Clinical Resource Guide: Clinical & Pre-Clinical

DUROLANE®
hyaluronic acid, stabilized single injection

bioventus®

Clinical

1. 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: 17-25.

Study Design

Level-I clinical study: prospective, multi-centre, randomized (1:1), corticosteroid-controlled, double-blind.

Objective

To compare, in a non-inferiority trial, the effectiveness and safety of a single intra-articular injection of NASHA® (DUROLANE®) with the commonly used steroid; Methylprednisone Acetate (MPA).

Results

442 patients with knee OA were randomly assigned to a treatment group (221 DUROLANE, 221 MPA). Results were similar between MPA and DUROLANE at 6-18 weeks. However, there was a significant reduction in the responders from weeks 18-26 in the MPA group which was not observed in the DUROLANE group. In response to a second DUROLANE treatment at 26 weeks, sustained improvements were seen in WOMAC outcomes irrespective of initial treatment. No serious device-related AEs were reported.

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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. *Current Medical Research & Opinion* Vol. 2014; 30(2): 279–286.

Study Design

Level-I clinical study: multi-centre, randomized, double-blind, saline-controlled.

Objective

A 6 week saline-controlled study to investigate the safety and efficacy of NASHA in patients with mild–moderate structural OA confined to the study knee.

Results

218 patients with KL grade II –III OA in a single knee were randomized into two treatment groups (DUROLANE 108, saline 110). No statistically significant difference in responder rate was found between the two groups at 6 weeks (NASHA: 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 responder rate with NASHA (NASHA: 40.6%; saline: 19.7%).

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3. 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.

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-II and KL-III grade osteoarthritis. Patients were followed up at 3, 6, 9 and 12 months. Significant improvement is seen in the VAS, SF 36 V2 and Oxford Knee Scores (p=0.01). At 6 months, this difference is extended in the DUROLANE group (p=0.0001) compared to Synvisc® (P=0.783). The abstract states AEs occurred significantly less with DUROLANE, but the only mention of this in the text is that 9 patients suffered an AE. Results suggest that HA treatment for mild to moderate OA can provide pain relief for up to six months along with reducing the need for analgesic and anti-inflammatory medication.

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4. Study Title

Factors Related with the Time to Surgery in Waiting-list Patients for Knee Prostheses

Full list of Authors

Jurado MR, Fidalgo AE, Villar VR, Medina JM, Lopez BS.

Full AMA Reference

Jurado MR, Fidalgo AE, Villar VR, Medina JM, Lopez BS. Factors Related with the Time to Surgery in Waiting-list Patients for Knee Prostheses. *Reumatol Clin*. 2013; 9(3): 148–155.

Study Design

Level-II clinical study: single centre, retrospective cohort study.

Objective

To assess if DUROLANE treatment could delay the need for a total knee replacement.

Results

Data was collected on 224 patients requiring TKR, 202 (90.2%) of these patients were treated with DUROLANE. KL grades varied from grade I to grade 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 close to statistical significance (P=0.064). The median survival of patients with grade 3 lesions and DUROLANE treatment was 1278 days (95%, 474–2081) and for those not receiving treatment it was 596 days (95% CI, 14–1179).

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5. 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, Vincent FM, 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: 843–848.

Study Design

Level-III clinical study: single centre, uncontrolled study.

Objective

To report on the efficacy and tolerability of a single intra-articular injection of NASHA in patients treated for symptomatic hip OA.

Results

34 patients with primary hip OA ranging from KL grades I – IV were treated with DUROLANE. All clinical variables (Walking Pain, Patient Global Assessment, WOMAC, Lequesne index) decreased significantly between baseline and last evaluation at 180 days. The percentage of “responder” patients according to the OMERACT-OARSI criteria (71% of the assessable patients, 55% of the total number of treated patients) suggested that a majority of patients derived benefit of the treatment.

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6. 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. *Rheumatol.* 2006; 65: 327–331.

Study Design

Level-III clinical study: single centre, uncontrolled study.

Objective

To examine the efficacy of a single intra-articular injection of DUROLANE measured based on pain, functioning, and quality of life in patients with knee joint arthritis.

Results

50 patients with KL grade 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, ROM, KOOS, EQ5D and VAS scores were recorded. Two weeks post injection there was an improvement in quality of life, 24 weeks after the injection there was a significant improvement ($p<0.01$) in all parameters.

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7. 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.

Full AMA Reference

Altman RD, Åkermark C, Beaulieu AD, Schnitzer T. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *OsteoArthritis and Cartilage*. 2004; 12: 642-649.

Study Design

Level-I clinical study: multi centre, randomized, double blind and saline controlled.

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 randomized 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 response to NASHA than placebo was observed at week 6 (P=0.025).

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8. 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-III clinical study: single centre, prospective open label, pilot study.

Objective

To assess the safety and potential efficacy of intra-articular non-animal stabilised hyaluronic acid (NASHA) in patients with hip OA.

Results

31 patients with KL II-III osteoarthritis in the hip were treated with DUROLANE. Follow up was made at 2 weeks and 3 months post injection. A positive response was defined as a > or = 40% reduction in the WOMAC pain score from baseline, together with an absolute decrease of > or = 5 points. The response rate was 50% at 2 weeks and 54% at 3 months. In the extension population the response rates were 69% at 3 months and 44% at 6 months. There were 9 treatment related adverse events, the majority of which were arthralgia. The reaction was generally transient and all patients made a full recovery.

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9. Study Title

Elimination of Stabilised Hyaluronan from the Knee Joint in Healthy Men

Full list of Authors

Lindqvist U, Tolmachev V, Kairemo K, Astrom G, Jonsson E, Lundqvist H.

Full AMA Reference

Lindqvist U, Tolmachev V, Kairemo K, Astrom G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet*. 2002; 41(8): 603-613.

Study Design

Level-III clinical study: single center, uncontrolled study.

Objective

To investigate the elimination of stabilised hyaluronan following intra-articular injection into the knee joint of healthy men.

Results

6 male subjects were injected with 3ml 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-times of 1.5 hours, 1.5 days and 4 weeks. Most likely, the last value reflects the true half-life of DUROLANE.

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10. 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, Bjorkman A, Malm P.

Full AMA Reference

Åkermark C, Berg P, Bjorkman A, Malm P. (2002). Non-animal stabilised hyaluronic acid in the treatment of osteoarthritis of the knee: A tolerability study. *Clinical Drug Investigation*, 22(3): 157-166.

Study Design

Level-III clinical study: multi-centre, non-blinded, prospective tolerability study with extension phase.

Objective

To evaluate the safety of an intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) in patients with osteoarthritis (OA) of the knee, with an extension phase to assess the safety of a second repeat injection.

Results

103 patients (128 knees) with arthroscopically verified OA were treated with a single injection of DUROLANE. Patients were followed up 2 weeks and 3 months post injection. VAS was measured at each clinic visit and overall satisfaction was measured at the 3 month follow up. 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). 53 patients received a second injection (6.5-9.5 months after first injection), this was followed up 1 month later. After the second injection 11 events were considered potentially related to the study product or the injection procedure, of which three were classed as device-related, unanticipated adverse events, 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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Pre-Clinical

1. Study Title

Non-Animal Stabilized Hyaluronic Acid: A New Formulation for the Treatment of Osteoarthritis

Full list of Authors

Agerup B, Berg P, Akermark C.

Full AMA Reference

Agerup B, Berg P, Akermark C. Non-Animal Stabilized Hyaluronic Acid: A New Formulation for the Treatment of Osteoarthritis. *Biodrugs.* 2005; 19(1): 23-30.

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

Agerup et al. clearly describe how Hylan G-F 20 is produced by combining Hylan A and Hylan B. Hylan is extracted from rooster combs following pretreatment with formaldehyde to produce crosslinks between amino acids and animal proteins. This crosslinking results in a protein content of 0.4 – 0.8% in Hylan A. Hylan B is produced by further crosslinking Hylan A with divinyl sulfone to produce a gel. The crosslinking in Hylan B is approximately 20%. They also discuss the half life of Hylan A being 1.5 days and 8.5 days for Hylan B and that Hylan G-F 20 has been associated with adverse events and complications such as swelling and pain in the treated joint, but also serious adverse events such as aseptic acute arthritis, synovitis, pseudogout and anaphylactic shock.

In comparison, Agerup et al. describe the production of DUROLANE using NASHA technology. This involves the secretion of HA from the cellular membrane of bacteria into media. The HA is then extracted from the media and crosslinked at the hydroxyl groups with 1, 4-butanediol diglycidyl ether, this crosslinking is limited to 0.5 – 1%. The true half life of DUROLANE is described as being 4 weeks. Regarding safety, the authors discuss that NASHA products have been used for cosmetic purposes without any safety concerns. Lastly, in a tolerability study as a viscosupplementation treatment only general transient reactions were experienced which required no treatment.

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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 2009; Las Vegas, NV.

Study Design

Preclinical investigation.

Objective

This preclinical investigation was carried out 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 result 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 the storage (G´) and loss (G´´) moduli. These were then compared to data of 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 for the undiluted as well as for the diluted sample. Immediately after the onset of degradation, 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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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 Research & Therapy*. 2011; 13:46.

Study Design

Preclinical investigation using control groups and TGFβ1 and exercise induced osteoarthritis model in mice.

Objective

The objective of this study was to examine the effect of intraarticular HA injection on well-defined stages of the initiation and progression of murine OA. Using a TGFβ1 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 TGFβ1 and running the mice uphill for 2 weeks. Animals were injected with either HA or saline the day before running commenced. A control group was run only. 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. HA injection (but not saline injection) blocked all

gait changes. Analysis of the joints also showed that HA protected joints from femoral cartilage erosion as well as tibial and femoral tissue fibrosis. Both HA injection and saline injection attenuated acute allodynia, but the HA effect was more pronounced and prolonged than the saline injection.

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4. Study Title

Evaluation of the biocompatibility of Durolane using the murine air pouch model

Full list of Authors

Wooley PH, Song Z, Harrison A.

Full AMA Reference

Wooley PH, Song Z, Harrison A. Evaluation of the biocompatibility of Durolane using the murine air pouch model. Poster presented at: 55th Annual Meeting of the *Orthopaedic Research Society*; February 2009; Las Vegas, NV.

Study Design

Preclinical in-vivo study using an air pouch model in mice, an in-vitro testing to analyse inflammatory response.

Objective

This study investigated the antigenicity of DUROLANE in the murine air pouch biocompatibility evaluation, and examined the potential to generate an antibody reaction in mice exposed to viscosupplement using the air pouch model.

Results

Air pouches were created in the backs of 30 mice after 6 days these were then divided into 5 treatment groups and injected with 500ul saline, DUROLANE, Synvisc®, EUFLEXXA® or Positive control pouches were stimulated by the injection of 500ul 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 control for all HA products except DUROLANE, with Synvisc® creating the largest amount of tissue inflammation. The cause of the inflammation was shown to be in infiltration of both inflammatory cells and fibroblasts with the largest inflammatory cell infiltration being caused by Synvisc®. DUROLANE only stimulated fibroblast infiltration. Moderate increases in both TNFalpha and IL-6 in membrane extracted proteins supported the histological observations of modest inflammation and fibroblast proliferation. There was no significant antibody production created by the injection of DUROLANE or EUFLEXXA®, however, there were consistently elevated levels of antibodies created by the injection of Synvisc®.

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5. 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.

Study Design

Preclinical in-vivo study using an air pouch model in mice.

Objective

The objective of this work was to compare two HA supplements from non-mammalian sources (LMWHA and NASHA) 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 these mice were divided into 5 treatment groups and injected with 500ul saline, DUROLANE, Synvisc®, low molecular weight HA, or Positive control. Pouches were stimulated by the injection of 500ul 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 control for all HA products except DUROLANE, with Synvisc® creating the largest amount of tissue inflammation. The cause of the inflammation was shown to be an infiltration of both inflammatory cells and fibroblasts with the largest inflammatory cell infiltration being caused by Synvisc®. DUROLANE only stimulated fibroblast infiltration. Moderate increases in both TNFalpha and IL-6 in membrane extracted proteins supported the histological observations of modest inflammation and fibroblast proliferation. An additional 24 animals were immunized with HA products in complete freunds adjunvant, in order to stimulate the immune system, these animals were then treated with HA products. A high antibody response was seen in mice injected with 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 HA from a non-avian source.

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Summary of Indications for Use
DUROLANE (3ml): 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 SJ (1ml): Symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, elbow, wrist, fingers, and toes.
Both DUROLANE and DUROLANE SJ are also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure.
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 pregnant or lactating women, or children.
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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