DUROLANE®
hyaluronic acid, stabilized single injection

20 YEARS

DUROLANE
POWERFUL &
LONG-LASTING
PAIN RELIEF

Read More About DUROLANE's Value to Healthcare Professionals and Patients

Key Preclinical & Clinical Publication Resource Guide

bioventus®
Innovations For Active Healing

*For DUROLANE's full summary of indications, go to page 47

Let the DUROLANE Numbers Speak

20 years of clinical use[1]

20+ clinical studies published[2]

2 million+ patients treated[3]

Why is the DUROLANE Clinical Resource Guide an important resource for healthcare professionals using nonoperative treatments to treat OA?

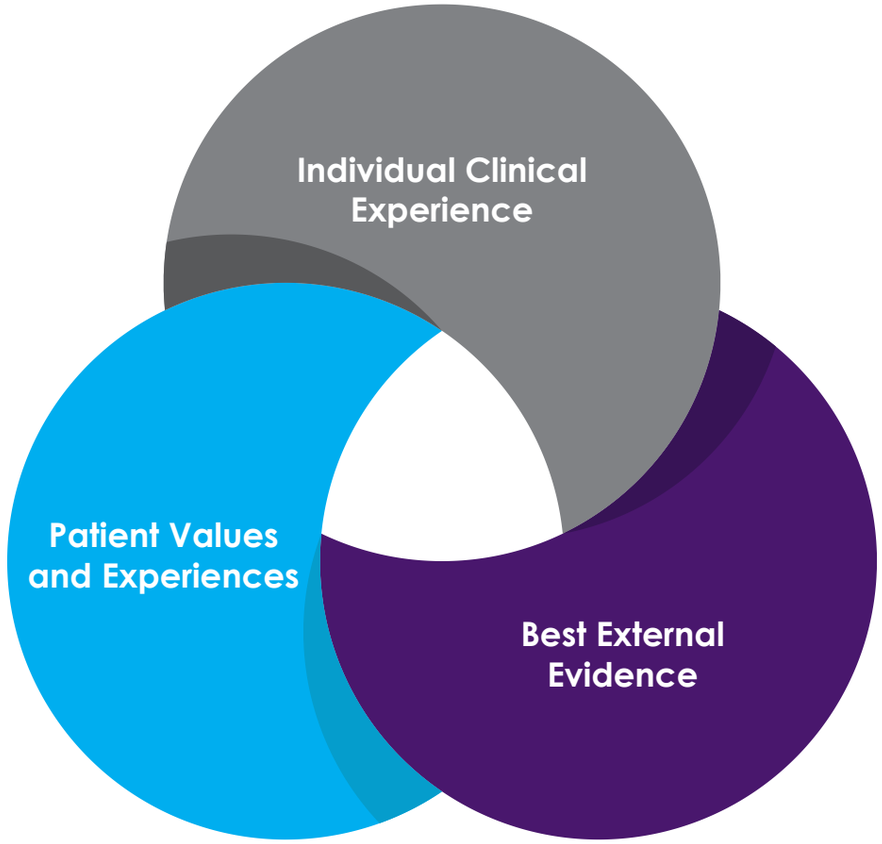
In recent updates by the European Union's Medical Device Regulations (MDR), there is now an increased emphasis on clinical evidence for medical devices in the marketplace. This further instills the importance of evidence-based medicine with the medical devices that you choose for your patients. That is why DUROLANE continues to strive to provide healthcare professionals and their patients with the best clinical evidence and experience, and responses to patients' needs and values.

With an increasing OA treatment backlog, there is an increased emphasis on nonoperative treatments for knee OA patients. In recent years, multiple studies have evaluated the clinical importance of nonoperative OA treatments.[4-6]

Recently, research has demonstrated that within the class of intra-articular knee OA pain relief treatments, **high**-molecular-weight IAHA is a clinically effective treatment, with the highest clinically significant outcomes when treating OA knee pain.[6]

Further outcomes in preclinical studies have recognized that high-molecular-weight IAHA promotes an anti-inflammatory response.[7]

Evidence-Based Medicine



Explore our Bioventus Academy site and medical education webinars to learn more about why **DUROLANE should be your preferred nonoperative OA treatment.**

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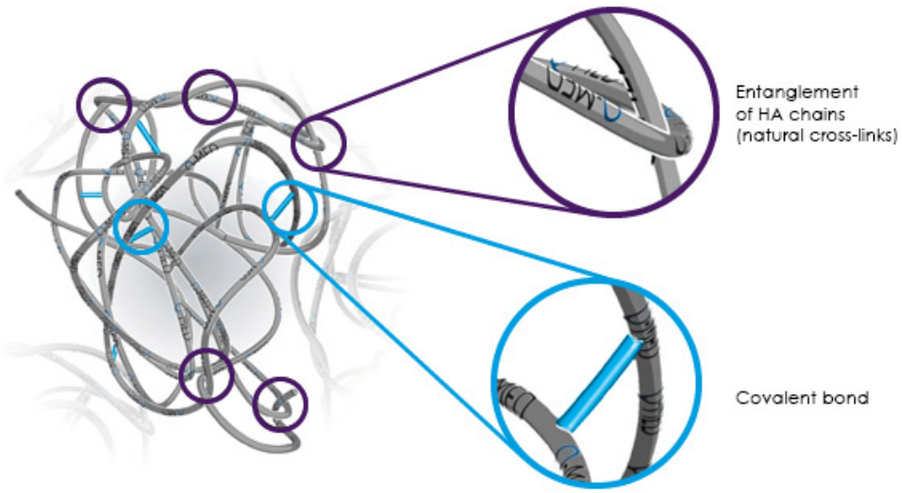
The DUROLANE Difference

Keep your patients moving!

NASHA® technology is used to stabilize and lightly cross-link HA, producing a gel-bead structure with a **high molecular weight of 10^{15} kDa.**[8]

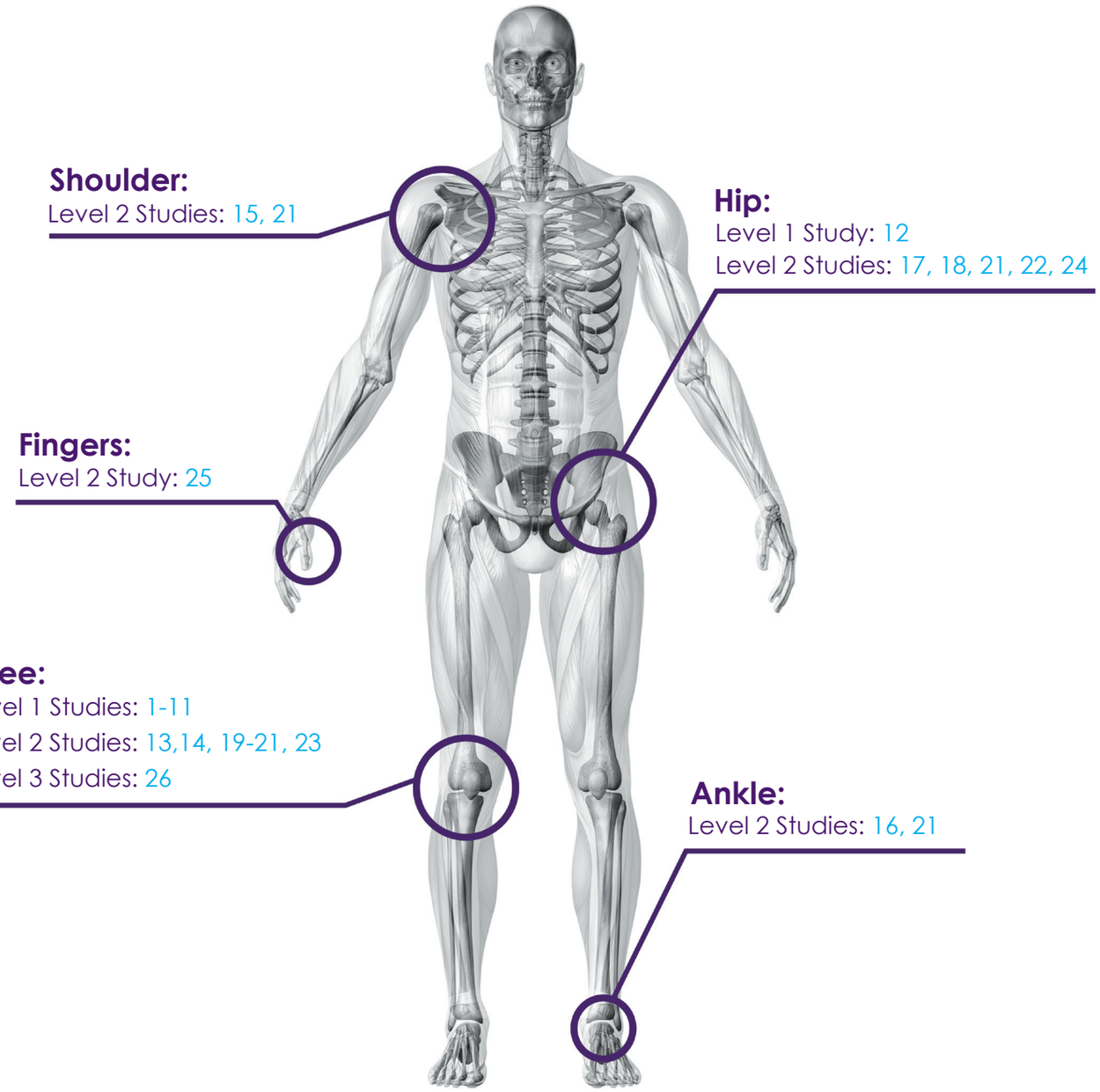


DUROLANE's patented NASHA technology prolongs joint residence time and increases resistance to degradation.[9,10] This gel-bead structure has a 30 day (approx 4 week) half-life in the joint, proven to provide up to 6 months of pain relief.[9,11] DUROLANE also helps to protect the joint from the damage of progressive OA, which may help to delay the need for TKR.[12,13] By promoting DUROLANE, a minimally cross-linked and stabilized HA, you can be sure that you are selling and promoting a safe and effective product, which will help you maintain the trust of your OA patients.[14,15] DUROLANE's efficacy and safety has been studied in Level 1 clinical studies.[16-27]

The difference is not only in the numbers, but in the results as well!

To learn more about DUROLANE, visit our website www.DUROLANE.com

Quick View of Clinical Studies by Indication*



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Study 2. Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD.
A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis

Study 3. Leighton R, Åkermark C, Therrien R, et al.
NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial

Study 4. Zhang H, Zhang K, Zhang X, et al.
Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz

Study 5. Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S.
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Analgesic control and functional outcome after knee arthroscopy: results of a randomized double-blinded trial comparing a hyaluronic acid supplement with bupivacaine

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Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial

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Growth factors levels determine efficacy of platelets rich plasma injection in knee osteoarthritis: a randomized double blind noninferiority trial compared with viscosupplementation

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Study 10. Vaquerizo V, Plasencia MÁ, Arribas I, et al.
Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial

Study 11. Vega A, Martín-Ferrero MA, Del Canto F, et al.
Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial

Study 12. Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F.
Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis

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A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis

Study 15. McKee MD, Litchfield R, Hall JA, Wester T, Jones J, Harrison AJ.
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Study 16. Younger ASE, Penner M, Wing K, et al.
Nonanimal hyaluronic acid for the treatment of ankle osteoarthritis: a prospective, single-arm cohort study

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Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid

Study 20. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H.
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Study 21. Carney G, Harrison A, Fitzpatrick J.
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Study 22. Long DM, Fitzpatrick J.
Safety and efficacy of a single intra-articular injection of hyaluronic acid in osteoarthritis of the hip: a case series of 87 patients

Study 23. Åkermark C, Berg P, Björkman A, Malm P.
Non-animal stabilised hyaluronic acid in the treatment of osteoarthritis of the knee: A tolerability study

Study 24. Daivajna S, Bajwa A, Villar R.
Outcome of arthroscopy in patients with advanced osteoarthritis of the hip

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Study 1

Study Title	**Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee**
Full List of Authors	Altman RD, Åkermark C, Beaulieu AD, Schnitzer T.; DUROLANE International Study Group.
Full AMA Reference	Altman RD, Åkermark C, Beaulieu AD, Schnitzer T.; Durolane International Study Group. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2004;12(8):642-9. doi:10.1016/j.joca.2004.04.010
Study Design	Level 1 clinical study: multicentre, randomized, double-blind, saline controlled.
Indication	OA Knee
Objective	This study was performed to investigate the safety and efficacy of single-injection NASHA compared with placebo in patients with OA of the knee.
Results	346 patients with knee OA were randomised to a treatment group (172, DUROLANE; 174, saline). WOMAC and SF-36 scores were recorded at baseline and follow-up visits at weeks 2, 6, 13 and 26 post injection. For the overall population, there were no statistically significant between-group differences in response rates for any efficacy parameters. In patients with OA confined to the knee (n=216), a greater WOMAC responder rate* to DUROLANE than placebo was observed at week 6 (p=0.025). *Pain responder rate: the percentage of patients with ≥40% improvement from baseline in WOMAC pain score and an absolute improvement of ≥5 points.
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Study 2

Study Title	**A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis**
Full List of Authors	Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD.
Full AMA Reference	Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. *Curr Med Res Opin*. 2014;30(2):279-86. doi:10.1185/03007995.2013.855631
Study Design	Level 1 clinical study: multicentre, randomized, double-blind, saline-controlled.
Indication	OA Knee
Objective	A 6 week saline-controlled study to investigate the safety and efficacy of DUROLANE in patients with mild–moderate structural OA confined to the study knee.
Results	218 patients with KL grades II-III OA in a single knee were randomised into two treatment groups (DUROLANE, 108; saline, 110). No statistically significant difference in WOMAC responder rate* was found between the two groups at 6 weeks (DUROLANE, 30.6%; saline, 26.4%). A post-hoc subgroup analysis of patients without clinical effusion in the study knee at baseline showed a significantly higher (p=0.0084) 6 week WOMAC pain responder rate with DUROLANE (DUROLANE, 40.6%; saline, 19.7%).
	*Pain responder rate: the percentage of patients with ≥40% improvement from baseline in WOMAC pain score and an absolute improvement of ≥5 points.
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Study 3

Study Title	**NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial**
Full List of Authors	Leighton R, Åkermark C, Therrien R, Richardson JB, Andersson M, Todman MG, Arden NK.
Full AMA Reference	Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. *Osteoarthritis Cartilage*. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009
Study Design	Level 1 clinical study: prospective, multicentre, randomised (1:1), corticosteroid-controlled, double-blind. Weeks 1-26, double-blinded. Weeks 26-52 open-label.
Indication	OA Knee
Objective	To compare, in a non-inferiority trial, the effectiveness and safety of a single intra-articular injection of NASHA (DUROLANE) at 12 weeks with a commonly used steroid, methylprednisolone acetate (MPA).
Results	442 patients with unilateral knee OA were randomly assigned to a treatment group (DUROLANE, 221; MPA, 221). In the blinded phase, patients were followed up at 6, 12, 18 and 26 weeks. This was followed by an open-label phase where patients irrespective of their first treatment were offered DUROLANE. This second phase was followed up at 39 and 52 weeks. The primary objective was met, with DUROLANE producing a non-inferior WOMAC pain responder rate vs MPA at 12 weeks (DUROLANE: 44.6%; MPA: 46.2%; difference [95% CI]: 1.6%[-11.2%; +7.9%]). Effect size for WOMAC pain, physical function and stiffness scores favored DUROLANE over MPA from 12 to 26 weeks. Patients who received DUROLANE at 26 weeks (during the open-label phase of the study) showed higher WOMAC pain responder rates at 39 and 52 weeks than at 26 weeks. The extent of improvement was similar whether patients initially received DUROLANE or MPA. No serious device-related AEs were reported. *Pain responder rate: the percentage of patients with ≥40% improvement from baseline in WOMAC pain score and an absolute improvement of ≥5 points.
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Study 4

Study Title	**Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz**
Full List of Authors	Zhang H, Zhang K, Zhang X, Zhu Z, Yan S, Sun T, Guo A, Jones J, Steen RG, Shan B, Zhang J, Lin J.
Full AMA Reference	Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x
Study Design	Level 1 clinical study: multicentre, randomised, double-blind, active-controlled, 26-week, head-to-head, non-inferiority comparison of efficacy and safety.
Indication	OA Knee
Objective	Compare safety and efficacy of intra-articular hyaluronic acid (HA) in two formulations: one 3.0-mL injection of DUROLANE versus five 2.5-mL injections of Artz for the treatment of knee (OA) pain.
Results	Patients were randomised to receive either 5 x 2.5 ml injections of Artz (N=158) or 1 x 3 ml injection of DUROLANE plus 4 sham injections (N=161). WOMAC scores equally improved from baseline in both treatment groups, at 18 and 26 weeks (p<0.0001 for each value, for both groups, at both weeks), suggesting a single injection of DUROLANE can be as beneficial in improving OA-related pain as a five-injection course of HA. Differences between the two HA treatments in the primary and secondary assessments were statistically insignificant through week 26, showing non-inferiority of DUROLANE. However, at weeks 18 and 26, there were twice as many nonresponders to the WOMAC pain walking on a flat surface item in the DUROLANE group (7.5% and 8.1%, respectively) vs. the Artz group (3.8% and 3.2%, respectively; p=0.0176 and 0.0082, respectively). Overall, 14% of patients across both treatment groups used rescue medication in weeks 4 to 6; this decreased to 5% in weeks 10 to 18. Between weeks 10 and 26, fewer patients in the DUROLANE group used rescue medication compared to those in the Artz group (n=28 vs n=40). In terms of safety, the incidence of treatment-related adverse events (TRAEs) was similar and considered low for both groups. Incidence of TRAEs: DUROLANE, 13.1%; Artz, 9.8%. The most common TRAE was arthralgia: DUROLANE, 8.6%; Artz, 7.5%. There were few serious AEs in either treatment group and none were considered TRAEs. Overall for the treatment of mild to moderate OA knee pain a single-injection of DUROLANE was found to be non-inferior to 5-injections of Artz in terms of knee pain, physical function, stiffness, and global self-assessment.
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Study 5

Study Title	**Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee--hyaluronan versus triamcinolone: a prospective, randomized, double blind, monocentric study**
Full List of Authors	Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S.
Full AMA Reference	Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee--hyaluronan versus triamcinolone: a prospective, randomized, doubleblind, monocentric study. *Eur J Med Res*. 2009;14(4):157-64. doi:10.1186/2047-783x-14-4-157
Study Design	Level 1 study, prospective, randomised, double-blind, monocentric.
Indication	OA Knee
Objective	Evaluation of gait performance and muscle activity patterns, as well as clinical efficacy and safety after single intraarticular injection with hyaluronan (DUROLANE) compared with triamcinolone in patients with knee osteoarthritis.
Results	Each therapy group consisted of 30 patients; complete analysis was achieved in 50 patients (DUROLANE, n=24; triamcinolone, n=26). Patients were followed up, 2 weeks following a wash-out period and 12 weeks post-injection. In the DUROLANE treatment group, significant improvements were seen in maximum hip flexion (p=0.0177), hip range of motion (p=0.0043) and knee range of motion in stance (p=0.0425). In the triamcinolone treatment group, gait analysis documented a significantly shorter stance phase (p=0.0258) and longer swing phase (p=0.0258). Pain measured using the visual analogue scale (VAS) for pain revealed a significant decrease in the DUROLANE group, from 54.9 mm in the screening visit to 44.0 mm (p=0.041). In the steroid group, VAS for pain declined from 52.9 mm to 42.5 mm, without reaching significance. Lequesne scores significantly improved (p<0.0001) in both treatment groups. Quality of life showed greater improvement in the triamcinolone group.
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Study 6

Study Title	**Analgesic control and functional outcome after knee arthroscopy: results of a randomized double-blinded trial comparing a hyaluronic acid supplement with bupivacaine**
Full List of Authors	Baker JF, Solayar GN, Byrne DP, Moran R, Mulhall KJ.
Full AMA Reference	Baker JF, Solayar GN, Byrne DP, Moran R, Mulhall KJ. Analgesic control and functional outcome after knee arthroscopy: results of a randomized double-blinded trial comparing a hyaluronic acid supplement with bupivacaine. *Clin J Sport Med*. 2012;22(2):109-15. doi:10.1097/JSM.0b013e318240e123
Study Design	Level 1 study, double-blinded randomised controlled trial.
Indication	OA Knee
Objective	After completion of surgery, all patients were randomised to receive either 10 mL of 0.5% bupivacaine or 3 mL of HA into the knee joint. The VAS and WOMAC scores were used to determine whether there was a difference in pain score after arthroscopy if patients were injected with HA vs. bupivacaine.
Results	On completion of the arthroscopic procedure and before the camera was removed from the joint cavity, group 1 (N=49) received 10 mL of 0.5% bupivacaine, as is common practice after knee arthroscopy to attain postoperative pain control. Group 2 (N=49) received 3 mL of DUROLANE into the joint via a separately introduced needle. The main outcome measures used were the VAS pain scores obtained at baseline, 1, 2, and 24 hours; and 1, 2, and 6 weeks after surgery. WOMAC and Tegner-Lysholm scores were obtained at baseline and then at 1, 2, and 6 weeks after surgery. There was no statistical difference in any of the outcome measures (VAS pain scores, WOMAC, and Tegner-Lysholm) at any point between the groups. Overall DUROLANE was as effective as bupivacaine for analgesic control in the short-term following arthroscopy.
Open Access	No

Study 7

Study Title	**Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial**
Full List of Authors	Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín MÁ.
Full AMA Reference	Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín MÁ. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. *J Orthop Traumatol*. 2018;19(1):3. doi:10.1186/s10195-018-0501-3
Study Design	Level 1, controlled and randomised trial.
Indication	OA Knee
Objective	To determine the effect of a single intra-articular injection of NASHA in the treatment of ankle OA. The hypothesis was that pain during the first 26 weeks post-treatment would be less than pain at baseline, as measured with the use of a visual analogue scale (VAS).
Results	One hundred and six patients were enrolled and randomized into one of three treatment arms, a total of 98 patients completed the study. The PRP group (n=33) received a 5-ml PRP injection. In the HA group (n=32), patients were treated with DUROLANE. The control group (n=33) received daily NSAID dose for 52 weeks. Patients were prospectively evaluated at baseline, 26 and 52 weeks using the WOMAC and VAS scores, and at baseline and 52 weeks with X-ray and MRI. Results showed a 20% decrease in WOMAC pain and increase in physical function was found in 30 patients who received PRP treatment, at the 52-week follow-up. WOMAC pain and VAS improved in the HA and NSAID groups. However, better results were obtained in the PRP group compared to HA and NSAIDs ($p<0.05$). No differences in Kellgren–Lawrence rating or cartilage thickness progression were found.
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Study 8

Study Title	**Growth factors levels determine efficacy of platelets rich plasma injection in knee osteoarthritis: a randomized double blind noninferiority trial compared with viscosupplementation**
Full List of Authors	Louis ML, Magalon J, Jouve E, Bornet CE, Mattei JC, Chagnaud C, Rochwerger A, Veran J, Sabatier F.
Full AMA Reference	Louis ML, Magalon J, Jouve E, et al. Growth factors levels determine efficacy of platelets rich plasma injection in knee osteoarthritis: a randomized double blind noninferiority trial compared with viscosupplementation. *Arthroscopy.* 2018;34(5):1530-1540.e2. doi:10.1016/j.arthro.2017.11.035
Study Design	Level 1, randomised double-blind controlled trial.
Indication	OA Knee
Objective	To assess the noninferiority of a single platelet-rich plasma (PRP) injection compared with hyaluronic acid (HA), to alleviate pain and enhance functional capacity in knee OA, and identify biological characteristics of PRP that may affect their efficacy
Results	Fifty-four patients with symptomatic knee osteoarthritis were randomised to receive a single injection of either PRP (N=26) or HA (N=28). In each treatment group final complete data sets were achieved in 24 patients. They were assessed at baseline and at 1, 3, and 6 months. Both treatments proved their improvement in knee functional status and symptom relief, with a significant decrease observed at 1 month on all scores, except for pain VAS in PRP group and WOMAC function score in the HA group. No differences between groups regarding WOMAC and VAS scores were observed. The satisfaction rate was 82% in the PRP group and 79% in the HA group at 3 months. A higher percentage of responders was observed in the PRP group (72.7%) than in the HA group (45.8%), without significance (p=0.064)
Open Access	No

Study 9

Study Title

Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial

Full List of Authors

Matas J, Orrego M, Amenabar D, Infante C, Tapia-Limonchi R, Cadiz MI, Alcayaga-Miranda F, Gonzalez PL, Muse E, Khoury M, Figueroa FE, Espinoza F.

Full AMA Reference

Matas J, Orrego M, Amenabar D, et al. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. *Stem Cells Transl Med*. 2019;8(3):215-24. doi:10.1002/sctm.18-0053

Study Design

Level 1, controlled, randomised trial.

Indication

OA Knee

Objective

To assess and compare the safety and efficacy of single and repeated injections of HA and umbilical cord-derived MSCs in knee OA.

Results

Patients with symptomatic knee OA were randomized to receive DUROLANE at baseline and 6 months (HA, N=8), stem cells at baseline and a placebo at 6 months (MSC-1, N=9) or repeated doses of stem cells at baseline and 6 months (MSC-2, N=9). Outcomes (WOMAC, VAS, Quality of Life and OMERACT-OARSI responder rates) were recorded by a second orthopaedic surgeon blinded to the treatment regime, these are reported at 24 and 52 weeks. Cell-treated groups tended to have more severe baseline disease (although not significantly) as gauged by the total WOMAC score and the percent Kellgren-Lawrence grade 3 patients in the MSC-1 and MSC-2 group (50% and 40%) as opposed to the HA group (23%). At 24 weeks (6 months) WOMAC sores in the HA group were improved but did not reach significance, in comparison WOMAC scores in both MSC groups significantly improved (p=0.001). In the MSC-2 treatment group, pain reduction at 12 months, was superior to the HA group, with 86% pain reduction and 89% disability reduction (p=0.001) as opposed to 38% and 50% in the HA group. Those in the HA group lost effect for pain after 6 months, but regained improvement after the second injection. Based on OMERACT-OARSI responder rates, at 12 months those treated with two doses of stem cells (MSC-2) achieved 100% compared to 62.5% (p=0.08). Both MSC and HA showed to be safe treatments with little to no adverse events.

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Study 10

Study Title	**Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial**
Full List of Authors	Vaquerizo V, Plasencia MÁ, Arribas I, Seijas R, Padilla S, Orive G, Anitua E.
Full AMA Reference	Vaquerizo V, Plasencia MÁ, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. *Arthroscopy*. 2013;29(10):1635-43. doi:10.1016/j.arthro.2013.07.264
Study Design	Level 1, randomised, double-blind, controlled trial.
Indication	OA Knee
Objective	To compare the efficacy and safety in a randomised, clinical trial of 3 injections of PRGF-Endoret versus one single intra-articular injection of DUROLANE HA as a treatment for reducing symptoms in patients with knee OA.
Results	96 patients with symptomatic knee OA were randomly assigned to receive PRGF-Endoret (3 injections on a weekly basis, N=48) or one infiltration with DUROLANE HA (N=42). Primary outcome measures were a 30% decrease and a 50% decrease in the summed WOMAC and Lequesne scores from baseline to weeks 24 and 48. The percentage of OMERACT-OARSI responders was also documented. Treatment with PRGF-Endoret was significantly more effective than treatment with DUROLANE HA in reducing knee pain and stiffness and improving physical function in patients with knee OA. The rate of response to PRGF-Endoret was significantly higher than the rate of response to HA for all the scores including pain, stiffness, and physical function on the WOMAC subscales, Lequesne index, and OMERACT-OARSI responders at 24 and 48 weeks. Adverse events were mild and evenly distributed between the groups.
Open Access	No

Study 11

Study Title	**Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial**
Full List of Authors	Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A,Orozco L, Soler R, Fuertes JJ, Huguet M, Sánchez A, and García-Sancho J.
Full AMA Reference	Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation*. 2015;99(8):1681-90. doi:10.1097/TP.0000000000000678
Study Design	Level 1, randomised, double-blind, controlled trial.
Indication	OA Knee
Objective	Assess the feasibility and safety of treating knee OA with allogeneic MSCs, and document the therapeutic value of allogeneic MSCs in treating knee OA.
Results	30 patients with chronic knee pain who were unresponsive to conservative treatment with radiological evidence of OA were randomised and divided into 2 groups of 15 patients. The test group was treated with allogeneic bone marrow MSCs, and control group with HA. Patients were clinically followed for 1 year to measure and evaluate pain, disability, and quality of life using the WOMAC, VAS and Lequesne scores. Feasibility and safety were confirmed and indications of clinical efficacy were identified. In the MSC treated group VAS and WOMAC pain both significantly improved at 6 ($p<0.05$) and 12 months ($p<0.01$) compared to baseline. VAS pain at 12 months ($p<0.05$) compared to baseline was the only improvement in pain seen in the DUROLANE group. Overall the analgesic effect of allogeneic MSC resulted in 38% to 42% improvement in pain compared to 10% to 14% in active controls with DUROLANE. Quantification of cartilage quality by MRI T2 relaxation measurements showed a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients.
Open Access	No

Study 12

Study Title	**Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis**
Full List of Authors	Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F.
Full AMA Reference	Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. *Ann Rheum Dis*. 2011;70(1):110-116. doi:10.1136/ard.2009.127183
Study Design	Level 1, prospective, randomised controlled trial. Randomised study with four treatment groups: standard care (no injection); normal saline; non-animal stabilised HA (DUROLANE) or methylprednisolone acetate (depomedrone).
Indication	OA Hip
Objective	Assess and predict response to a single ultrasound-guided injection in moderate to severe hip OA.
Results	77 patients were randomised to one of four groups: standard care (no injection, N=20); normal saline (N=19); non-animal stabilised HA (DUROLANE, N=19) or methylprednisolone acetate (depomedrone, N=20). The outcome measures used were the WOMAC score, OMEARCT-OARSI, and NRS pain score. Assessment was performed at baseline, 1 week, 4 weeks, 8 weeks, and 16 weeks post-injection. The study demonstrated that over an 8-week period, a single injection of IA-CS has a benefit for hip OA patients. Demonstrating p values of 0.002, 0.003 and 0.009 (analysis of variance) for the numerical rating scale (NRS) for pain, WOMAC pain and WOMAC function, respectively. The number of OMERACT-OARSI responders was significantly greater in the steroid group (p<0.001) (steroid, 14 (74%); saline, four (21%); DUROLANE, two (11%); and no injection, two (10%). There was no demonstrable improvement from the injection DUROLANE in this study cohort.
Open Access	No

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Study 13

Study Title	**Knee viscosupplementation: cost-effectiveness analysis between stabilized hyaluronic acid in a single injection versus five injections of standard hyaluronic acid**
Full List of Authors	Estades-Rubio FJ, Reyes-Martín A, Morales-Marcos V, García-Piriz M, García-Vera JJ, Perán M, Marchal JA, Montañez-Heredia E.
Full AMA Reference	Estades-Rubio FJ, Reyes-Martín A, Morales-Marcos V, et al. Knee viscosupplementation: cost-effectiveness analysis between stabilized hyaluronic acid in a single injection versus five injections of standard hyaluronic acid. *Int J Mol Sci.* 2017;18(3):658. doi:10.3390/ijms18030658
Study Design	Level 2 clinical study: prospective, randomised, non-blinded study.
Indication	OA Knee
Objective	Compare the effectiveness and treatment costs of NASHA in a single injection with standard preparations of HA in five injections in OA of the knee.
Results	Fifty-four patients with knee OA (KL grades II-III) and WOMAC pain score greater than 7 were included. Patients were randomised into two groups: Group I was treated with NASHA (a single injection of DUROLANE) and Group II with 5 weekly injections of an alternative HA (GO-ON®). At week 26, statistically significant improvements ($p=0.01$) were observed for patients treated with DUROLANE vs GO-ON in total WOMAC, as well as subscale scores for pain, stiffness, and function. In addition, the need for analgesia was significantly reduced at week 26 in the DUROLANE-treated group compared to the alternative HA treatment group ($p=0.006$). Finally, the economic analysis showed an increased cost of overall treatment with HA injections with GO-ON vs DUROLANE.
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Study 14

Study Title	**A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis**
Full List of Authors	McGrath AF, McGrath AM, Jessop ZM, Gandham S, Datta G, Dawson-Bowling S, Cannon SR.
Full AMA Reference	McGrath A, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. *J Arthritis.* 2013:2(1);1000108. doi:10.4172/2167-7921.1000108
Study Design	Level 2
Indication	OA Knee
Objective	To compare the efficacy and complications of two single-injection HA treatments for knee OA (Synvisc-One® and DUROLANE).
Results	182 knees were treated with KL, grades II-III OA with either a single injection of DUROLANE or Synvisc®.* Patients were followed up at 3, 6, 9 and 12 months. Significant improvements were seen in the VAS, and Oxford Knee Scores and analgesic use. The difference from baseline values was significantly different in the DUROLANE group (p=0.0001), but not for the Synvisc group (p=0.783) for VAS scores at 6 months. Nine patients experienced an adverse event. Oxford Knee Scores were significantly higher in the DUROLANE group compared to the Synvisc scores at 3, 6 and 9 months (p=0.0001). There was a significant reduction in the use of analgesia for up to 9 months in the Synvisc group (p=0.0001 at 3 and 6 months). This improvement remained significant but was greatly reduced at 9 months (p=0.046). In the DUROLANE group, reduction in analgesia use followed the same trend as Synvisc and reduced at 9 months but remained significant (p=0.0001) at 3 , 6 and 9 months. The reduction in analgesia use was significantly greater in the DUROLANE group compared to Synvisc at 3, 6 and 9 months (p=0.0001). Adverse reactions occurred significantly less with the more effective product. *Some patients were treated with a 3-injection Synvisc regimen. A 3-injection Synvisc regimen is equivalent to one injection of Synvisc-One.
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Study 15

Study Title	**NASHA hyaluronic acid for the treatment of shoulder osteoarthritis: a prospective, single-arm clinical trial**
Full List of Authors	McKee MD, Litchfield R, Hall JA, Wester T, Jones J, Harrison AJ.
Full AMA Reference	McKee MD, Litchfield R, Hall JA, Wester T, Jones J, Harrison AJ. NASHA hyaluronic acid for the treatment of shoulder osteoarthritis: a prospective, single-arm clinical trial. *Med Devices (Auckl)*. 2019;12:227-34. doi:10.2147/MDER.S189522
Study Design	Level 2 clinical study: single-arm, open-label, prospective study.
Indication	OA Shoulder
Objective	Follow up with patients 26 weeks post-treatment after a single injection of NASHA in the shoulder to observe whether there was a reduction in shoulder pain on movement (SPOM), measured by VAS scores.
Results	41 patients with mild-moderate glenohumeral osteoarthritis were enrolled and received a single intra-articular injection of NASHA in the shoulder. The least square mean (LS Mean) change from baseline in shoulder pain on movement (SPOM VAS) score over the whole 26-week study period was −20.1 mm (95% CI: −25.2, −15.0 mm), corresponding to a significant reduction of 29.5% ($p<0.0001$). A statistical improvement ($p<0.0001$) with a LS Mean change percentage change of 16.6% was also found in shoulder pain at night (SPAN VAS). Patient global assessment scores also improved after study treatment, with scores higher than baseline at every time-point post-treatment. For the whole period of the study, the LS Mean change from baseline was +9.80 mm, which corresponded to a LS Mean percentage change of 69.08% ($p=0.0006$). The greatest improvement in patient global assessment was evident at 18 weeks.
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Study 16

Study Title	**Nonanimal hyaluronic acid for the treatment of ankle osteoarthritis: a prospective, single-arm cohort study**
Full List of Authors	Younger ASE, Penner M, Wing K, Veljkovic A, Nacht J, Wang Z, Wester T, Harrison A.
Full AMA Reference	Younger A SE, Penner M, Wing K et al. Nonanimal hyaluronic acid for the treatment of ankle osteoarthritis: a prospective, single-arm cohort study. *J Foot Ankle Surg*. 2019;58(3):514-8. doi:10.1053/j.jfas.2018.10.003
Study Design	Level 2 clinical study: prospective, single-arm, open-label study.
Indication	OA Ankle
Objective	To determine the effect of a single intra-articular injection of NASHA in the treatment of ankle OA. The hypothesis is that pain after the first 26 weeks post-treatment would be less than pain at baseline, as measured with the use of a visual analogue scale (VAS).
Results	37 patients who had mild to moderate ankle OA, a VAS pain score of 30 to 90 mm, chronic pain for more than 6 months, and willingness to discontinue oral and topical analgesic were enrolled in the study. At baseline, each participant received a single injection of NASHA (DUROLANE). Follow-ups were performed at 6, 12, 18, and 26 weeks post treatment. During the 26-week follow-up period, the least squares (LS) mean change from baseline in ankle OA VAS pain score was −20.5 mm corresponding to a LS mean percentage reduction of 40.0% ($p<0.001$). The decrease versus baseline value in the ankle OA VAS pain score was >25% at every time point, and the improvement from baseline was greatest at week 12. Similar results were found with the LS mean change from baseline in the VAS disability score during the 26 weeks, with a significant ($p<0.001$) a percentage reduction of 34%.
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Study 17

Study Title	**Intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) for osteoarthritis of the hip: a pilot study**
Full List of Authors	Berg P, Olsson U.
Full AMA Reference	Berg P, Olsson U. Intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) for osteoarthritis of the hip: a pilot study. *Clin Exp Rheumatol*. 2004;22(3):300-6.
Study Design	Level 2 clinical study: single centre, prospective, open-label, pilot study.
Indication	OA Hip
Objective	To assess the safety and potential efficacy of intra-articular non-animal stabilised hyaluronic acid (NASHA) in patients with hip OA.
Results	Thirty-one patients with KL grades II-III OA in the hip were treated with DUROLANE. Follow-up evaluations were at 2 weeks and 3 months post injection. A positive response was defined as a ≥40% reduction from baseline in the WOMAC pain score, together with an absolute decrease of ≥5 points. The response rate was 50% at 2 weeks and 54% at 3 months. Patients demonstrating reduced pain at 3 months participated in an extension phase (n=18), assessment at 6-11 months (mean 7 months). In the extension population, the response rates were 69% at 3 months and 44% at the extension visit. There were 9 treatment-related adverse events, the majority of which were arthralgia. Adverse reactions were generally transient and all patients made a full recovery.
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Study 18

Study Title	**Safety, efficacy and predictive factors of efficacy of a single intra-articular injection of non-animal-stabilized-hyaluronic acid in the hip joint: results of a standardized follow-up of patients treated for hip osteoarthritis in daily practice**
Full List of Authors	Conrozier T, Couris CM, Mathieu P, Merle-Vincent F, Piperno M, Coury F, Belin V, Tebib J, Vignon E.
Full AMA Reference	Conrozier T, Couris CM, Mathieu P, et al. Safety, efficacy and predictive factors of efficacy of a single intra-articular injection of non-animal-stabilized-hyaluronic-acid in the hip joint: results of a standardized follow-up of patients treated for hip osteoarthritis in daily practice. *Arch Orthop Trauma Surg*. 2009;129(6):843-8. doi:10.1007/s00402-008-0778-4
Study Design	Level 2 clinical study: single centre, uncontrolled study.
Indication	OA Hip
Objective	To report on the efficacy and tolerability of a single intra-articular injection of DUROLANE in patients treated for symptomatic hip OA.
Results	Fourty patients with primary hip OA, ranging from KL grades I-IV, were treated with DUROLANE, thirty-four patients were assessable. The mean follow-up duration was 159 days (range 60–180). Most clinical variables decreased significantly between baseline and final follow up (walking pain, p=0.0001; patient global assessment, p=0.001; WOMAC (A) pain, p=0.043 and WOMAC (B) function, p=0.019). Lequesne index and WOMAC (C) stiffness also improved but did not reach significance (p=0.12 and p=0.107 respectively). Twenty-two of the 34 assessable patients (71%) and of the 40 total patients treated (55%) were classified as of OMERACT-OARSI* responders, suggesting the majority of patients derived benefit from the treatment. *Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage.* 2004;12(5):389-99. doi:10.1016/j.joca.2004.02.001
Open Access	No Click here to view the abstract

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Study 19

Study Title	**Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid**
Full List of Authors	Krocker D, Matziolis G, Tuischer J, Funk J, Tohtz S, Buttgereit F, Perka C.
Full AMA Reference	Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol*. 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2
Study Design	Level 2 clinical study: single centre, uncontrolled study.
Indication	OA Knee
Objective	To examine the efficacy of a single intra-articular injection of DUROLANE, based on changes in measurements of pain, functioning, and quality of life in patients with knee joint OA.
Results	Fifty patients with KL grades I-III OA of the knee were treated with a single injection of DUROLANE. Patients were followed up at 2 and 24 weeks post injection. At all three visits, range of motion (ROM), VAS pain was not found to be improved at 2 weeks post treatment but was significantly improved however at 24 weeks, the pain symptoms in the affected knee joint as compared to the baseline value at the screening visit decreased (–25%, $p<0.001$). The treatment with DUROLANE resulted in a significant improvement of all KOOS parameters at both follow-up visits. There was an improvement at 24 weeks of 19% and 56% ($p<0.001$), respectively, as compared to the baseline. The active ROM of the knee joints did not increase 2 weeks after the injection compared to the screening value (109° vs. 110°). At the second follow-up visit, however, a significant increase in active range of movement from 109° to 115° was measured after the therapy ($p=0.006$). The passive range of movement remained constant at 116° over the entire period of observation.Using the EQ-5D, a significant improvement ($p<0.001$) in quality of life by 21% and 36% after 2 and 24 weeks was recorded.
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Study 20

Study Title	**Elimination of stabilised hyaluronan from the knee joint in healthy men**
Full List of Authors	Lindqvist U, Tolmachev V, Kairemo K, Aström G, Jonsson E, Lundqvist H.
Full AMA Reference	Lindqvist U, Tolmachev V, Kairemo K, Aström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet*. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004
Study Design	Level 2 clinical study: single centre, uncontrolled study.
Indication	OA Knee
Objective	To investigate the elimination of stabilised hyaluronan following intra-articular injection into the knee joint of healthy men.
Results	Six male subjects were injected with 3 mL of radiolabeled DUROLANE into the knee joint. Radioactivity levels were then measured to assess how long it took for the DUROLANE to be eliminated from the human knee joint. Elimination of DUROLANE from the joint was described by three distinct phases, with half-lives of 1.5 hours, 1.5 days and 30 days (approximately 4 weeks). Most likely, the last value reflects the true half-life of DUROLANE, with the shorter half -lives attributable to the presence of small radio labelled fragments and small quantities of non-stabilized, low-molecular-weight HA.
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Study 21

Study Title	**Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients**
Full List of Authors	Carney G, Harrison A, Fitzpatrick J.
Full AMA Reference	Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol*. 2021;13:285-92. doi:10.2147/OARRR.S331562
Study Design	6-year observational cohort study.
Indication	OA Knee, hip, shoulder, ankle
Objective	To determine the duration of symptom relief following repeated administration of HA injections for OA in different joints.
Results	The analysis included 727 joint in 623 consecutive patients, each receiving between 1-8 injections. The mean time between initial injection and the 2nd treatment was 466.8 ± 321.7 days (157 joints), days between further injections remained high at; 400.5 ± 164.7 (2nd - 3rd injection, 58 joints), 378.2 ± 223.1 (3rd - 4th injection, 27 joints), 405.3 ± 216.3 (4th - 5th injection, 7 joints), 268.4 ± 104.4 (5th- 6th injection, 5 joints), 289.8 ± 99.4 (6th - 7th injection, 4 joints), and 272.5 ± 33.2 (7th - 8th injection, 2 joints). Patients with grades II and III, compared to grade IV osteoarthritis experienced a longer time between injections ($p = 0.0316$). No statistically significant differences were observed between age, gender, or joint groups. In a survey of 233 participants, 222 patients responded to whether they would recommend this treatment for OA. A total of 144 respondents (64.9%) recommended hyaluronic acid injections for osteoarthritis. Conclusion: Pain relief from hyaluronic acid injections was sustained for on average 466.8 days post initial treatment. Patients who received subsequent 3rd, 4th, and 5th injections also experienced extended duration of benefit. Patients with grades 2 or 3 osteoarthritis are more likely to experience a longer duration of relief.
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Study 22

Study Title	**Safety and efficacy of a single intra-articular injection of hyaluronic acid in osteoarthritis of the hip: a case series of 87 patients**
Full List of Authors	Long DM, Fitzpatrick J.
Full AMA Reference	Long DM, Fitzpatrick J Safety and efficacy of a single intra-articular injection of hyaluronic acid in osteoarthritis of the hip: a case series of 87 patients. *BMC Musculoskelet Disord.* 2021;22(1):797. doi:10.1186/s12891-021-04672-0
Study Design	Level 2 evidence, prospective, cohort study.
Indication	OA Hip
Objective	To assess the safety and efficacy of ultrasound guided injection of a high molecular weight, non-animal derived, stabilised HA (NASHA;DUROLANE) in patients with mild to moderate hip OA. This is an analysis of prospectively collected outcome data for 87 consecutive patients over a 2-year period who received single HA injections in symptomatic hip OA.
Results	Single injection of HA (NASHA) in the setting of hip joint OA was both safe and efficacious in this 87 patient cohort. Pain and function were assessed at baseline and at the 6 week follow-up using the modified Harris Hip Score (mHHS)*. The mean mHHS score improved from 58.47 (SD 14.82) to 71.30 (SD 16.46), a change of 12.83 ($p<0.01$). This was greater than the minimal clinically important difference (MCID) of 10 for clinical improvement at 6 weeks. Only 5 patients (5.7%) had any discomfort and there were no cases of severe acute localised reactions (SALR).
	*mHHS: Modified Harris Hip Score; measures both pain and function.
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Study 23

Study Title	**Non-animal stabilised hyaluronic acid in the treatment of osteoarthritis of the knee. A tolerability study**
Full List of Authors	Åkermark C, Berg P, Björkman A, Malm P.
Full AMA Reference	Åkermark C, Berg P, Björkman A, Malm P. Non-animal stabilised hyaluronic acid in the treatment of osteoarthritis of the knee. A tolerability study. *Clin Drug Investig.* 2002;22(3):157-66. doi:10.2165/00044011-200222030-00002
Study Design	Level 2 clinical study: multicentre, non-blinded, prospective, tolerability study with an extension phase.
Indication	OA Knee
Objective	To evaluate the safety of an intra-articular injection of DUROLANE (non-animal stabilised hyaluronic acid [NASHA]) in patients with OA of the knee, with an extension phase to assess the safety of a second repeat injection.
Results	One hundred and three patients (128 knees) with arthroscopically verified OA were treated with a single injection of DUROLANE. Patients were followed up at 2 weeks and 3 months post injection. Knee pain variables (at rest, during non-weight-bearing motion, during weight-bearing motion, and at night) were assessed on a VAS scale at each clinic visit. Overall satisfaction with treatment was assessed at the 3-month visit after the first injection. After the first injection, 7 of the reported local reactions fulfilled the criteria to be classed as a device-related adverse event (AE) (knee pain and swelling). Fifty-three patients received a second injection (6.5 to 9.5 months after the first injection). This was followed up 1 month later. After the second injection, 11 AEs were considered potentially related to the study product or the injection procedure, of which 3 were classed as device-related, unanticipated AEs, giving an event frequency of 4% in 72 injections. A statistically significant reduction in knee pain ($p < 0.0001$) was seen after both injections.
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Study 24

Study Title	**Outcome of arthroscopy in patients with advanced osteoarthritis of the hip**
Full List of Authors	Daivajna S, Bajwa A, Villar R.
Full AMA Reference	Daivajna S, Bajwa A, Villar R. Outcome of arthroscopy in patients with advanced osteoarthritis of the hip. *PLoS One*. 2015;10(1):e0113970. doi:10.1371/journal.pone.0113970
Study Design	Level 2 study.
Indication	OA Hip post-arthroscopy
Objective	Determine whether young and active patients with advanced OA should be treated with hip arthroscopy as part of their treatment pathway to delay joint replacement. DUROLANE was also injected post-arthroscopy to help reduce pain during the postoperative period.
Results	77 consecutive patients with grade II and III OA in the hip undergoing hip arthroscopy each received an injection of DUROLANE at the end of the procedure. Patients' medical notes, plain radiographs and outcome scores (modified Harris Hip Score (mHHS), Non-Arthritic Hip Score (NAHS) were collected preoperatively and postoperatively at 6 weeks, 6 months, one year and annually thereafter. The scores were obtained by using a postal questionnaire. The mean improvement scores for the mHHS were statistically significant with p=0.003 and p=0.0001 at one and two years respectively. For NAHS (non-arthritic hip score), the scores were statistically improved p=0.002 and p=0.003 at one and two years respectively. The study concluded that hip arthroscopy followed by an infiltration of DUROLANE improves outcome scores in 56% of patients with severe OA of the hip up to 2 years after surgery.
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Study 25

Study Title	**Single-arm open-label study of Durolane (NASHA nonanimal hyaluronic acid) for the treatment of osteoarthritis of the thumb**
Full List of Authors	Velasco E, Ribera MV, Pi J.
Full AMA Reference	Velasco E, Ribera MV, Pi J. Single-arm open-label study of Durolane (NASHA nonanimal hyaluronic acid) for the treatment of osteoarthritis of the thumb. *Open Access Rheumatol.* 2017;9:61-6. doi:10.2147/OARRR.S128675
Study Design	Level 2 clinical study: prospective, single-arm, multicentre, open-label study.
Indication	OA Trapeziometacarpal (TMC) joint of the thumb (rhizarthrosis)
Objective	Confirm the safety and effectiveness of viscosupplementation with DUROLANE (NASHA) in rhizarthrosis.
Results	Thirty-five patients were treated with DUROLANE and completed the study. Treatment was well tolerated and effective in reducing symptoms. Measured on a VAS scale, pain scores improved significantly, the least-squares mean change from baseline in VAS pain score over 6 months was –2.00, a reduction of 27.8% ($p<0.001$), exceeding the threshold for minimum clinically meaningful improvement (25% change in VAS score). The mean percentage decrease versus baseline was greater than 25% at all three assessment time-points, with continuous improvement throughout the study period (month 1, 26.5%; month 3, 28.7%; month 6, 32.6%). A positive response to viscosupplementation was also evident in joint function (QuickDASH and Kapandji scores) and biomechanical function (radial abduction, metacarpophalangeal flexion, and strength of clamp).
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Study 26

Study Title	**Factors related with the time to surgery in waiting-list patients for knee prostheses**
Full List of Authors	Romero Jurado M, Enrique Fidalgo A, Rodríquez Villar V, Mar Medina J, Soler López B.
Full AMA Reference	Romero Jurado M, Enrique Fidalgo A, Rodríguez Villar V, Mar Medina J, Soler López B. Factors related with the time to surgery in waiting-list patients for knee prostheses. *Reumatol Clin*. 2013;9(3):148-55. doi:10.1016/j.reuma.2012.09.003
Study Design	Level 3 clinical study: single centre, retrospective cohort study.
Indication	OA Knee
Objective	To assess if DUROLANE treatment could delay the need for a total knee replacement.
Results	Data was collected on 224 patients requiring total knee replacement (TKR), 202 (90.2%) of these patients were treated with DUROLANE. Kellgren-Lawrence grades varied from I to IV (9% KL-I, 27.5% KL-II, 48.2% KL-III, 15.3% KL-IV). In the stratified analysis, treatment with DUROLANE extended time until surgery in the group of patients with KL-III, which was close to statistically significant (p=0.064). The median time until TKR surgery in patients with grade III lesions and who received DUROLANE treatment, was 1278 days (95% CI, 474-2081) and for those not receiving treatment it was 596 days (95% CI, 14-1179).
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Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis

Study 2. Edsman K, Melin H, Nässtrom J.
A study of the ability of Durolane™ to withstand degradation by free radicals while maintaining its viscoelastic properties

Study 3. Plaas A, Li J, Riesco J, Das R, Sandy JD, Harrison A.
Intraarticular injection of hyaluronan prevents cartilage erosion, periarticular fibrosis and mechanical allodynia and normalizes stance time in murine knee osteoarthritis

Study 4. Wooley PH, Song Z, Harrison A.
Hyaluronic acid viscosupplements from avian and non-mammalian sources exhibit biocompatibility profiles with unique, source-specific, antigenic profiles

Study 1

Study Title	**Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis**
Full List of Authors	Ågerup B, Berg P, Åkermark C.
Full AMA Reference	Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs.* 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003
Study Design	Preclinical review article.
Objective	This article aims to describe the structures of HA products, how they are produced and summarises clinical findings. The two main HA treatments addressed in this review are hylan G-F 20 and DUROLANE.
Results	Ågerup et al clearly describe how hylan G-F 20 is produced by combining hylan A and hylan B strands. Hylan is extracted from rooster combs after pretreatment with formaldehyde to produce cross-links between amino acids and animal proteins. This cross-linking results in a protein content of 0.4-0.8% hylan A. Hylan B is produced by further cross-linking hylan A with divinyl sulfone to produce a gel. The extent of cross-linking in hylan B is approximately 20%. They also discuss the fact that the half-life of hylan A is 1.5 days, and 8.5 days for hylan B. The discussion includes the AEs and complications associated with hylan G-F 20, such as swelling and pain in the treated joint, but also serious AEs, such as aseptic acute arthritis, synovitis, pseudogout and anaphylactic shock. In comparison, Ågerup et al describe the production of DUROLANE using NASHA technology. This involves the secretion of HA from the cellular membrane of fermented bacteria into media. The HA is then extracted from the media and cross-linked with 1,4 butanediol diglycidyl ether which reacts with the hydroxyl group of the repeating disaccharide unit, this cross-linking is limited to 0.5-1.0%. The half-life of DUROLANE is 4 weeks. Regarding safety, the authors discuss that NASHA products have been used for cosmetic purposes without any reported safety concerns. Lastly, in a tolerability study of NASHA as a viscosupplementation treatment, only general transient reactions were experienced, which required no treatment.
Open Access	No Click here to view the abstract

Study 2

Study Title	**A study of the ability of DUROLANE™ to withstand degradation by free radicals while maintaining its viscoelastic properties**
Full List of Authors	Edsman K, Melin H, Näsström J.
Full AMA Reference	Edsman K, Melin H, Näsström J. A study of the ability of DUROLANE™ to withstand degradation by free radicals while maintaining its viscoelastic properties. Poster presented at: 55th Annual Meeting of the Orthopaedic Research Society; February 22-25 2009; Las Vegas, NV. Poster #1149.
Study Design	Preclinical investigation.
Objective	To determine how Synvisc® and DUROLANE are degraded by reactive oxygen species (ROS) compared to normal and osteoarthritic synovial fluid.
Results	Oxidative stress, with increased concentrations of ROS, results in HA degradation in inflammatory diseases of the joints. DUROLANE and Synvisc were exposed to free radicals in both their normal and diluted state. Their viscoelastic property was measured over a 90-minute period using storage (G´) and loss (G´´) moduli. These measurements were then compared to data from normal and arthritic human synovial fluids. DUROLANE showed the ability to retain its storage modulus, which represents the elasticity of the product, over the level of normal synovial fluid during the degradation. This was found to be true for the undiluted as well as for the diluted sample. The loss modulus, which represents the viscosity of the material, was above the level of normal synovial fluid for undiluted DUROLANE and similar for diluted DUROLANE and 20 mg/ml HA solution. Immediately after the onset of degradation, levels of both the storage and loss moduli of undiluted Synvisc were in the same order of magnitude as normal synovial fluid, but this dropped rapidly. The diluted Synvisc showed properties closer to pathologic synovial fluid.
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Study 3

Study Title	**Intraarticular injection of hyaluronan prevents cartilage erosion, periarticular fibrosis and mechanical allodynia and normalizes stance time in murine knee osteoarthritis**
Full List of Authors	Plaas A, Li J, Riesco J, Das R, Sandy JD, Harrison A.
Full AMA Reference	Plaas A, Li J, Riesco J, Das R, Sandy JD, Harrison A. Intraarticular injection of hyaluronan prevents cartilage erosion, periarticular fibrosis and mechanical allodynia and normalizes stance time in murine knee osteoarthritis. *Arthritis Res Ther.* 2011;13(2):R46. doi:10.1186/ar3286
Study Design	Preclinical investigation using control groups and TGF-ß1, and exercise-induced OA model in mice.
Objective	To examine the effect of intraarticular HA injection on well-defined stages of the initiation and progression of murine OA. Using a TGF-ß1 and exercise-induced OA model in mice, investigators performed macroscopic and microscopic evaluations of joint tissue structure, determined mechanical allodynia (pain caused by stimuli that do not normally evoke pain) and locomotive function of the hindlimbs.
Results	Osteoarthritis was induced in mice by injecting TGF-ß1 and running the mice uphill at 32cm/second for 20 minutes a day for 2 weeks. Animals were injected with either DUROLANE or saline the day before running commenced. A control group, without any intervention, also ran uphill for 2 weeks. Gait analysis showed that OA development in this model was accompanied by significant ($p < 0.01$) enhancement of the stance and propulsion times of affected legs. DUROLANE injection (but not saline injection) blocked all gait changes. Analysis of the joints also showed that DUROLANE protected joints from femoral cartilage erosion, as well as tibial and femoral tissue fibrosis. Both DUROLANE injection and saline injection attenuated acute allodynia, but the DUROLANE effect was more pronounced and prolonged with the saline injection.
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Study 4

Study Title	**Hyaluronic acid viscosupplements from avian and non-mammalian sources exhibit biocompatibility profiles with unique, source-specific, antigenic profiles**
Full List of Authors	Wooley PH, Song Z, Harrison A.
Full AMA Reference	Wooley PH, Song Z, Harrison A. Hyaluronic acid viscosupplements from avian and non-mammalian sources exhibit biocompatibility profiles with unique, source-specific, antigenic profiles. *J Biomed Mater Res B Appl Biomater*. 2012;100(3):808-16. doi:10.1002/jbm.b.32514
Study Design	Preclinical in-vivo study using an air pouch model in mice.
Objective	To compare two HA supplements from non-mammalian sources (low molecular weight HA [LMWHA] and NASHA [DUROLANE]) with a viscosupplement derived from an avian source (hylan G-F 20) with respect to their biocompatibility within an inflammatory tissue model, and their immunogical profile.
Conclusion	Air pouches were created in the back of 30 mice. After 6 days, the 30 mice were divided into 5 treatment groups and injected with 500 µL saline, DUROLANE, Synvisc, Synvisc, LMWHA, or a positive control of ultra high-molecular weight polyethylene (UHMWPE). Pouches were stimulated by the injection of 500 µL of sterile saline UHMWPE particle suspension. After 14 days, the tissue thickness of the pouch and antibody levels were measured by ELISA in order to evaluate if the injected products created an inflammatory response. Analysis of the air pouch tissue showed significant increase in thickness beyond that of the saline control for all products (p<0.03-0.001) except DUROLANE (p=0.02); the largest amount of tissue inflammation was observed in the pouches injected with Synvisc. The cause of the inflammation was shown to be an infiltration of both inflammatory cells and fibroblasts, with the positive UHMWPE control and Synvisc significantly increasing both cell populations compared to the PBS control (p<0.02) and (p<0.001 respectively). DUROLANE only stimulated a significant increase in fibroblastic cells (p<0.02). Moderate increases in both TNF-alpha and IL-6 in membrane-extracted proteins supported the histological observations of modest inflammation and fibroblast proliferation. An additional 24 animals were immunised with HA products in complete Freund's adjunvant. After 10 days the animals were treated with the appropriate HA product in incomplete Freund's adjuvant, in order to stimulate the immune system. These animals were then treated with one of the HA products. A high antibody response was seen in mice injected with the HA from an avian source, while low reactivity was observed in sera from mice injected with HA from bacterial sources. There was no indication of a cross-reaction, suggesting that patients with adverse immune responses to HA from an avian source should be unresponsive to a subsequent injection with the HA from a non-avian source.
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Nonoperative treatments for knee osteoarthritis: an evaluation of treatment characteristics and the intra-articular placebo effect: a systematic review

Study 1

Study Title	**Association between hyaluronic acid injections and time-to-total knee replacement surgery**
Full List of Authors	Altman R, Fredericson M, Bhattacharyya SK, Bisson B, Abbott T, Yadalam S, Kim M.
Full AMA Reference	Altman R, Fredericson M, Bhattacharyya SK et al. Association between hyaluronic acid injections and time-to-total knee replacement surgery. *J Knee Surg*. 2016;29(7):564-70. doi:10.1055/s-0035-1568992
Study Design	Level 2 study: retrospective cohort study, analysis of a large insurance claims database.
Indication	OA Knee
Objective	Assess the association between HA injections and time-to-total knee replacement surgery for patients with knee OA.
Results	Patients 18 to 64 years of age who had total knee replacement (TKR) surgery between January 1, 2006 and December 31, 2001 were identified from the MarketScan Commercial claims database. The MarketScan commercial claims database encompasses more than 60 million employees, spouses, and dependents located in all 10 US census regions. DUROLANE was not approved for use in the US at the time this data was collected, therefore DUROLANE is not one of the HA products used within this dataset. Results from this retrospective analysis included 22,555 patients who had TKR surgery: 14,132 in the non-HA-treated cohort and 8,423 in the HA-treated cohort. In patients undergoing TKR, the median time-to-TKR surgery was 326 days for the non-HA cohort and 908 days for the HA cohort, a difference of 582 days. Those receiving HA injections had a median 1.6-year longer time-to-TKR surgery versus those who did not receive HA injections.
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* This study has been included in the review section since DUROLANE was not available in the United States when the patients included in the study were treated.

Study 2

Study Title	**Anti-inflammatory effects of intra-articular hyaluronic acid: a systematic review**
Full List of Authors	Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P.
Full AMA Reference	Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P. Anti-inflammatory effects of intra-articular hyaluronic acid: a systematic review. *Cartilage.* 2019;10(1):43-52. doi:10.1177/1947603517749919
Study Design	Level 2 clinical study: systematic review to summarise the published literature on the anti-inflammatory properties of HA in OA
Indication	OA Knee
Objective	To summarize the published literature on the anti-inflammatory properties of hyaluronic acid in OA through a number of pathways, including the suppression of pro-inflammatory cytokines and chemokines.
Results	Forty-eight articles were included in this systematic review that focused on the general anti-inflammatory effects of HA in knee OA, mediated through receptor-binding relationships with cluster determinant 44 (CD44), toll-like receptor 2 (TLR2) and 4 (TLR-4), intercellular adhesion molecule-1 (ICAM-1), and layilin (LAYN) cell surface receptors. High molecular weight HA (HMWHA) can bind to the sites of CD44, TLR-2, and TLR4, to promote anti-inflammatory effects within the cell. Through CD44 receptor binding, HMWHA downregulates the expression of IL-8, IL-33, MMPs, proteoglycans and PGE2 and suppresses NF-κB activation. HMWHA also suppresses pro-inflammatory cytokine levels through interactions with ICAM-1 by downregulation of NF-κB and I-κB. In comparison low molecular weight HA (short HA oligosaccharides) produce inflammatory reactions. The review summarises that intra-articular HA (IHA) is a viable therapeutic option in treating knee OA, and may help suppress the inflammatory response with the affected knee joint.
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Study 3

Study Title	**A comparison of treatment effects for nonsurgical therapies and the minimum clinically important difference in knee osteoarthritis: a systematic review**
Full List of Authors	Concoff A, Rosen J, Fu F, Bhandari M, Boyer K, Karlsson J, Einhorn TA, Schemitsch E.
Full AMA Reference	Concoff A, Rosen J, Fu F, et al. A comparison of treatment effects for nonsurgical therapies and the minimum clinically important difference in knee osteoarthritis: a systematic review. *JBJS Rev*. 2019;7(8):e5. doi:10.2106/JBJS.RVW.18.00150
Study Design	Level 2 clinical study: systematic review.
Indication	OA Knee
Objective	Identify guidelines and meta-analyses evaluating pain outcomes for nonsurgical knee OA interventions. The MCID was used to evaluate the perception of the relative benefit of each nonsurgical treatment.
Results	Systematic and manual searches were conducted to identify guidelines and meta-analyses evaluating pain outcomes for nonsurgical knee osteoarthritis interventions. Individual treatment effects for pain were presented on a common scale (the standardized mean difference [SMD]). Thirty-seven guidelines and meta-analyses were included. MCIDs were often presented as an SMD or a mean difference (MD) on a validated scale and varied in magnitude across sources. This analysis demonstrated that intra-articular hyaluronic acid, intra-articular corticosteroids, and acetaminophen all had relatively larger effect sizes than topical nonsteroidal anti-inflammatory drugs (NSAIDs). Higher-molecular-weight intra-articular hyaluronic acid had a greater relative effect compared with both non-selective and cyclooxygenase-2-selective oral NSAIDs. The review confirmed the variability in the MCIDs for pain assessments that are used across guidelines and meta-analyses evaluating nonsurgical interventions for knee osteoarthritis. This variability may yield conflicting treatment recommendations, ranging from rejecting treatments that are indeed efficacious to accepting treatments that may not be beneficial.
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Study 4

Study Title	**Systematic clinical evidence review of NASHA (Durolane hyaluronic acid) for the treatment of knee osteoarthritis**
Full List of Authors	Leighton R, Fitzpatrick J, Smith H, Crandall D, Flannery CR, Conrozier T.
Full AMA Reference	Leighton R, Fitzpatrick J, Smith H, Crandall D, Flannery CR, Conrozier T. Systematic clinical evidence review of NASHA (Durolane hyaluronic acid) for the treatment of knee osteoarthritis. *Open Access Rheumatol*. 2018;10:43-54. doi:10.2147/OARRR.S162127
Study Design	Level 2 systematic review and meta-analysis of Level 1 and Level 2 studies (PRISMA). DUROLANE versus: alternative HA, saline, steroid, platelet-rich plasma (PRP), mesenchymal, stem cells.
Indication	OA Knee
Objective	Assess in patients with OA of the knee, the efficacy and safety of intra-articular treatment with NASHA relative to control (saline) injections, other HA products, and other injectables (corticosteroids, PRP, mesenchymal stem cells).
Results	Based on the clinical outcomes reported in the 11 studies included in this review, NASHA treatment provides: • Significant reductions from baseline pain • Improvements in physical function and joint stiffness from baseline levels at 26 weeks after a single injection of NASHA in 3 studies, and after 24 weeks in a fourth study • Significant improvements in self-reported QoL outcomes over an extended time frame • Extends time to arthroplasty - 694 days without NASHA viscosupplementation to 1093 days with NASHA - 596 days without NASHA viscosupplementation to 1278 days with NASHA in KL grade III patients • A favorable safety and tolerability profile, with a low incidence of reported, transient TRAEs
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Study 5

Study Title	**Differentiating factors of intra-articular injectables have a meaningful impact on knee osteoarthritis outcomes: a network meta-analysis**
Full List of Authors	Phillips M, Vannabouathong C, Devji T, Patel R, Gomes Z, Patel A, Dixon M, Bhandari M.
Full AMA Reference	Phillips M, Vannabouathong C, Devji T, et al. Differentiating factors of intra-articular injectables have a meaningful impact on knee osteoarthritis outcomes: a network meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2020;28(9):3031-9. doi:10.1007/s00167-019-05763-1
Study Design	Level 2 clinical study: frequentist network meta-analysis.
Indication	OA Knee
Objective	To compare intra-articular injectable treatment outcomes on knee OA. The following treatment groups were included within the network meta-analysis: High MW HA (≥ 3000 kDa), Low MW HA (<3000kDa), PRP, standard release corticosteroids, and extended-release corticosteroids. Outcomes for pain at 3 months were analysed in 47 articles, function at 3 months in 24 articles and treatment related adverse events (AEs) in 38 articles.
Results	High molecular weight HA was the only treatment to surpass the minimum important difference threshold for both pain and function outcomes. Extended-release corticosteroids may provide additional clinical benefit over standard-release corticosteroids. PRP demonstrated possibly beneficial results, however there are wide confidence intervals making its efficacy uncertain.
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Study 6

Study Title	**Nonoperative treatments for knee osteoarthritis: an evaluation of treatment characteristics and the intra-articular placebo effect: a systematic review**
Full List of Authors	Vannabouathong C, Bhandari M, Bedi A, Khanna V, Yung P, Shetty V, Khan M.
Full AMA Reference	Vannabouathong C, Bhandari M, Bedi A, et al. Nonoperative treatments for knee osteoarthritis: an evaluation of treatment characteristics and the intra-articular placebo effect: a systematic review. *JBJS Rev.* 2018;6(7):e5. doi:10.2106/JBJS.RVW.17.00167
Study Design	Level 2 clinical study: systematic review, meta-analysis.
Indication	OA Knee
Objective	To compare treatment effect sizes from recent meta-analyses evaluating pharmacological or medical device interventions for the treatment of knee OA, and to further assess the clinical impact that intra-articular placebo effect may have on intra-articular injection therapies.
Results	This review presents effect estimates on a standardized mean difference (SMD) scale and compares them against a threshold for clinical importance of 0.50 standard deviation (SD) units. Ten meta-analyses providing a total of 19 different effect sizes for pain were included in this review. SMD estimates ranged from 0.08 to 0.79 for various electrical modalities, orthotic devices, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), dietary supplements, and intra-articular injection therapies. Seventeen treatments demonstrated significant improvements in terms of pain when patients who had received treatment were compared with controls. After accounting for the intra-articular placebo effect, the greatest effect estimates were those of intra-articular platelet-rich plasma and high molecular weight hyaluronic acid. When these were judged according to our threshold for clinical importance, high molecular weight intra-articular hyaluronic acid (>6000kDa) was found to have the most precise effect estimate that surpassed this threshold with an average score of 0.58 SMD.. Platelet-rich plasma was found to provide the greatest point estimate of the treatment effect, but the precision around this estimate had the largest amount of uncertainty across all treatments.
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Summary of Instructions for Use

EU, Turkey, Switzerland, Norway

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. In addition, DUROLANE has been approved in the EU for the symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, shoulder, elbow, wrist, fingers, and toes.

DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure.

There are no known contraindications.

DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Australia

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. In addition, DUROLANE has been approved for the symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, shoulder, elbow, wrist, fingers, and toes.

DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure.

DUROLANE is contraindicated in patients with known sensitivity to hyaluronic acid based products.

DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

UAE, Indonesia, Jordan, Colombia

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications.

DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

New Zealand

DUROLANE (3 mL): Symptomatic treatment associated with mild to moderate osteoarthritis pain in the knee, hip, shoulder, ankle, elbow, wrist, fingers, and toes.

DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure.

DUROLANE is contraindicated in patients with known sensitivity to hyaluronic acid based products.

DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Chile

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications.

You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

India

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications.

You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Mexico

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee osteoarthritis. There are no known contraindications.

You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Russia

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis.

There are no known contraindications.

DUROLANE should not be used if patients have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Taiwan

DUROLANE (3 mL): Treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Brazil

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. It should be injected by an authorized physician, or in accordance with local legislation.

There are no known contraindications.

DUROLANE should not be injected if the synovial joint is infected or severely inflamed. DUROLANE should not be injected if there is an active skin disease or infection present at or near the injection site. DUROLANE should not be injected intravascularly or extra-articularly or in the synovial tissues or capsule.

Full prescribing information can be found in product labeling, or at www.durolane.com.

Egypt, Morocco, Malaysia, Argentina

DUROLANE (3 mL): Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications.

You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women.

Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

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