following treatment

Mean baseline score: 50.3



Similar clinically relevant and highly statistically significant reductions when analysis were performed using the data from available participants in the extension phase as well as using the most conservative "baseline observation carried forward" approach (imputation of missing values)

CI: confidence interval; ITT: intent to treat; LS: least square; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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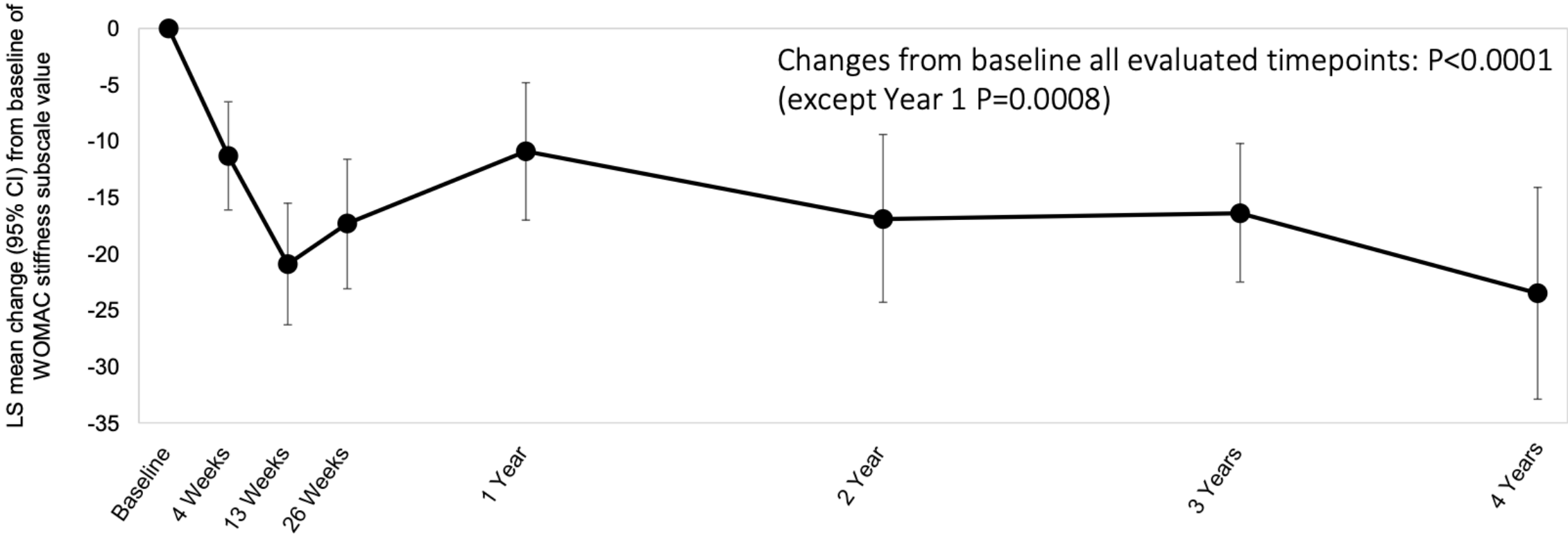
Results – Changes from Baseline WOMAC Stiffness Subscale (ITT) for IDA-Study

Clinically relevant and statistically significant reduction in WOMAC stiffness score up to 4 years following treatment

Mean baseline score: 55.6



Similar clinically relevant and highly statistically significant reductions when analysis were performed using the data from available participants in the extension phase as well as using the most conservative "baseline observation carried forward" approach (imputation of missing values)

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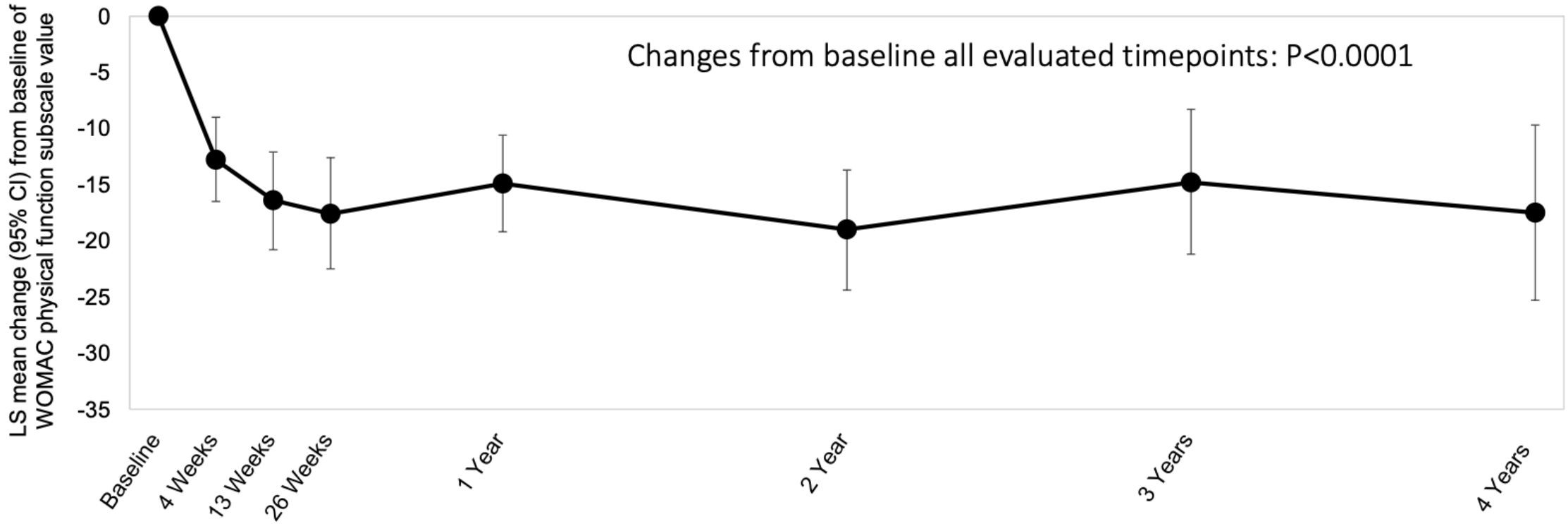
Data on file: Clinical Investigation Reports IDA Study

Results – Changes from Baseline WOMAC Physical Function Subscale (ITT) for IDA-Study

Mean baseline score: 46.6

Clinically relevant and statistically significant improvement in WOMAC physical function score up to 4 years following treatment



Similar clinically relevant and highly statistically significant reductions when analysis were performed using the data from available participants in the extension phase as well as using the most conservative "baseline observation carried forward" approach (imputation of missing values)

CI: confidence interval; ITT: intent to treat; LS: least square; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Results – WOMAC Pain, Stiffness and Physical Function Subscales (ITT) for IDA-Study

	WOMAC Pain		WOMAC Stiffness		WOMAC Physical Function	
	Actual values	**Change from Baseline**	**Actual values**	**Change from Baseline**	**Actual values**	**Change from Baseline**
Baseline (N) Mean (SD) Range	49 50.3 (11.8) 20–75	NA	49 55.6 (17.5) 0–88	NA	49 46.6 (16.1) 9–87	NA
Week 4 (N) Mean (SD) Range	49 34.9 (16.4) 0–75	49 -15.4 (15.3) -50–15	49 44.1 (20.6) 0–88	49 -11.5 (17.3) -50–38	49 33.4 (16.7) 1–63	49 -13.2 (13.8) -38–22
Week 13 (N) Mean (SD) Range	48 32.1 (18.2) 0–75	48 -18 (18.5) -55–35	48 34.6 (21.0) 0–75	48 -20.8 (19.9) -63–38	48 29.4 (18.0) 0–60	48 -17.1 (16.1) -44–25
Week 26 (N) Mean (SD) Range	46 28.9 (18.6) 0–70	46 -21.7 (19.6) -60–25	46 37.2 (21.5) 0–75	46 -17.9 (21.2) -50–50	46 28.6 (20.3) 0–62	46 -18.4 (17.0) -47–21
1 Year (N) Mean (SD) Range	45 32.1 (20.0) 0–70	45 -18.4 (17.7) -60–20	45 43.9 (24.8) 0–88	45 -11.7 (20.9) -50–50	43 31.0 (22.3) 0–69	43 -16.0 (13.5) -40–16
2 Years (N) Mean (SD) Range	32 28.9 (19.0) 0–70	32 -20.3 (18.8) -50–15	32 35.9 (23.7) 0–75	32 -19.1 (19.8) -75–13	32 23.9 (18.0) 0–62	32 -18.8 (16.0) -50–13
3 Years (N) Mean (SD) Range	29 28.8 (18.0) 0–70	29 -20.5 (17.7) -60–5	29 37.1 (19.9) 0–75	29 -16.8 (15.4) -50–13	29 26.9 (18.8) 0–62	29 -15.2 (18.1) -54–13
4 Years (N) Mean (SD) Range	27 24.6 (17.0) 0–55	27 -23.5 (21.4) -65–20	27 28.7 (24.2) 0–75	27 -24.5 (22.1) -63 - 25	27 23.9 (19.1) 0–62	27 17.6 (21.6) 69–26

ITT: intent to treat; NA: not applicable; SD: standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Bliddal H, et al. J Orthop Res Ther 6. 2021; 1188
Bliddal, H, et al. J Orthop Surg Res. 2024; 19:274
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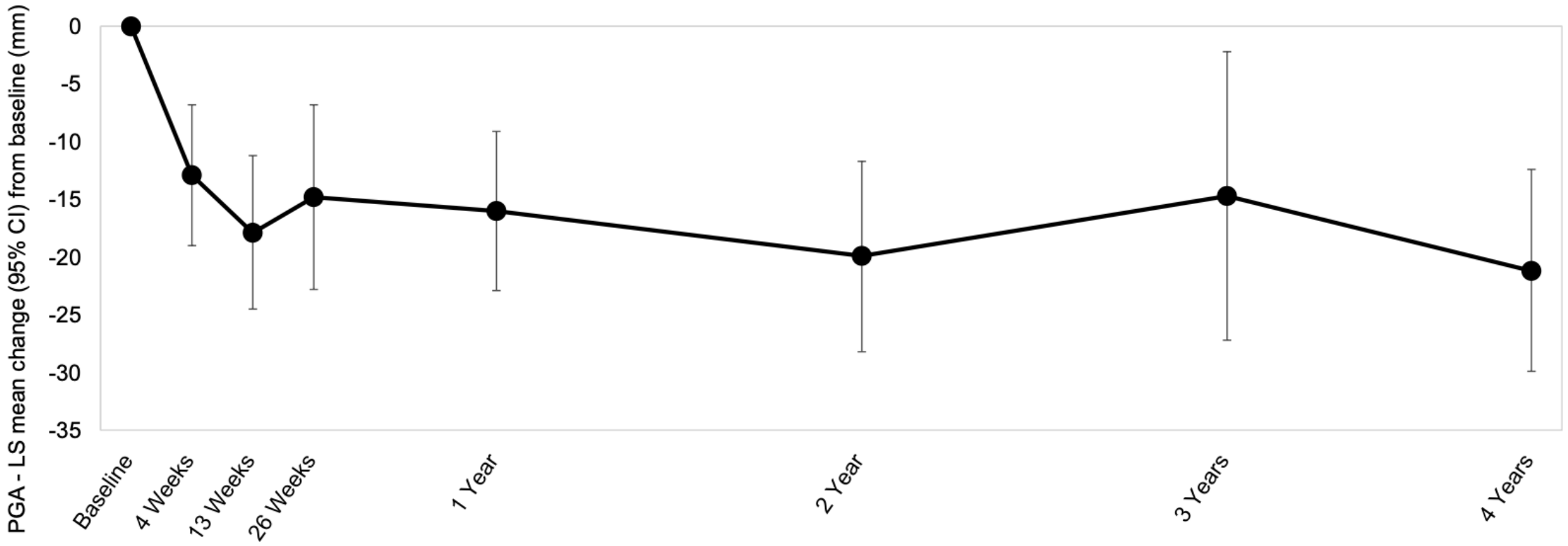
Results – Patient Global Assessment (ITT) for IDA-Study

Statistically significant improvements in PGA versus baseline up to 4 years following treatment

Mean baseline PGA score: 61.1



Significance reached at all evaluated timepoints (year 3: 0.0234)

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CI: confidence interval; ITT: intent to treat. LS: least square; PGA: patient global assessment

Results – Patient Global Assessment (ITT) for IDA-Study

	PGA (mm)	
	Actual values	**Change from Baseline**
Baseline (N) Mean (SD) Range	49 61.1 (18.3) 22-100	NA
Week 4 (N) Mean (SD) Range	49 47.7 (24.8) 12–95	49 -13.4 (21.5) -54–49
Week 13 (N) Mean (SD) Range	48 42.6 (24.7) 2–95	48 -18.6 (24.4) -67–53
Week 26 (N) Mean (SD) Range	44 43.9 (27.6) 0–97	44 -17.2 (27.5) -89–46
1 Year (N) Mean (SD) Range	45 43.3 (27.1) 1–95	45 -17.7 (22.7) -67–24
2 Years (N) Mean (SD) Range	32 33.9 (23.6) 0–84	32 -21.4 (22.5) -78–31
3 Years (N) Mean (SD) Range	29 37.2 (28.0) 0–89	29 -18.3 (30.5) -88–38
4 Years (N) Mean (SD) Range	27 33.2 (19.4) 7–68	27 -21.6 (22.2) -66–27

NA: not applicable; PGA: patient global assessment; SD: standard deviation

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Results – OMERACT OARSI (ITT) for IDA-Study

	Proportion Responders
Week 4	53.1% (95% CI 38.3 to 67.5)
Week 13	64.6% (95% CI 49.5 to 77.8)
Week 26	67.4% (95% CI 52.0 to 80.5)
1 Year	62.2% (95% CI 46.5 to 76.2)

The OMERACT-OARSI response was only evaluated up to 1 year following treatment

After 13 weeks, 64.6% of the patients were OMERACT-OARSI responders and this was maintained at 1 year (62.2%)

CI: confidence interval; ITT: intent to treat; OMERACT-OARSI: Outcome Measures in Rheumatology - Osteoarthritis Research Society International

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Safety Analysis – Adverse Events (up to 4 Years) for IDA-Study

	Number of subjects (%)	Number of events
AEs	36 (73.5%)	80
Serious AEs	9 (18.4%)	9
Non-serious AEs	36 (73.5%)	71
ADEs	12 (24.5%)	14
Serious ADEs	0	0
Unanticipated serious ADEs	0	0
AEs leading to study withdrawal	1 (2.0%)	1
Deaths	0	0

- No ADEs were reported after 12 months
- Most frequently reported AEs were arthralgia (18 events in 15 subjects), corona virus infection (7 events in 7 subjects), joint swelling (6 events in 6 subjects), back pain (4 events in 4 subjects) and synovial cyst (4 events in 4 subjects)
- Most AEs were of mild intensity (47 events in 30 subjects); 25 events in 18 subjects were of moderate intensity, and 8 events in 7 subjects were severe (arthralgia, cerebrovascular accident, corona virus infection, lumbar spinal stenosis, presyncope, prostate cancer, uterine prolapse and complicated appendicitis)

ADEs: adverse device effects; AEs: adverse events

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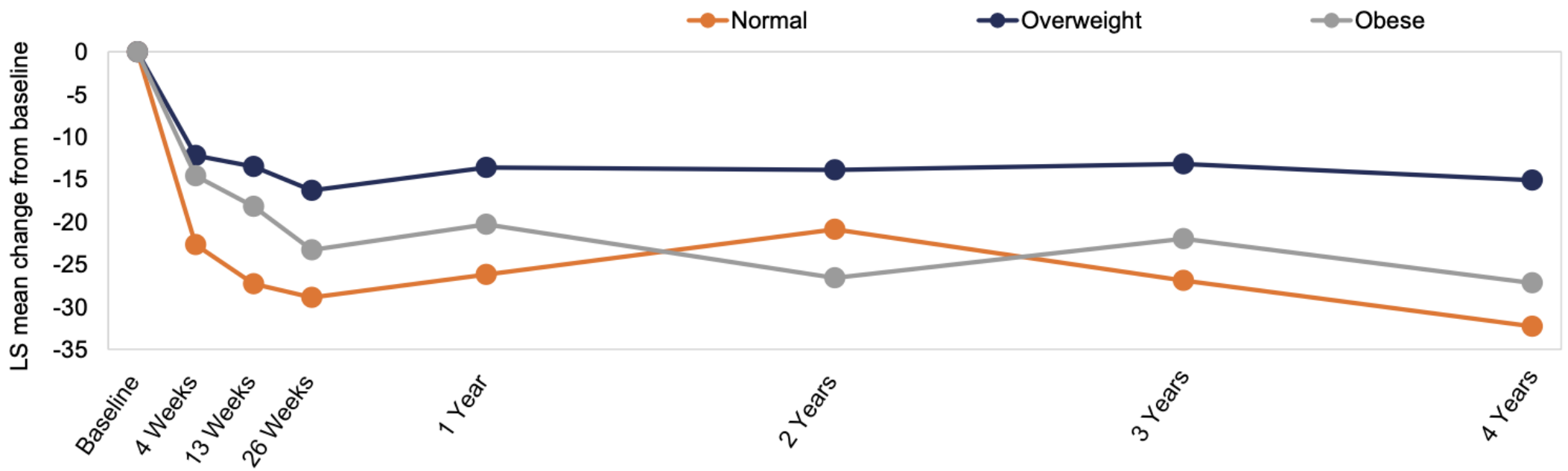
Non-serious AEs	36 (73.5%)	71
ADEs	12 (24.5%)	14
Serious ADEs	0	0
Unanticipated serious ADEs	0	0
AEs leading to study withdrawal	1 (2.0%)	1
Deaths	0	0

- No ADEs were reported after 12 months
- Most frequently reported AEs were arthralgia (18 events in 15 subjects), corona virus infection (7 events in 7 subjects), joint swelling (6 events in 6 subjects), back pain (4 events in 4 subjects) and synovial cyst (4 events in 4 subjects)
- Most AEs were of mild intensity (47 events in 30 subjects); 25 events in 18 subjects were of moderate intensity, and 8 events in 7 subjects were severe (arthralgia, cerebrovascular accident, corona virus infection, lumbar spinal stenosis, presyncope, prostate cancer, uterine prolapse and complicated appendicitis)

ADEs: adverse device effects; AEs: adverse events

Data on file: Clinical Investigation Reports IDA Study
Bliddal, H, et al. J Orthop Surg Res. 2024; 19:274

Results – Subgroup Analysis WOMAC Pain Subscale by BMI for IDA-Study



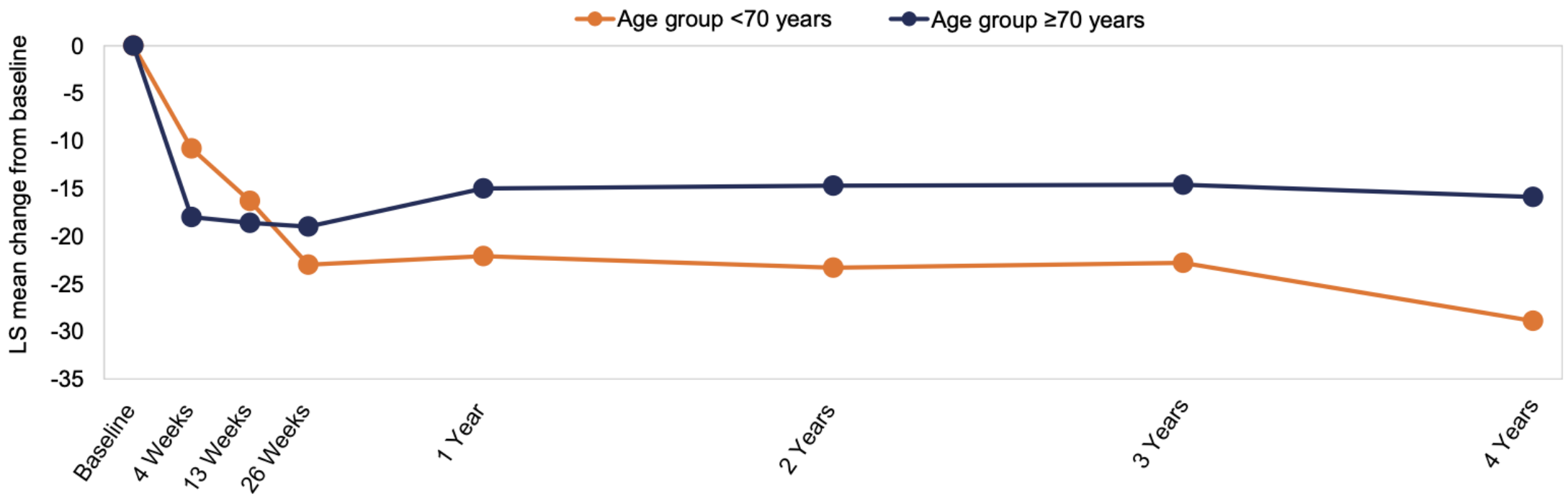
Significance reached at all evaluated timepoints for all BMI subgroups

Clinically relevant and statistically significant decreases in the WOMAC pain subscale from baseline up to 4 years for all BMI subgroups, largest decrease for participants with normal BMI

BMI: body mass index (normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (above 30 kg/m^2); LS: least square; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Data on file: Clinical Investigation Reports IDA Study
Bliddal, H, et al. J Orthop Surg Res. 2024; 19:274

Results – Subgroup Analysis WOMAC Pain Subscale by Age for IDA-Study



Clinically relevant and statistically significant decreases in the WOMAC pain subscale from baseline up to 4 years for both age groups

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Data on file: Clinical Investigation Reports IDA Study
Bliddal, H, et al. J Orthop Surg Res. 2024; 19:274

Summary of IDA-Study

- Clinically relevant and statistically significant reduction in WOMAC pain score at Week 13 (primary endpoint) (mean change -18.2 points; 95% CI: -23.1 to -13.0)[1], which was maintained up to 4 years following treatment
- Similar benefits were found for WOMAC stiffness, physical function, and PGA
- After 13 weeks, 64.6% of the patients were OMERACT-OARSI responders and this was maintained at 1 year
- Clinically relevant and statistically significant decreases from baseline in WOMAC pain subscale for age and BMI subgroups, largest decrease up to 4 years for participants <70 years and those with a normal BMI
- No serious adverse events related to treatment for the relief of knee OA
- A single injection of 6 ml Arthrosamid® was well tolerated and demonstrated clinically relevant and highly statistically significant effectiveness up to 4 years after treatment as measured by the WOMAC pain, stiffness and function subscales and PGA

BMI: body mass index; CI: confidence interval; OA: osteoarthritis; OMERACT-OARSI: Outcome Measures in Rheumatology - Osteoarthritis Research Society International; PGA: patient global assessment; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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