## White Paper

# Clinical Efficacy and Safety of MONOVISC™: A lightly cross-linked highly concentrated hyaluronan specially formulated for single injection in osteoarthritis

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## Abstract

Intra-articular hyaluronic acid (HA) injections have been used in treating osteoarthritis (OA) knee pain for over two decades. The first generation HAs required multiple weekly injections and were derived from rooster combs, and more recently bacterial fermentation. Second generation high molecular weight HA fractions extended duration of effect in the knee but continued to require multiple injections for efficacy. In the last decade, HAs have been specifically formulated as single injection regimens. This treatment modality holds great promise for the effective treatment of OA knee pain: the ideal single injection viscosupplement safely delivers durable pain relief equal to or better than the multi-injection regimens with a faster onset of pain relief for the patient.

There are no randomized clinical studies conducted comparing the safety and effectiveness of these single injection HAs. This analysis reviews data from published pivotal clinical studies and post-marketing safety databases from different manufacturers to provide insight about how MONOVISC™ may have the optimal benefit to risk profile for patients.

MONOVISC™ provides early and durable pain relief in a single high dose injection that is not only safe and effective, but is also conveniently packaged in 4 mL volume for ease of use by physicians and treatment comfort for patients.

## Objective

The objective of this paper is to compare MONOVISC™, a third generation hyaluronan, to DUROLANE®, Gel-One®, and the second generation single injection Synvisc-One®, in the absence of head-to-head trials.

## Introduction

OA is a common disease characterized by the degeneration of cartilage, underlying bone changes, and decreases in concentration/molecular weight of HA within the joint. Bony overgrowth can also occur. OA typically begins at age 40 and worsens gradually. The common symptom of OA is persistent pain.[1]

Several treatments are used to treat OA, most of which address pain symptoms associated with the disease. The most common treatments are non-steroidal anti-inflammatory drugs (NSAID), which carry potential gastrointestinal risks and cardiovascular complications.[2] Also, the magnitude of efficacy for NSAIDs in controlled studies has raised questions about their benefit/risk profile.[3]

Finding treatments that act locally in the joint without systemic side effects has led to the practice of replacing the diseased synovial fluid associated with OA with injections of HA to alleviate symptoms.[4] While the precise mechanism by which HA reduces pain associated with OA is not known, the following actions are proposed: HA improves the viscoelastic properties of the synovial fluid; protects the surface of articular cartilage; inhibits inflammation; induces its own endogenous biosynthesis; reduces pain perception; and may suppress cartilage degeneration.[5,6,7,8]

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[1] Estimates of the Prevalence of Arthritis and other Rheumatic Conditions in the US, Part II. Arthritis Rheum, 2008 January; 58(1): 26-35.

[2] Roth SH, Anderson S. The NSAID dilemma: managing osteoarthritis in high-risk patients. Phys Sportsmed. 2011; 39: 62-74.

[3] Bjordal JM, et al. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomized placebo controlled trials. BMJ 2004; 329: 1317 – 20.

[4] Pelletier JP, Martel-Pelletier J. The pathophysiology of osteoarthritis and the implication of the use of hyaluronan and hylan as therapeutic agents in viscosupplementation. J Rheumatol Suppl. 1993; 39: 19-24.

[5] Fukuda K, Dan H, Takayama M, Kumano F, Saitoh M, Tanaka S. Hyaluronic acid increases proteoglycan synthesis in bovine articular cartilage in the presence of interleukin-1. J Pharmacol Exp Ther 1996; 277: 1672-1675.

HA, also referred to as sodium hyaluronate, or hyaluronan, was isolated and characterized from the vitreous humor of a bovine eye in 1934 by Karl Meyer and John Palmer, at Columbia University, NY, USA.[9] It was discovered that HA is a polymer consisting of repeats of the

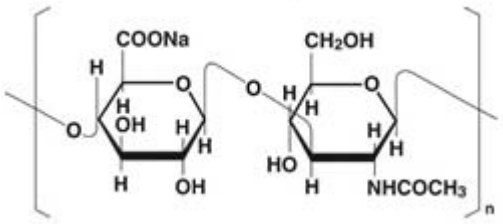


**Figure 1. Structure of D-glucoronic acid and N-acetyl-D-glucosamine disaccharide.**

disaccharide, D-glucoronic acid and D-N-acetylglucosamine linked in alternative β-1,4 and β-1,3 glycosidic bonds. HA was found throughout the body and observed to be the dominant component in the synovial fluid of articulated joints, and was later extracted from rooster comb tissue for commercial use.[10]

First generation HA treatments for treat OA were relatively low in average molecular weight and required multiple (typically 5) weekly injections for optimal efficacy (Table 1).

Second generation formulations of higher molecular weight were then developed. Among these, two were manufactured from high molecular weight unmodified HA (ORTHOVISC®, Euflexxa®) and one from chemically modified HA (SYNVISC®).

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[6] Asari A, Mizuno S, Tanaka I, Sunose A, Kuriyama S, Miyazaki K, Namiki O. Suppression of hyaluronan and prostaglandin E2 production in traumatic arthritic synovial cells by NaHA. Connective Tissue 1997; 29: 1-5.

[7] Takahashi K, Goomer RS, Harwood F, Kubo T, Hirasawa Y, Amiel D. The effects of hyaluronan on matrix metalloproteinase-3 (MMP-3), interleukin-1beta (IL-1beta), and tissue inhibitor of metalloproteinase-1 (TIMP-1) gene expression during the development of osteoarthritis. Osteoarthritis Cartilage 1999; 7: 182-190.

[8] Masuko K., M. Murata, K. Yudoh, T. Kato, H. Nakamura. Anti-inflammatory effects of hyaluronan in arthritis therapy: Not just for viscosity. Int J Gen Med. 2009; 2: 77–81.

[9] Meyer K., et al. J. Biol. Chem. 1934; 107: 629.

[10] Kogan, G. et al. Hyaluronic acid: a natural biopolymer with a broad range of biomedical and industrial applications. Biotechnol Lett 2007; 29:17-25.

Single injection HA products were developed recently (Gel-One®, Durolane®, and MONOVISC™). These third generation products seek to provide safe and durable pain relief with the convenience of a single treatment. Chemical cross-linking techniques prolong HA's residence time following injection; higher molecular weight HAs may promote longer duration of effect. The ability of exogenous HA to stimulate HA synthesis in synovial fibroblasts in an arthritic joint has been shown to be concentration-dependent.[11] However, due to their relatively high viscosity, formulations of high molecular weight, highly concentrated HA can be difficult to administer. An overview of HA viscosupplement products is presented in Table 1.

**Table 1. Generations of HA developed for treatment of osteoarthritis**

| Product Developed | Product | Source | | Modified | Injection Regimen | | Dosing |
|---|---|---|---|---|---|---|---|
| | Examples | Rooster Combs | Fermented | Chemically Modified | Multiple | Single | Total Tx Dose (mg) |
| First Generation | HYALGAN® Supartz™/Artz® | ✓ | | | ✓ | | 60/100 75/125 |
| | Ostenil® | | ✓ | | ✓ | | 60 |
| Second Generation | ORTHOVISC® Euflexxa® | | ✓ | | ✓ | | 90 60 |
| | SYNVISC®* | ✓ | | ✓ | ✓ | | 48 |
| | Synvisc-One®* | ✓ | | ✓ | | ✓ | 48 |
| Third Generation | Gel-One® | ✓ | | ✓ | | ✓ | 30 |
| | DUROLANE® | | ✓ | ✓ | | ✓ | 60 |
| | MONOVISC™ | | ✓ | ✓ | | ✓ | 88 |

***SYNVISC® and Synvisc-One® are the same formulation with the latter being supplied in a single syringe instead of three**

[11] Smith, M.M., Ghosh P. The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. Rheumatol Int 1987; 7: 113-122.

## Characteristics of third generation HAs

Gel-One® is composed of cross-linked hyaluronate from sodium hyaluronate extracted from rooster combs. In Gel-One®, strands of hyaluronan are bound by dimers of cinnamic acid. Gel-One® is supplied in a 3 mL syringe containing 10mg/mL of HA.

DUROLANE® is composed of HA stabilized by 1,4-butanediol diglycidyl ether to allow cross-linking of the polymers. DUROLANE® is supplied in a 3 mL syringe containing 20 mg/mL of HA.

MONOVISC™ is composed of cross-linked high-molecular weight HA with proprietary p-phenylene bis (ethylcarbodiimde) (BCDI) from ultra-pure fermented source. MONOVISC™ is delivered as a 4 mL injection with a HA concentration of 22 mg/mL. MONOVISC™ delivers more HA (88mg in one treatment) than any other single injection available on the market today. Both MONOVISC™ and ORTHOVISC® are manufactured by Anika Therapeutics, Inc.

# Clinical efficacy and safety of MONOVISC™

MONOVISC™ is a single injection formulation that delivers a high dose of high molecular weight HA with the convenience of a concentrated single injection. While providing a rapid onset of pain relief from a single treatment, MONOVISC™ was designed to achieve the same magnitude and duration of pain relief as ORTHOVISC®. These performance characteristics were first evaluated in an 80 patient pilot study, followed later by a 369 patient pivotal study.

## Pilot study of MONOVISC™ conducted in the EU

The safety and efficacy of MONOVISC™ was evaluated in 80 patients in an open-label pilot study of 6 months duration at three European centers.[12] Inclusion criteria included subjects, 40-80 years of age, with BMI 20-35 with symptomatic idiopathic Kellgren-Lawrence (K-L) severity grade I, II or III OA of the knee for at least 6 months. Patients with symptoms of OA in other joint(s) which could potentially interfere with the pain assessment of the index knee or other joint diseases were excluded.

[12] Anika Therapeutics, Inc. Data on File 2012. MONOVISC™ data from the study: A post-approval study of a single injection cross-linked HA to provide symptomatic relief of osteoarthritis of the knee.

Safety was assessed by monitoring reported adverse events (AE). Two mild injection site reactions were reported (2.5%). These reactions (light swelling of the injected knee for 48 hrs that resolved without therapy) were anticipated within the product labeling. No subject experienced a serious adverse event (SAE).

At their six month assessment, 46.6% of the patients experienced a highly significant clinical improvement of 40.0% or more in total WOMAC score and over 90.0% reported improvement in total WOMAC pain score from their baseline assessments.

## Comparison of MONOVISC™ with ORTHOVISC®

ORTHOVISC® is a second-generation HA product which delivers a total of 90 mg of HA in three 2 mL injections. ORTHOVISC® has been proven safe and effective in randomized controlled clinical studies and is approved for sale in markets worldwide, including the United States.

Although a head-to-head study has not been performed, MONOVISC™ can be compared to ORTHOVISC® through a review of pivotal studies conducted over a 12 week time frame with the same study design, inclusion/exclusion criteria and follow-up, using saline as control.[13] Results for the intent-to-treat (ITT) populations from the two studies were compared to assess non-inferiority for three common endpoints: Responder Rate (proportion of patients with ≥40% and ≥15 mm improvement in WOMAC pain from baseline); mean improvement from baseline; and the mean percent improvement from baseline. The results indicate non-inferiority between MONOVISC™ and ORTHOVISC®.

The non-inferiority between MONOVISC™ and ORTHOVISC® is further supported by a direct, short-term comparison study in which twenty patients diagnosed with knee OA (Kellgren-Lawrence grade II or III) were either administered a 4 mL single injection of MONOVISC™ or three or four weekly injections of 2 mL of ORTHOVISC®.[14] WOMAC scores and subscales, and patient/physician global assessment scores, were collected at baseline and at 1 month. Both groups demonstrated significant improvement in WOMAC from baseline. No significant

[13] Anika Therapeutics, Inc. Clinical Data Analysis Report for MONOVISC™. M. Frank-Molnia, Mar 2012. Data on File.

[14] Anika Therapeutics, Inc. Single injection of lightly cross-linking hyaluronic acid in patients with knee osteoarthritis: A pilot study. Demirhan Dıraçoğlu, Tuğba Baysak and Cihan Aksoy. Data on File 2012.

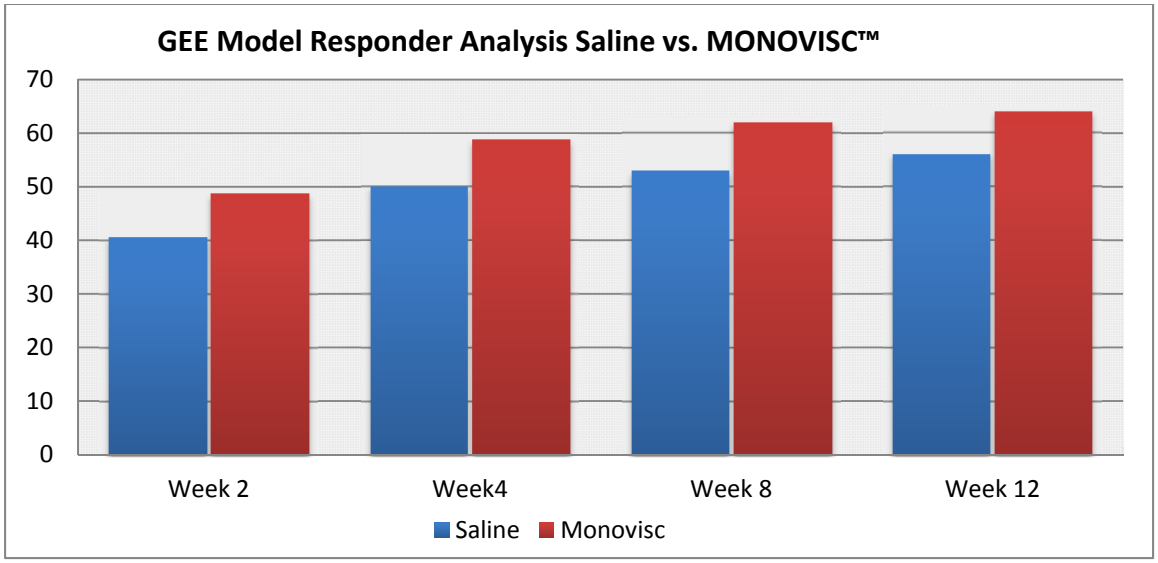
difference was noted between the single or three-injection regimens for WOMAC or patient's and physician's global assessment scores.

## Pivotal clinical study in the U.S. and Canada

The 80 patient pilot study was followed by a large (N=369) prospective, multi-center, randomized, double-blind, placebo-controlled clinical study to evaluate the safety and efficacy of a single injection of MONOVISC™ to treat OA knee pain. 184 patients received MONOVISC™ and 185 received saline as placebo. The primary endpoint was a proportion of treatment successes in the MONOVISC™ and the placebo groups, where 'Patient Success' was defined as a patient who achieved ≥ 40% improvement in WOMAC Pain score and a ≥ 15mm improvement as compared to baseline with assessments at 2, 4, 8, 12 (primary endpoint), 20 and 26 weeks post-injection. Secondary outcomes included patient and evaluator global assessments, WOMAC physical function subscales, and range of motion. Product safety was evaluated by comparison of adverse event rates in HA and placebo groups using a two-sided Fisher Exact test. 365 patients were included in the ITT population (4 patients did not attend any follow-up visits); 334 were included in the per-protocol (PP) population.

An analysis of responders at 12 weeks showed statistical significance for the MONOVISC™ treatment compared with the saline control. The results are graphically displayed in Figure 2.

**Figure 2. Percent of Patients Responding 40% or Greater and > 15mm VAS from Baseline for WOMAC Pain.**



Despite the extremely strong response to the MONOVISC™ treatment, the ability to achieve statistical significance versus saline at the 26-week time point was challenged by the unanticipated strength of the control group response. To differentiate the results between control and treatment arms after week 12, an additional analysis was performed using a patient success threshold 10 percentage points higher than the 40% improvement primary endpoint. This analysis used a Patient Success threshold of a 50% improvement and $\geq$ 20 mm of improvement from baseline. Using this higher threshold, the data show statistical significance compared to saline over the 26-week interval of the study at a level of $p \leq 0.04$ for the ITT population and $p \leq 0.04$ for the PP population.

## Safety of MONOVISC™

There were no statistically significant differences in the incidence of "any adverse event," "any device-related adverse event," or "any serious adverse event" between MONOVISC™ and the Saline control group. Only 4 patients in treatment group (2.2%) and one patient in control group (0.5 %) discontinued the study due to adverse events. All of the AEs for those who discontinued the study were unrelated to the study treatment. For those who remained in the study, the majority of reported AEs were mild or moderate severity; only 1 patient in the MONOVISC™ group experienced a severe AE which was considered "possibly related" to the study injection. All other severe AEs were assessed as "not related" or "unknown".

## Efficacy and safety comparison of HA to saline injections

Intra-articular HA injections decrease the pain associated with OA of the knee by 30% or more on average compared to the patient's baseline pain levels. However, when compared with saline injections, the efficacy of the multi-injection HAs is not always apparent, largely due to the robust (as high as 50% improvement) and/or durable (sometimes more than two months) clinical benefit of saline injections. Saline injections in the OA knee setting have been reported to elicit a placebo effect, and also deliver clinical benefits.[15,16,17] Saline injections given with

[15] Frías G, et al. Assessment of the Efficacy of Joint Lavage Versus Joint Lavage Plus Corticoids in Patients With Osteoarthritis of the Knee. Curr Med Res Opin. 2004; 20(6).

[16] Rosseland LA, Helgesen KG, Breivik H, Stubhaug A. Moderate-to-Severe Pain After Knee Arthroscopy Is Relieved by Intraarticular Saline: A Randomized Controlled Trial. Anesth Analg 2004; 98: 1546–51.

[17] Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomized controlled trials. Ann Rheum Dis 2008; 67: 1716–1723.

arthrocentesis can reduce inflammation and swelling. The injection of a diluting fluid may also decrease the concentration of pro-inflammatory and pain-inducing factors.

## Safety and Efficacy of MONOVISC™ compared to other HAs

Direct comparison between single injection products has not been conducted in a single study. PMA studies, which are typically large and well-controlled, also tend to have similar designs and endpoints. Therefore, comparisons are possible between different products. The following products are chosen due to the availability of publicly available PMA study results. A summary of these pivotal studies follows.

### Synvisc-One®

Synvisc-One® combines three 2 mL SYNVISC® (hylan G-F20) doses into a single 6 mL syringe. A randomized, double-blind, saline-controlled, multicenter trial of Synvisc-One® with 253 patients with moderate to severe OA knee pain was conducted.[18] Patients initially received arthrocentesis and then either one 6 mL injection of Synvisc-One® or one 6 mL injection of saline (placebo). The primary endpoint was the difference between the groups in the change from baseline in patient-assessed pain as measured by the WOMAC pain subscore over 26 weeks (Likert scale). Patients receiving Synvisc-One® experienced statistically significantly improvements in WOMAC A pain scores vs. saline.

### DUROLANE®

The U.S. study of DUROLANE® compared the efficacy of a single injection of HA with saline (placebo) in patients with OA of the knee.[19,20] 347 patients were randomized 1:1 in this 26-week, double-blind, multicenter study. The primary endpoint was an analysis of responders. A positive response was defined as a reduction in WOMAC pain score for the study knee of 40%

[18] Chevalier X, et al. Single, intra-articular treatment with 6 mL hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 2010; 69: 113-9.

[19] Q-Med AB, Orthopedic and Rehabilitation Devices Panel, August 19, 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM177386.pdf

[20] Altman RD, Akermark 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: 642-9.

from baseline with a minimum improvement of ≥ 5 points (Likert scale). For the overall population, there were no statistically significant between-group differences in response rates for any efficacy parameters. In addition, there was no significant difference in patient responder analysis between the two groups. There were few treatment-related events.

## Gel-One®

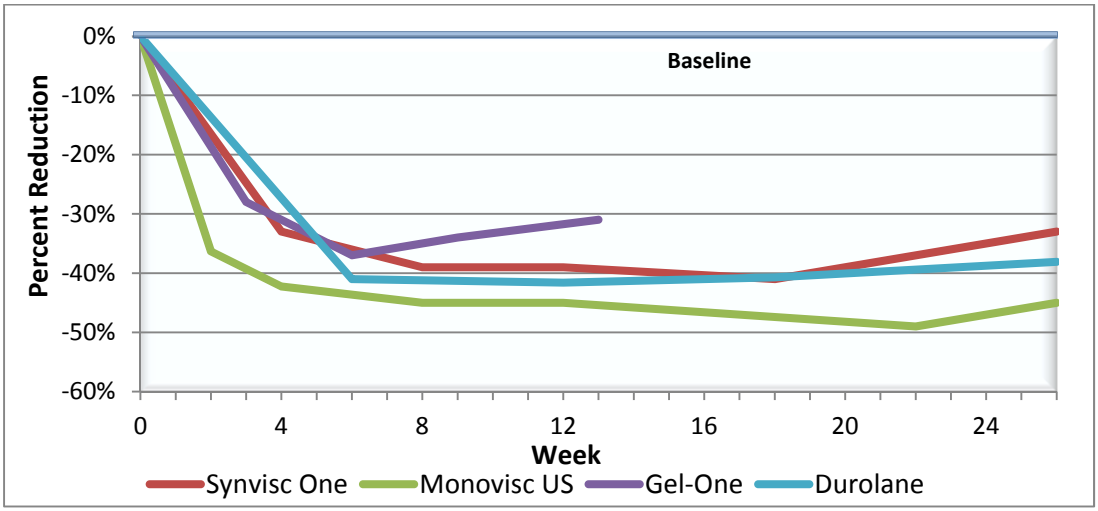
A 2:1 randomized controlled study testing the safety and effectiveness of a single intra-articular injection of Gel-One® to phosphate buffered saline (PBS) was conducted in 375 patients. [21] Follow-up was conducted at 1, 3, 6, 9, and 13 weeks using the WOMAC Visual Analog Scale (VAS). There was a statistically significant difference in the means of WOMAC pain reduction (Gel-One® - PBS) between the two groups over 13 weeks.

## Comparative effectiveness of single injection products

### *Magnitude and Persistence of Effect*

The results show that MONOVISC™ achieved the largest reduction from baseline with a remarkably durable effect (Figure 3). The mean pain reduction at 26 weeks for MONOVISC™ remained at a level greater than that obtained for the other products .

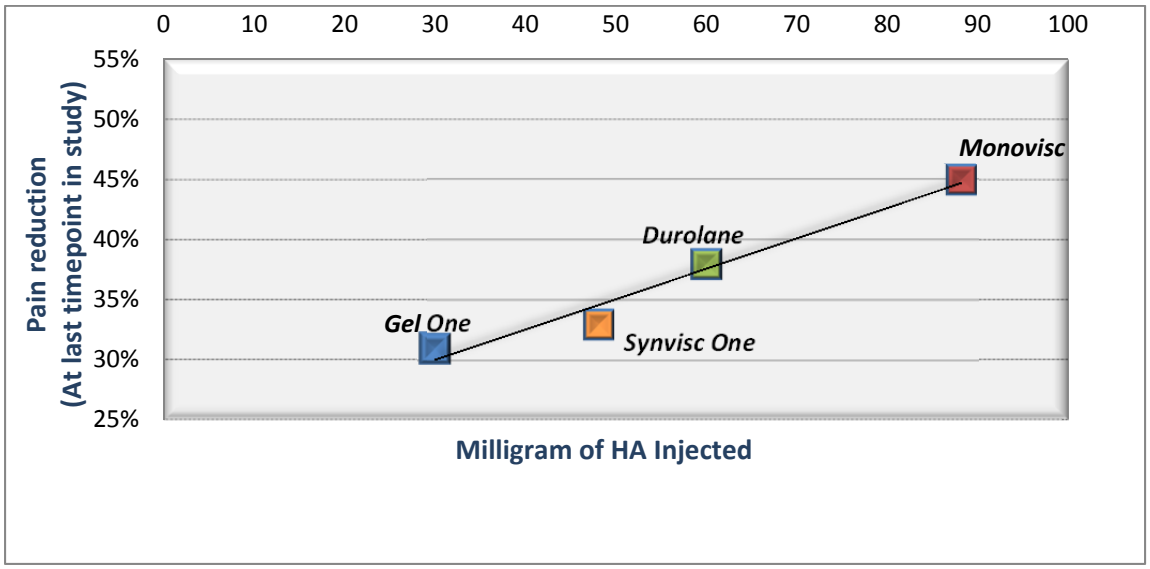
**Figure 3. Percent Reduction in WOMAC Pain for Four Single Injection HA Products Over the Length of their Pivotal Studies**




[21] P080020 - Gel-One® Summary of Safety and Effectiveness (Mar 21 2011). http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080020b.pdf

The relationship between pain reduction and the dose of HA is graphically depicted in Figure 4. While the exact mechanism for the effect of HA therapy is not known, these data give insight into the possible importance of a high dose of high molecular weight HA on greater pain reduction and durability of effect.

**Figure 4. Reduction in Baseline WOMAC Pain as a Function of the HA Dose of the Treatment**



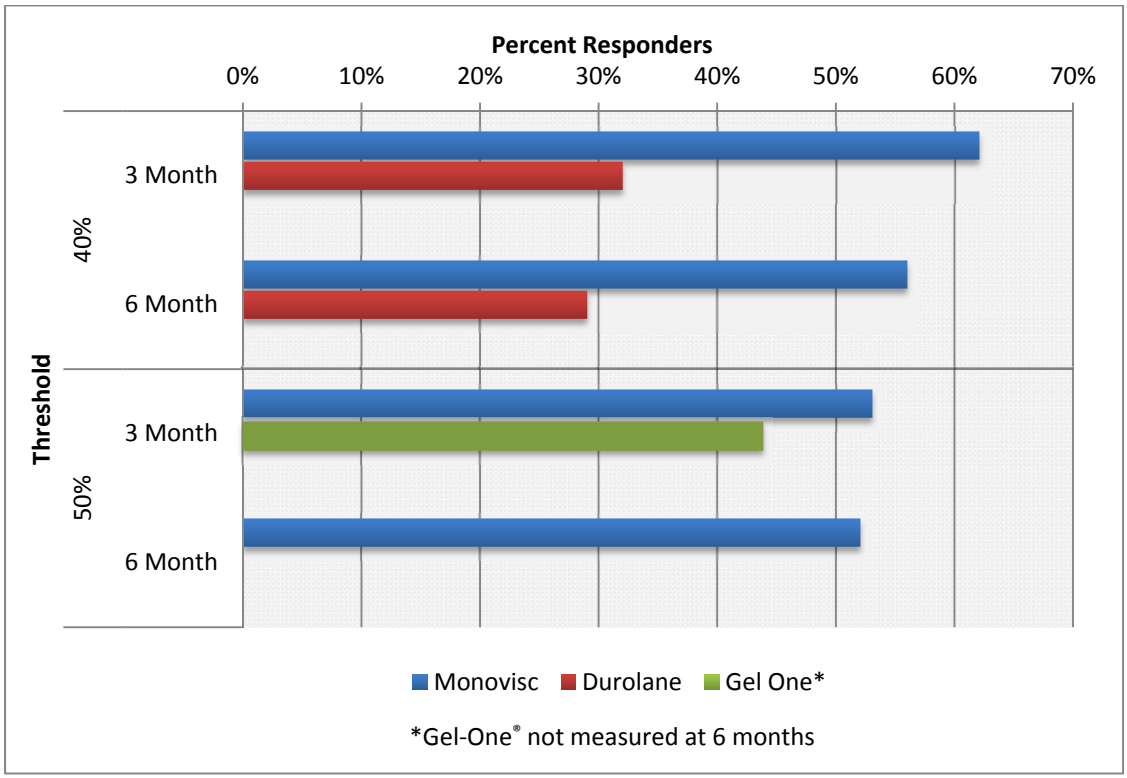

### *Faster Pain Relief: a significant outcome of single injection therapy*

Delivering the entire dose in a single injection provided faster pain relief – a clinically significant outcome. The mean improvement in WOMAC Pain from baseline by the earliest time point, week 2, for the MONOVISC™ ITT population was 36%. This is the highest level achieved compared to other single injection products and improvements continue to strengthened during subsequent visits.

### *Measuring the Extent of Achieving Significant Pain Relief in Study Population*

As with any therapy, not all patients respond to HA injections. Several of the single injection studies use an analysis of responders as a primary or secondary endpoint, using either a 40% or 50% threshold. DUROLANE® has reported data with a 40% threshold; Gel-One® used a 50% threshold. (Synvisc-One® used a Likert scale (0-5) making comparison difficult). Figure 5 shows a comparison of results at these threshold levels.

**Figure 5: Comparison of the Reduction in WOMAC Pain between MONOVISC™ and DUROLANE® at the 40% Threshold and MONOVISC™ and Gel-One® at the 50% Threshold**




The response to MONOVISC™ is impressive in terms of the proportion of patients who achieve clinically meaningful levels of pain reduction. At both the 3-month and 6-month time points, more than 50% of MONOVISC™ patients achieved longer lasting pain reduction from baseline of 50% or higher – a result not seen in other products.

## Patients treated and post-market adverse event reports

With data derived from the April 30, 2012 report in the Manufacturer and User Facility Device Experience (MAUDE) database, the overall safety record for the class is favorable: with almost 30 million estimated injections, 7.6 million unique patients treated and 22,000 days of exposure, there have collectively been just over 2,000 adverse events reported – an average frequency of only 3 for every 10,000 injections.[22] Secondly, while hylan G-F 20 (SYNVISC® and Synvisc-

[22] Manufacturer and User Facility Device Experience (MAUDE) database, April 30, 2012, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/ search.cfm

One®) only represents an estimated 36% of total injections, they represent 82% of adverse events in the MAUDE database. This may be related to pseudoseptic, or SAIRs, reactions specific to the hylan G-F 2-0 product. [23, 24, 25, 26, 27]

European post-marketing data, when compared to the MAUDE data for the other products, indicates that MONOVISC™ available in the market since 2007, has substantially less adverse events reported than any of the products in the database. [28]

## Conclusions

The development of cross-linked HA products specifically formulated for single injection regimens reduce the exposure of patients to the injection procedure; increase the probability of treatment completion/compliance; increase convenience for patients and healthcare professionals; and reduce healthcare visits, and therefore total treatment cost.

Within the single injection segment, MONOVISC™ is unique by providing the highest dose of lightly cross-linked HA available in a single 4 mL injection. Based on the comparisons detailed in this paper, MONOVISC™ offers patients with the fastest pain relief and durable treatment effects that continue more than 26 weeks after the injection. In addition to reducing total treatment costs and offering ease of use for healthcare professsionals, patient comfort and pain relief are greatly enhanced.

Acknowledgement: Michael J. Daley, Ph.D., Cognate Consultants LLC

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[23] Hamburger MI, Lakhanpal S, Mooar PA, Oster D. Intra-articular hyaluronans: a review of product-specific safety profiles. Semin Arthritis Rheum. 2003; 32: 296-309.

[24] Hammesfahr JF, Knopf AB, Stitik T. Safety of intra-articular hyaluronates for pain associated with osteoarthritis of the knee. Am J Orthop (Belle Mead NJ) 2003; 32: 277-83.

[25] Pullman-Mooar S, Mooar P, Sieck M, Clayburne G, Schumacher HR. Are there distinctive inflammatory flares after hylan G-F 20 intraarticular injections? J Rheumatol. 2002; 29: 2611-4.

[26] Leopold SS, Warme WJ, Pettis PD, Shott S. Increased frequency of acute local reaction to intra-articular hylan GF-20 (SsYNVISC®ynvisc) in patients receiving more than one course of treatment. J Bone Joint Surg Am. 2002; 84-A: 1619-23.

[27] Michou L, Job-Deslandre C, de Pinieux G, Kahan A. Granulomatous synovitis after intraarticular Hylan GF-20. A report of two cases. Joint Bone Spine. 2004; 71: 438-40.

[28] Anika product analysis data on file, 2013.



## www.monovisc.com



MONOVISC™ is indicated for the treatment of pain in osteoarthritis (OA) in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen). STERILE CONTENTS. The pre-filled syringe is intended for single use only. It is contraindicated to people with known hypersensitivity (allergy) to hyaluronan preparations, known hypersensitivity (allergy) to gram-positive bacterial proteins, infections or skin diseases in the area of the injection site or joint, or known systemic bleeding disorders. Intravascular injections of MONOVISC may cause systemic adverse events. For complete list of Warnings and Precautions please read the product Instructions for Use prior to use of the product. The most commonly reported adverse events associated with MONOVISC are arthralgia, injection site pain, joint swelling and joint effusion; other adverse events associated with intra-articular injections may occur (please consult product labeling). Federal (U.S.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).



MONOVISC is not for distribution in the United States.

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