

SAFE AND SUSTAINED PAIN RELIEF WITH A SINGLE INJECTION¹

A non-degrading viscoelastic hydrogel
for adults with knee osteoarthritis



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Contura Orthopaedics Ltd

ARTHROSAMID[®]
by
contura[®]
ORTHOPAEDICS

Osteoarthritis in the knee

Despite osteoarthritis (OA) being the most common type of arthritis and the fastest growing cause of disability worldwide,² the treatment area has seen minimal progression in the last 20 years. With so little known about exactly what causes knee OA, a permanent cure has yet to be discovered.

Treatments to date have focused on pain relief and managing the symptoms of the condition — meaning that the options available to the one third of over 65s currently living with OA worldwide have been limited.³ With surgical intervention through joint replacement the only option for end-stage disease, there is a real need for better treatment strategies.³

Pain is the most common symptom experienced by patients with knee OA.⁴ Whilst the exact cause and subsequent development of knee OA pain is unclear, clinical imaging and biochemical observations indicate that inflammation may contribute to both pain and structural disease progression.⁵



With synovial tissue inflammation existing in all stages of OA — even in the early stages — it's been suggested that this, rather than cartilage damage, might be a precursor to OA.⁶

Of 2,005 respondents surveyed in the UK in September 2021:



41%

would pay for non-surgical treatments,⁷



53%

are worried about post-op pain and discomfort, and⁷



58%

are anxious about surgery.⁷

Synovitis — the painful facts

Inflammation of the synovial membrane (**synovitis**), is common in OA joints⁸ and has been associated both with symptoms and structural degradation.⁹

Presenting early in the disease course, synovitis is also strongly associated with pain severity in patients with knee OA.¹⁰

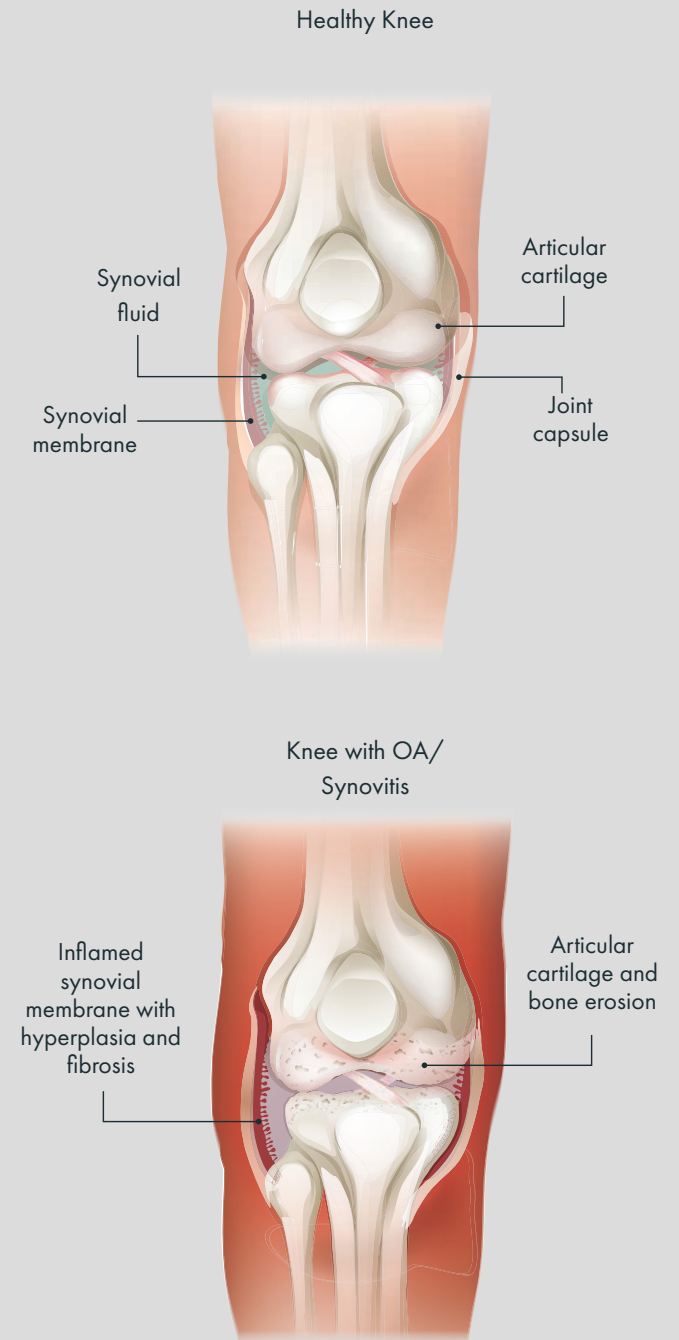
The characteristics of the synovium in OA knee patients are synovial lining hyperplasia, sublining fibrosis and stromal vascularization.⁸

In an inflamed state, the predominant immune cells found in the synovium of a knee OA patient are **macrophages** and **T-Cells**. This is due to an influx of white blood cells/leukocytes responding to cytokines and cell adhesion molecules.⁸

There is strong evidence that synovitis is associated with further worsening of OA structure.⁸

What is the synovium?

The synovium is a specialised connective tissue that lines the inside of the joint capsule. In the knee, the synovium seals the synovial cavity, maintains the synovial fluid and helps with chondrocyte nutrition and subchondral bone.⁸

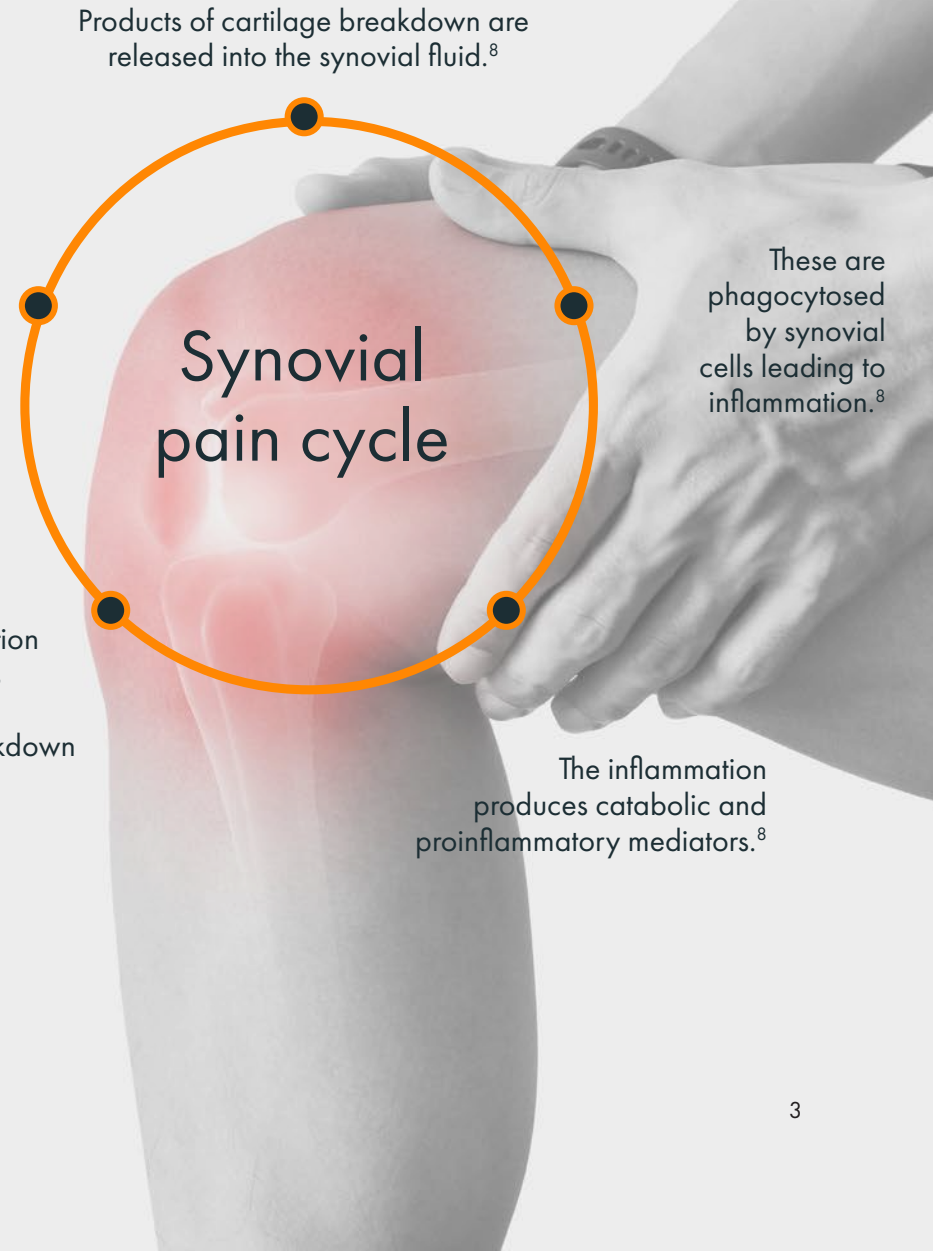


The link between synovitis and knee OA

Synovitis is known to play an important role in OA development. In addition to its relationship with knee pain, **synovitis is also strongly associated with more rapid progression of cartilage loss in OA joints** and the initiation of cartilage loss in joints without OA.⁸

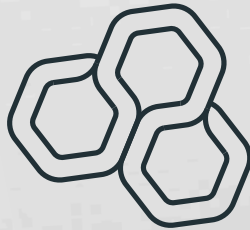
Targeting synovial inflammation in early OA could therefore prove a promising therapeutic approach for alleviating the symptoms suffered by patients, slowing down disease progression,¹¹ and potentially even preventing articular cartilage destruction.¹¹

Treating OA synovitis represents an important target for therapeutic intervention.⁸



Introducing Arthrosamid® — a new class of injectable therapy to treat knee OA

iPAAG



Offering patients an effective alternative to current therapies for knee OA, Arthrosamid® is an injectable polyacrylamide hydrogel (iPAAG) for intra-articular administration.

A non-biodegradable injectable implant, Arthrosamid® delivers **long-acting pain relief** — improving the quality of life for patients with knee osteoarthritis.¹

iPAAG: Injectable polyacrylamide hydrogel



**6ml per
treatment session¹²**

Supplied as 6 pre-filled, single use, sterile 1 mL syringes intended to be injected intra-articularly in the knee joint with a single 21G x 2 inches (0.8 x 50mm) needle.



Simple

A minimally invasive out-patient procedure **performed under local anaesthesia, with ultrasound guidance.**¹²



Safe

Arthrosamid® is safe for intended use¹⁸ — and **has undergone over 20 years of research and development.**⁷



Sustained

In clinical trials, patients reported a reduction in pain by Week 4. **This reduction was sustained over 2 years.**¹³

Tried and tested

Providing long-term relief from pain, iPAAG has been used for other indications with long-term follow up of 10 years with no migration.¹⁴

Researched for more than two decades,⁷ this hydrogel has been proven to be safe and effective:



705,000

syringes of Aquamid® or Aquamid® Reconstruction⁷



100,000

syringes of Arthramid® Vet⁷



280,000

syringes of Bulkamid®⁷

iPAAG: Injectable polyacrylamide hydrogel

What is iPAAG?

Arthrosamid® (iPAAG) is made up of 2.5% cross-linked polyacrylamide and 97.5% water.



BIOCOMPATIBLE

Permeable to salts and organic molecules, the hydrogel is able to integrate with soft tissue.⁷



VISCOELASTIC

Cross-linked chains of polymer allow flexible shear.⁷



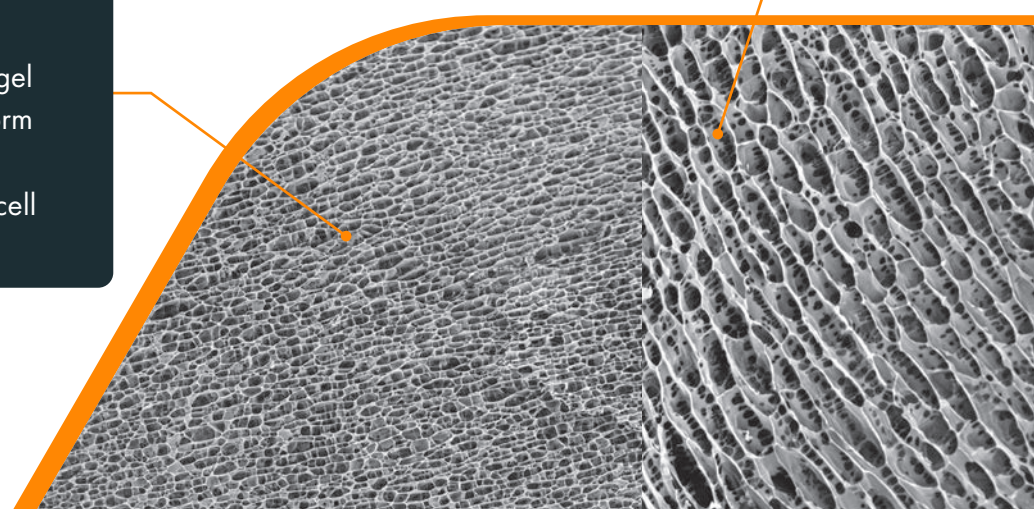
NON-DEGRADABLE

Structural stability of hydrogel provides longevity of action.⁷

The science behind iPAAG

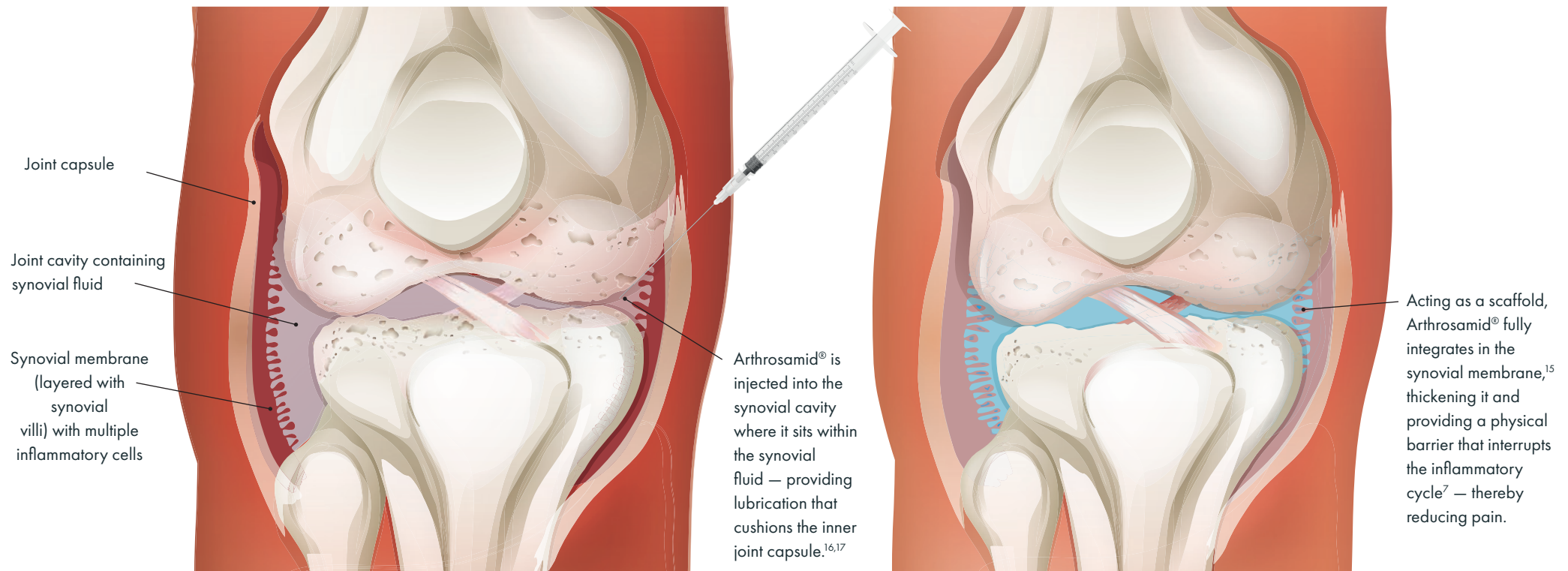
The three-dimensional structure of the polyacrylamide hydrogel presents in a tight uniform honeycomb structure providing a matrix for cell ingrowth.⁷

Electron microscopy images of cryo-frozen and fractured polyacrylamide hydrogel. Magnification on the left image is x1.600 and x6.000 on the right.⁷

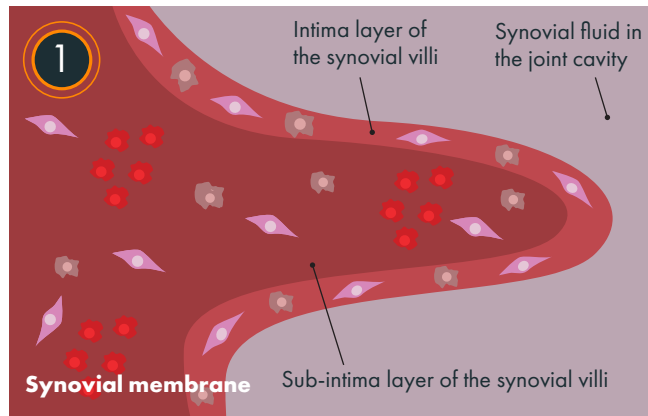


How does Arthrosamid[®] (iPAAG) work?

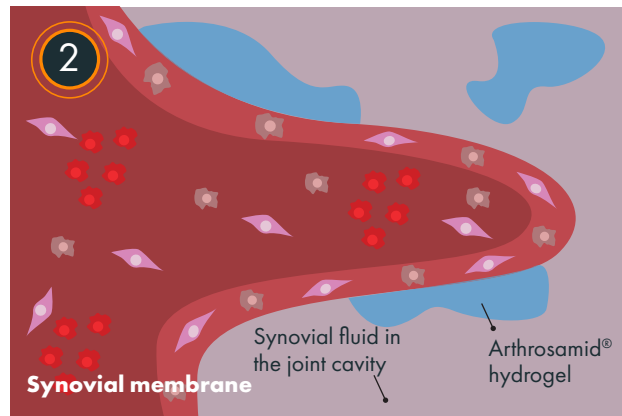
Arthrosamid[®] is the only approved iPAAG treatment in the world that permanently integrates into the synovial tissue of the inner capsule¹⁵ and decreases joint stiffness, thereby diminishing pain and improving function of the knee affected by OA.^{16,17} Its permanence means that it can provide long-term pain relief to treat knee OA.¹



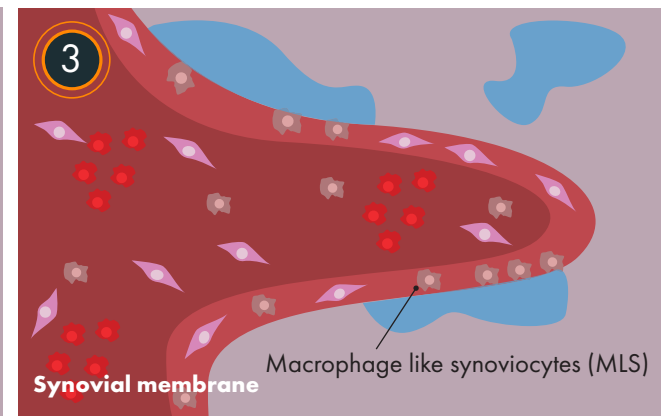
Mode of Action – let's take a closer look



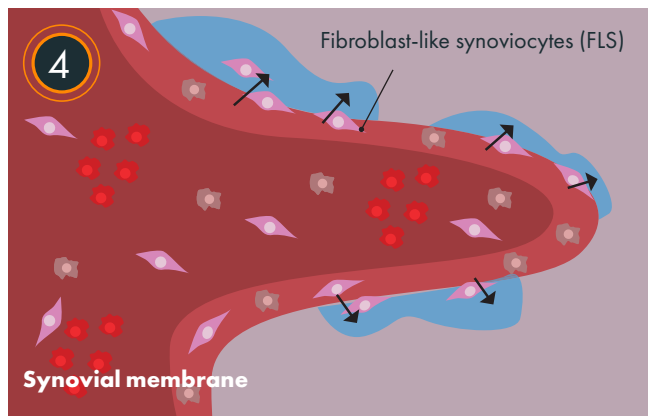
Untreated OA knee: the synovial fluid loses its viscoelastic properties. The synovial membrane contains an accumulation of inflammatory cells that are a precursor to pain and swelling.¹⁸



Arthrosamid is injected into the joint cavity, distributes within the joint fluid, and begins to adhere to the synovial lining.¹⁹

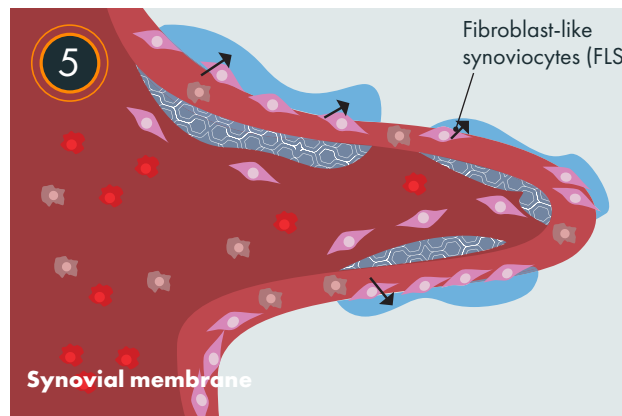


Macrophage like synoviocytes (MLS) enter the hydrogel but are unable to phagocytose it.¹⁹

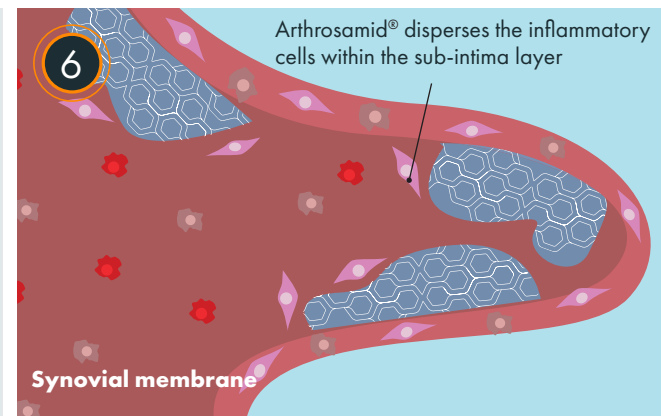


The MLS cells differentiate into fibroblast-like synoviocytes (FLS) which start integrating through the hydrogel, creating a thin vessel bearing fibrous network.¹⁹

iPAAG: Injectable polyacrylamide hydrogel



A new layer of intima forms on the top of the integrated iPAAG synovial membrane.¹⁹ This new layer consists of scattered non-inflammatory type cells, with the iPAAG acting as a scaffold within the sub-intima layer. This process takes 1 month.²⁰

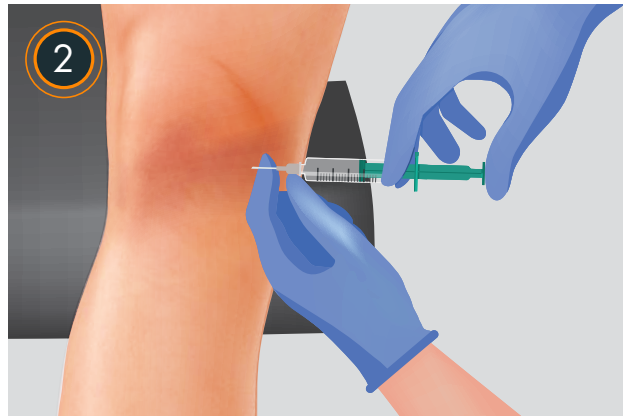


The thickening of the synovial sub-intima layer²⁰ causes distancing of the inflammatory cells⁷ and breaks the inflammatory cycle.

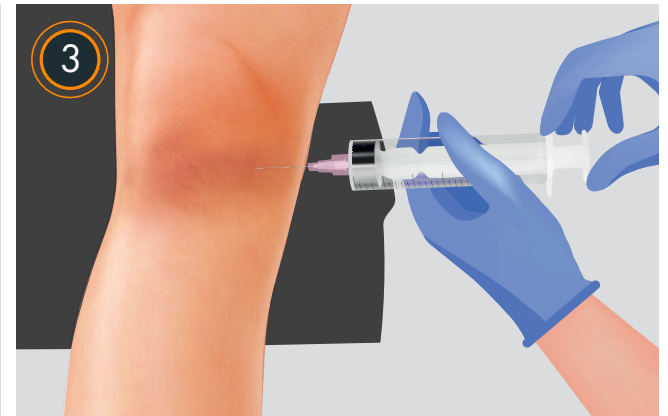
How to inject Arthrosamid® (iPAAG)



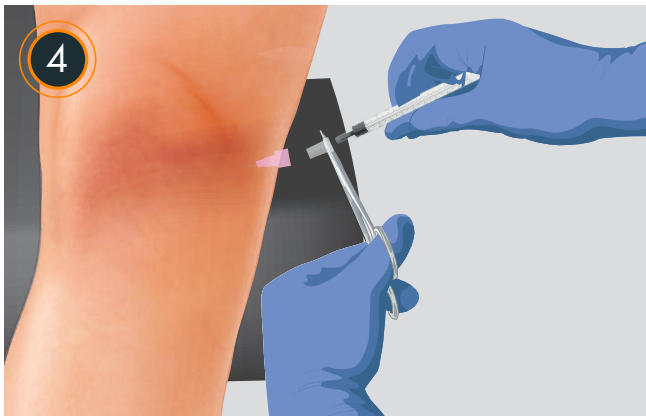
Oral antibiotics must be taken 1-2 hours before injection to reduce risk of infection. If available, use **Ultrasound** to ensure correct placement of needle into knee joint space.¹²



Conduct procedure using **aseptic conditions and no-touch technique**. Swab at least 5cm around injection site and use **local anaesthetic** to numb skin around it. Prepare **6 x 1ml Arthrosamid® syringes** by removing from blister packs and laying on table for easy access.¹²



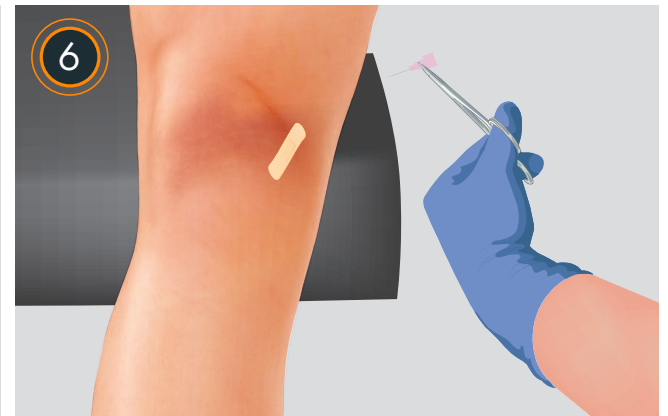
Swab knee again, 5cm around injection site. Ideally, use **21 G sterile needle** with Luer Lock fitting in lateral, proximal recess of knee joint. **Same needle must stay within knee for whole procedure**. Remove joint effusion, if present, before injecting Arthrosamid®.¹²



Remove syringe if used for effusion, but keep the needle in place. Remove protective Tip Cap from Arthrosamid® syringe **using Kelly forceps** to ensure no-touch technique.¹²



Turn syringe tight on Luer Lock to ensure needle is firmly in the socket and mounted correctly. Press firmly on syringe and inject 1ml of Arthrosamid into knee joint space. **Repeat until the recommended dosage of 6ml of Arthrosamid® is delivered into knee joint space.**¹²



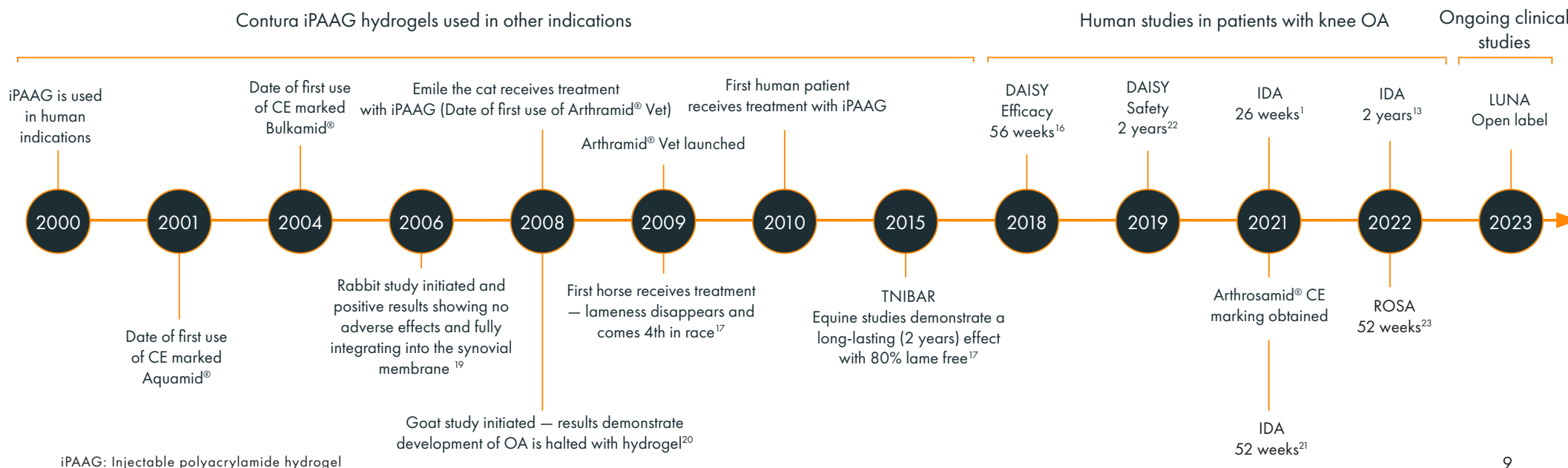
Using forceps, remove needle from knee. Swab knee for third time over injection site and cover with a plaster. Discard syringe, needle and any unused material after treatment.¹²

Arthrosamid® — an OA treatment 20 years in the making⁷



In April 2021, following the completion of a twelve-month prospective open label study which saw participants experience significant pain reduction,²¹ Arthrosamid® obtained CE marking for the symptomatic treatment of adult patients with knee OA.

This CE mark represented a major milestone for a product that has been in development for more than 20 years⁷ — and **provides an effective, safe, long-acting,¹ and minimally invasive treatment** that may postpone and potentially prevent knee surgery for those with OA.¹



Intra-articular 2.5% polyacrylamide hydrogel for the treatment of knee OA

Stable and statistically significant change on all WOMAC subscales and WOMAC total over the 56 week observation period.¹⁶

An observational proof-of-concept cohort 13 month study (DAISY Efficacy)^{7,16}

Objective

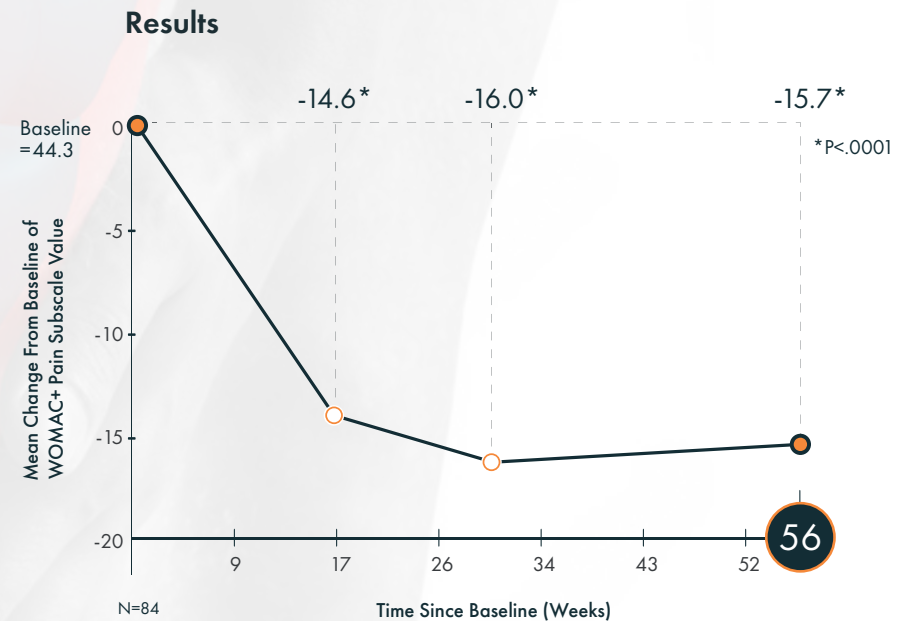
This study was conducted to establish an initial effectiveness of intra-articular (IA) injection of iPAAG for the treatment of knee OA symptoms.

Method

- 84 patients with knee OA were recruited into a prospective open-label cohort study, receiving up to up to 6ml of iPAAG.
- **Primary outcome — change from baseline of WOMAC[†] pain subscale after 4 months.** The WOMAC questionnaire was used to estimate effectiveness, and was collected at baseline and after 4, 7 and 13 months.

Conclusion

The primary outcome exceeded the established MCID^{**} of 9 points. The effect seemed to be long-term, with effectiveness maintained for up to 13 months.



[†] WOMAC or The Western Ontario and McMaster Universities Osteoarthritis Index is a measure of symptoms and physical disability LSMeans are modelled/estimated means. The estimated means are using data from the other visits and also the covariates.

^{**}MCID - Minimal Clinically Important Difference

iPAAG: Injectable polyacrylamide hydrogel

Polyacrylamide hydrogel injection (iPAAG) for knee osteoarthritis

Clinical application of iPAAG is safe and effective and can be conducted in a single injection.¹

A 26 week registration study (IDA 6 months)¹

Objective

This study evaluated the efficacy and safety of a single injection of 6ml of intra-articular iPAAG over 26 weeks.

Method

- Open-label study in patients with symptomatic and radiographically confirmed knee OA.
- **Primary outcome was change in WOMAC[†] pain at 13 weeks.**
- **Secondary outcomes were WOMAC subscales, PGA^{**} and proportion of OMERACT-OARSI^{***} responders, follow up points were 4, 13 and 26 weeks.**

Conclusion

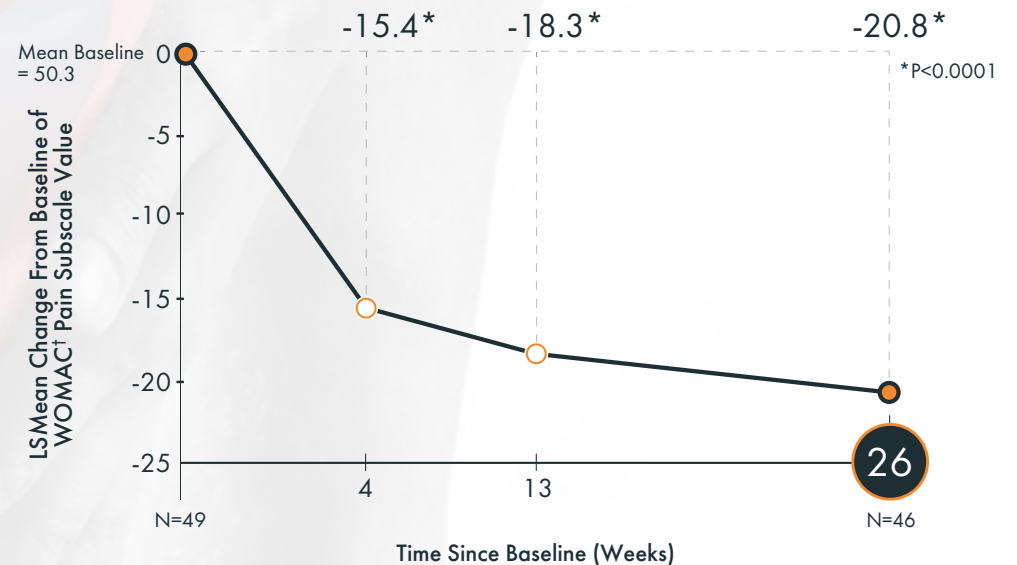
The study showed significant improvement in the WOMAC pain subscale at 4 and 13 weeks, which was sustained at 26 weeks. 2/3 of patients were OMERACT-OARSI responders. Clinical application of iPAAG is safe and effective and can be conducted in a single injection.¹

[†] WOMAC or The Western Ontario and McMaster Universities Osteoarthritis Index is a measure of symptoms and physical disability LSMeans are modelled/estimated means. The estimated means are using data from the other visits and also the covariates.

^{**}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 100mm Visual Analogue Scale (VAS) with anchors 0= "Not at all" and 100 = "The worst imaginable".

^{***}OMERACT-OARSI response was defined as either (1) improvement in WOMAC pain or physical function $\geq 50\%$ and an absolute change $\geq 20\%$ normalised units (0-100); or (2) $\geq 20\%$ improvement and an absolute change ≥ 10 points two of the three categories: WOMAC pain, WOMAC physical function, and PGA.

Results



Polyacrylamide hydrogel injection (iPAAG) for knee osteoarthritis

A 52 week prospective study (IDA 1 year)^{7,21}

Objective

The primary objective of this study was to evaluate the efficacy and safety of a single injection of iPAAG on knee symptoms in participants with moderate to severe knee OA.

Method

- Open-label study in patients with symptomatic and radiographically confirmed knee OA.
- **Primary outcome was change in WOMAC[†] pain at 13 weeks.**
- **Secondary outcomes were WOMAC subscales, PGA^{**} and proportion of OMERACT-OARSI^{***} responders, follow up points were 4, 13, 26 and 52 weeks.**

Conclusion

iPAAG can be delivered in a single injection and this non-randomised trial suggests that the good clinical effects at 13 weeks were maintained at 52 weeks in patients with moderate to severe knee OA. These encouraging results need to be confirmed in controlled studies.

† WOMAC or The Western Ontario and McMaster Universities Osteoarthritis Index is a measure of symptoms and physical disability LSMs are modelled/estimated means. The estimated means are using data from the other visits and also the covariates.

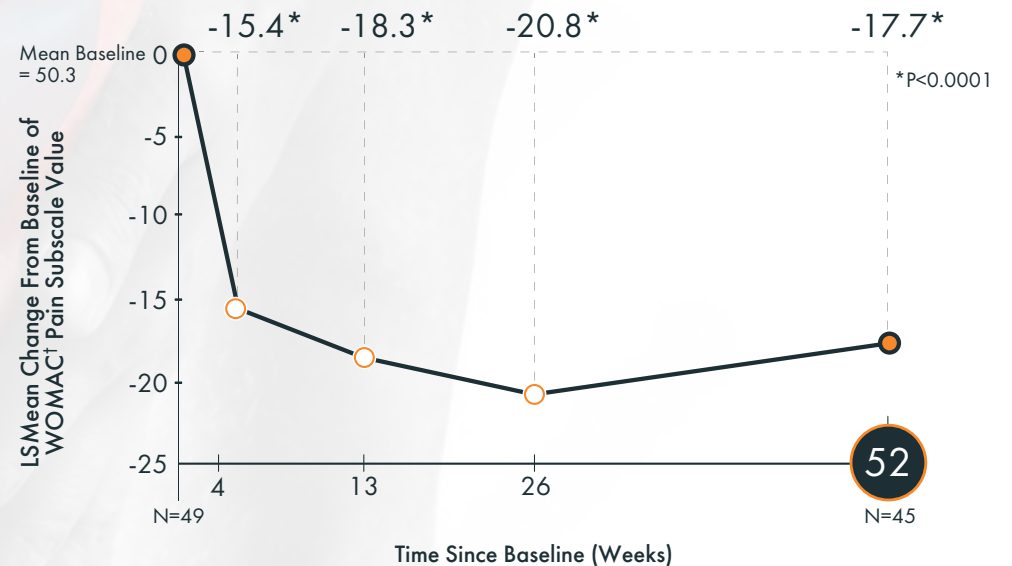
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iPAAG: Injectable polyacrylamide hydrogel

After 13 weeks, 64.6% of patients were OMERACT-OARSI responders, which was also maintained to 52 weeks.²¹

Results



A prospective study of polyacrylamide hydrogel injection (iPAAG) for knee osteoarthritis

Statistically significant reduction in pain maintained at 2 years.¹³

Results from 104 weeks after treatment (IDA 2 years)^{7,13}

Objective

The primary objective of this study was to evaluate the efficacy and safety of a single injection of iPAAG on knee symptoms in participants with moderate to severe knee OA.

Method

- Prospective, multicentre study (3 sites in Denmark) where 49 patients received a single intra-articular injection of 6ml Arthrosamid®.
- **Outcomes included the transformed pain, stiffness and function subscales and PGA** of disease impact.**
- **Changes from baseline to 52 weeks and 104 weeks were analysed using the mixed model for repeated measurement (MMRM).**

Conclusion

"Single injections of 6ml intra-articular Arthrosamid® continue to be well tolerated and demonstrate clinically relevant and statistically significant effectiveness, as measured by the WOMAC[†] pain, stiffness and physical function subscales and PGA** at 2 years after treatment."

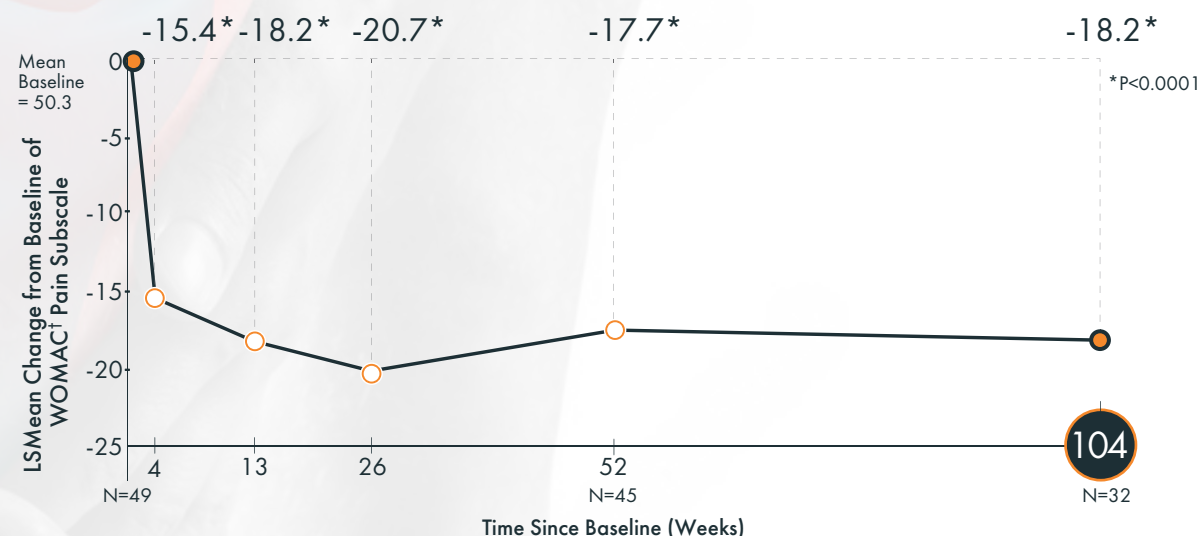
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The estimated means are using data from the other visits and also the covariates.

**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 100mm Visual Analogue Scale (VAS) with anchors 0= "Not at all" and 100 = "The worst imaginable".

iPAAG: Injectable polyacrylamide hydrogel

Results



One-year performance of polyacrylamide hydrogel (iPAAG) vs. hyaluronic acid

At 52 weeks after treatment, 74% of Arthroamid[®] patients responded^{7,11} with a 40% improvement in WOMAC pain score.²³

A randomised controlled study (ROSA)^{7,23}

Objective

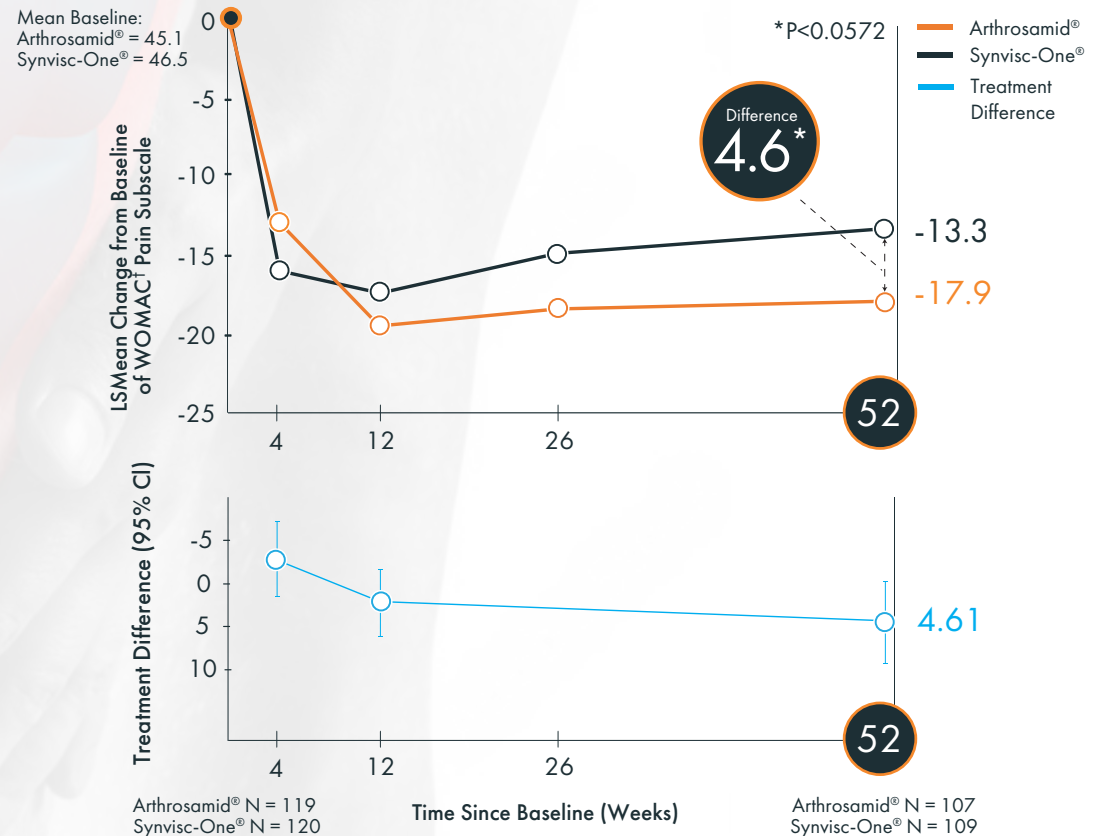
This randomised controlled study compared the effectiveness of a single intra-articular injection of polyacrylamide hyrogel (Arthroamid[®]) with that of a single injection of hyaluronic acid (Synvisc-One[®]) in participants with moderate to severe knee OA.

Method

- Prospective, double-blind (participant and assessor) study conducted at 3 sites in Denmark.
- Outcome assessments after 4, 12, 26 and 52 weeks.
- Subjects were randomised 1:1 to receive a single intra-articular injection of either 6ml Arthroamid[®] or 6mL Synvisc-One[®].

Conclusion

26 weeks after treatment, the effectiveness of Arthroamid[®] was non-inferior to hyaluronic acid, as measured by the WOMAC[†] pain subscale. 52 weeks after treatment, the effectiveness of Arthroamid[®] was numerically superior to hyaluronic acid but not statistically significantly different.²³



[†] WOMAC or The Western Ontario and McMaster Universities Osteoarthritis Index is a measure of symptoms and physical disability LSMs are modelled/estimated means. The estimated means are using data from the other visits and also the covariates.

Synvisc-One is a registered trademark of Sanofi-Aventis U.S. LLC. Arthroamid is a registered trademark of Contura International A/S. © copyright 2022 Contura International Ltd.

One-year performance of polyacrylamide hydrogel (iPAAG) vs. hyaluronic acid

Significant difference in change from baseline between Arthroamid[®] and Synvisc-One[®] at 52 weeks.²⁴

Analysis of change from baseline of subgroup <70 years (ROSA)^{7,24}

Objective

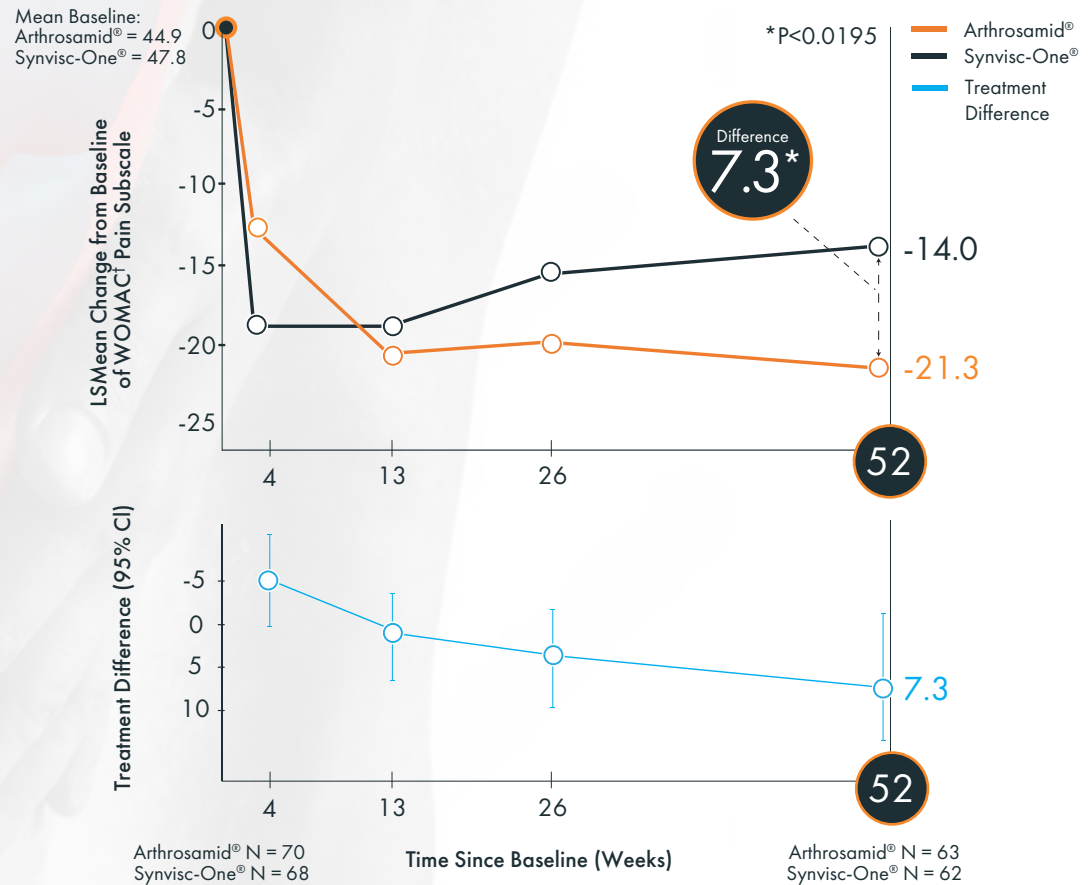
This randomised controlled study analysed subgroup of <70s for the effectiveness of a single intra-articular injection of polyacrylamide hydrogel (Arthroamid[®]) with that of a single injection of hyaluronic acid (Synvisc-One[®]) in participants with moderate to severe knee OA.

Method

- Prospective, double-blind, multicentre study (3 sites in Denmark) where randomised 1:1 subjects received a single intra-articular injection of 6ml Arthroamid[®] or 6ml Synvisc-One[®].
- Outcome assessments after 4, 12, 26 and 52 weeks.
- Subjects were randomised 1:1 to receive a single intra-articular injection of either 6ml Arthroamid[®] or 6ml Synvisc-One[®].

Conclusion

In participants <70 years old, Arthroamid[®] performed statistically significantly better than hyaluronic acid at 52 weeks after treatment.²⁴



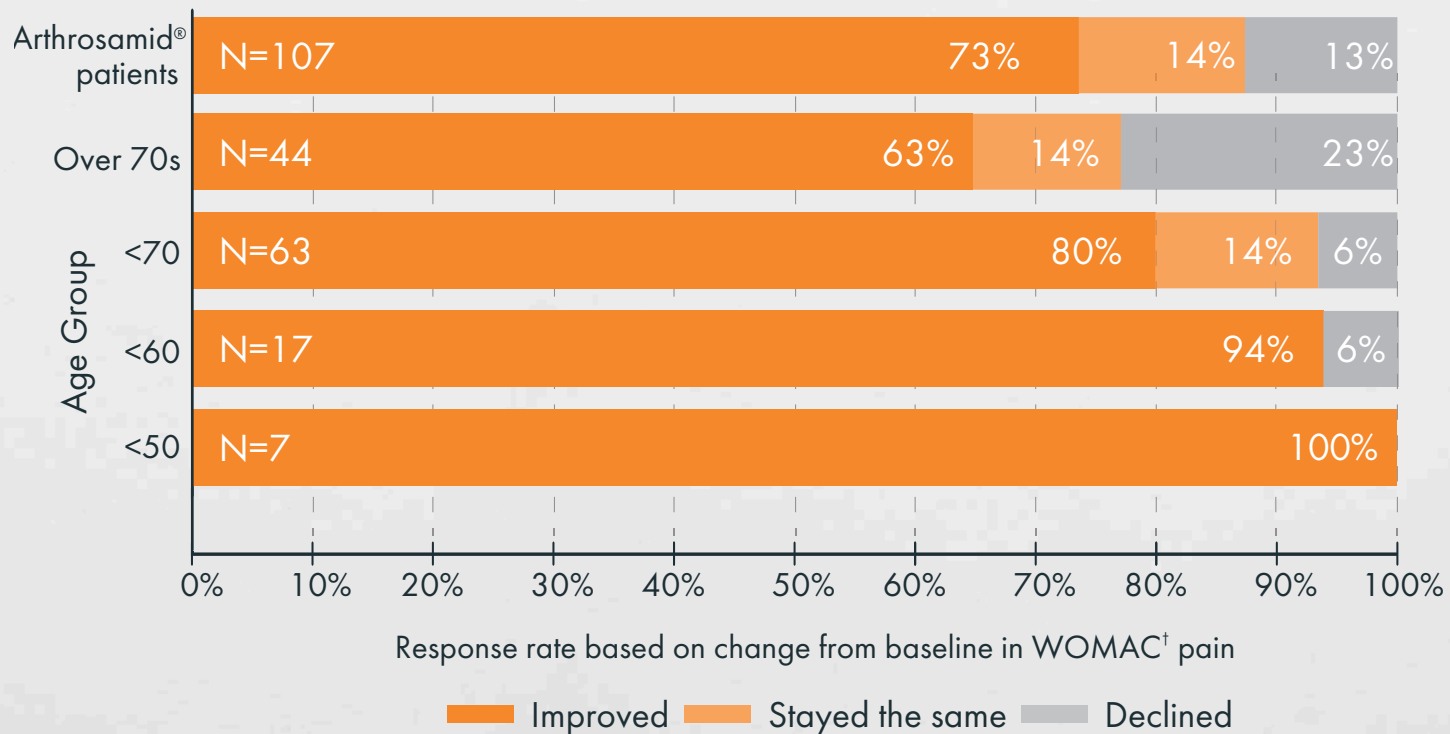
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iPAAG: Injectable polyacrylamide hydrogel

Response rate with Arthrosamid[®]7,23,24

A randomised study of one-year performance of polyacrylamide hydrogel (iPAAG) vs. hyaluronic acid.²³

80% response rate with the under 70 year olds.⁷

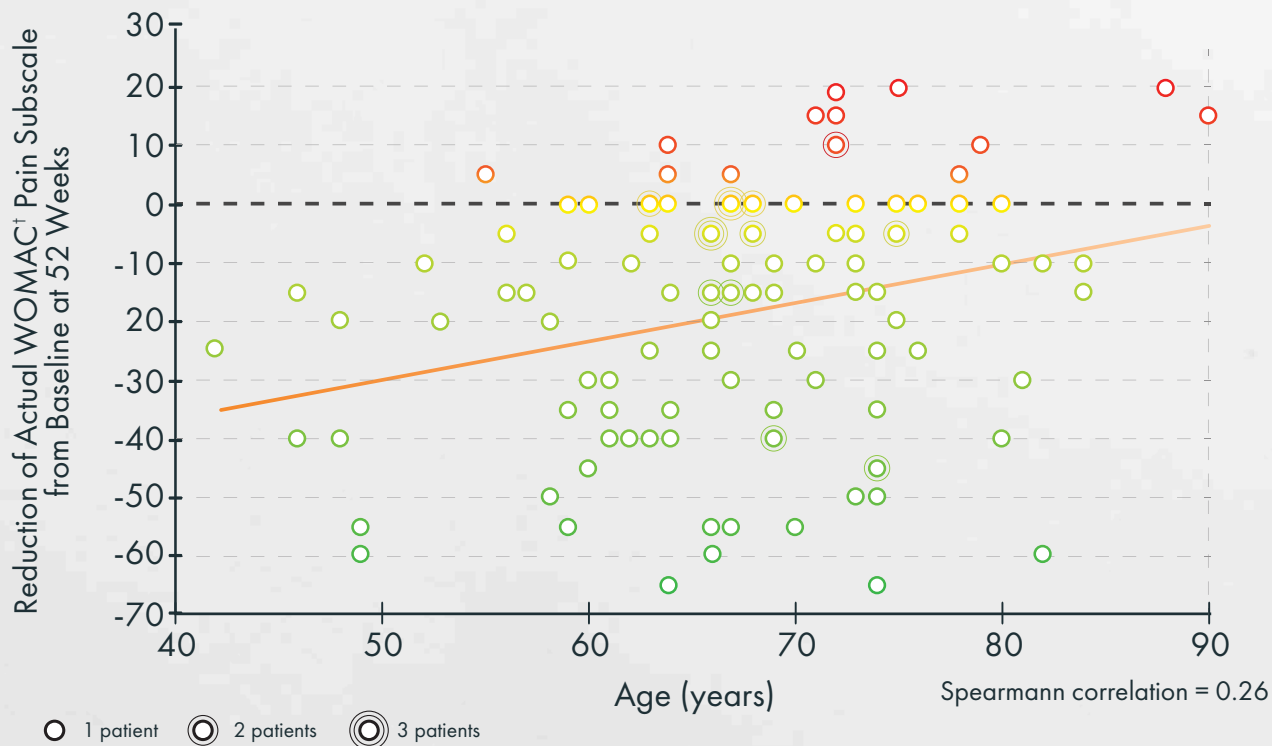


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A randomised study of one-year performance of polyacrylamide hydrogel vs. hyaluronic acid.²³

Scatterplot of age versus change from baseline to week 52 in transformed WOMAC pain subscale for Arthrosamid®.⁷



[†] WOMAC or The Western Ontario and McMaster Universities Osteoarthritis Index is a measure of symptoms and physical disability LSMeans are modelled/estimated means. The estimated means are using data from the other visits and also the covariates.

Over 60% of patients treated with Arthrosamid® achieved over the MCID of 9 points¹⁶ in WOMAC pain at 1 year.⁷





The clinical application of Arthrosamid® (iPAAG) is safe and effective.¹

Safety of intra-articular polyacrylamide hydrogel (iPAAG) for the treatment of knee osteoarthritis symptoms

	DAISY 2019 104 weeks ^{7,22}	IDA 2021 26 weeks ^{1,7}	IDA 2021 52 weeks ^{7,21}	IDA 2022 104 weeks ^{7,13}	ROSA 2022 52 weeks ^{7,23}
ITT	91	49	49	49	121
Number of AE device related	41	14	16	14	41
Sensation of distension	15	-	-	-	-
Pain from target knee	7	7	6	6	21
Reduced range of motion	4	-	-	-	-
Joint swelling	-	3	4	4	13
Other	15	4	6	4	7

16% of the participants had received arthroplasty surgery for knee OA of the treated knee.²²

There were no unexpected descriptions of abnormalities that could be associated with the prior treatment with iPAAG in the surgical reports.²²

“Of these patients, none reported dissatisfaction with the outcome of the surgery and the arthroplasties were well functioning.”²²

“No intra-articular infections or allergic reactions were reported in this retrospective study.”²²

“No patients had severe adverse events linked to Arthrosamid®.”¹

Patient Case Study #17

Female patient, aged 81

Patient history (pre-injection)

- Anterior Knee Pain
- KL4 -PFJ, KL2 -MFT, LFT

4 months post-injection

Used a walking stick	→	No walking stick
Unable to get up from chair without help	→	Able to get up from chair without help
Paracetamol, Tramadol	→	No more — Paracetamol, Tramadol
PRN – NSAID	→	PRN – NSAID
VAS – 9/10	→	VAS – 2/10
OKS – 27/48	→	OKS – 42/48
Lysholm – 33/100	→	Lysholm – 78/100



Pre-treatment



4 months post injection



6 months post injection

Patient Case Study #27

Male patient, aged 38

Patient history (pre-injection)

- Left knee recurrent patella dislocation, ACL deficiency, meniscus tear
- June 2019 – ACL reconstruction, lateral meniscus repair, Medial patella-femoral ligament – reconstruction

4 months post-injection

- Less pain
- Improved function
- Less clicking
- “Feels stronger, is stronger”
- Quads hypertrophy

Hopping – 8/10 Pain	→	Hopping – 2/10 pain but very weak
Step Down (25cm) – 6/10 Pain	→	Step down (25cm) – PAIN FREE
Split squats – 4/10 Pain	→	Split squats – PAIN FREE full ROM, weak eccentrically
Single leg sit to stand 10 reps – 4/10	→	Single leg sit to stand – PAIN FREE but weak
Running – 55% of body weight before pain	→	Running – 85% of body weight before pain



“Feels stronger, is stronger”

Key benefits of Arthrosamid®

Simple

Arthrosamid® is injected into the intra-articular space¹² as a minimally invasive, out-patient procedure.

Arthrosamid® integrates into the synovial tissue of the inner capsule.^{19,20}

Arthrosamid® is biocompatible, non-absorbable, non-biodegradable and non-migratory.⁷

Arthrosamid® improves function of the knee in patients with osteoarthritis.¹⁶



Arthrosamid® treatment is a minimally invasive, out-patient procedure.¹²

Arthrosamid® is safe for intended use.²²

Safe

Arthrosamid® is safe for intended use and is biocompatible which allows it to integrate with the tissues in the patient's knee. The overall safety profile of the hydrogel has undergone over two decades of research and development,⁷ with approximately 1,000,000 hydrogel syringes used for various indications in the body.⁷

Sustained

In clinical trials, patients reported a reduction in their pain levels by week 4 after their injection.²¹ The reduction in pain was sustained over 104 weeks.¹³ Arthrosamid® trials will continue to follow patients for 5 years.⁷

Improves quality of life of knee OA patients.¹

Because Arthrosamid® works to cushion the joint, it can reduce the patient's pain, decrease stiffness, and help movement. It has been shown to be safe and can give long-acting relief, improving quality of life.¹

Arthrosamid® diminishes pain of the knee joint in patients with osteoarthritis.¹⁶

Indications and Adverse Events

Indications, patient group and usage

Arthrosamid® is intended to be used for symptomatic treatment of adult patients with knee osteoarthritis.

Contraindications

Arthrosamid® should not be injected:

- If an active skin disease or infection is present at or near the injection site.
- If the joint is infected or severely inflamed.
- If the patient has previously received treatment with a different non-absorbable injectable/implant.
- If the patient has received a knee alloplasty or has any foreign material in the knee.
- If the patient has undergone knee arthroscopy within the last 6 months.
- In haemophilia patients or in patients in uncontrolled anti-coagulant treatment.

If a degradable intra-articular injectable such as hyaluronic acid is present, it must be expected to be absorbed according to manufacturer's information for the specific product before injection with Arthrosamid®.

A different non-absorbable implant should not subsequently be injected.

For more information, read the IFU for full details about warnings and precautions. The IFU is also available from <https://www.arthrosamid.com> or info@arthrosamid.com.



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