

# CLINICAL EFFICACY AND SAFETY OF MONOVISC® HIGH MOLECULAR WEIGHT HYALURONAN

Highly concentrated, single injection hyaluronic acid for the treatment of knee osteoarthritis

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## Abstract

Intra-articular hyaluronic acid (HA) injections have been used in the treatment of knee osteoarthritis (OA) for over two decades. The first generation HA products required multiple weekly injections, and contained HA derived from rooster combs. More recently, HA derived from bacterial fermentation has gained favor because of decreased patient risk due to avian allergies. The introduction of single injection regimens has now extended HA therapy as a treatment option to patients that are not amenable or well suited to multiple weekly injections. Ideally, a single injection HA product delivers safe, durable and rapid onset pain relief, in a formulation that maximizes treatment comfort for the patient.

There are presently no randomized clinical studies comparing the safety and effectiveness of single injection HA therapies. The present analysis reviews data from published pivotal clinical studies and post-marketing safety databases to compare FDA approved single injection HA products, and to provide insight into how MONOVISC® High Molecular Weight Hyaluronan may have the optimal risk/benefit profile for many patients. MONOVISC provides early and durable pain relief in a single high concentration injection that is not only safe and effective, but is also conveniently packaged in a 4 mL volume for ease of use by physicians and minimum injection discomfort for patients.

## Objective

The objective of this paper is to compare the formulations, safety and effectiveness of the three FDA-approved single injection HA products (MONOVISC, Gel-One®, and Synvisc-One®) in the absence of head-to-head clinical trials.

## Introduction

Osteoarthritis (OA) is a painful and potentially life-altering joint disease mainly affecting the hands, knees, and hips. It has been estimated that over 27 million adults in the U.S. currently have radiographic OA, and studies suggest that nearly one in two people will develop symptoms of painful OA in at least one knee over their lifetime.<sup>1-5</sup> The prevalence of symptomatic knee OA has been reported to be 12%-16%.<sup>4,5</sup> OA prevalence is higher among women than men at all ages > 45 years and the likelihood of developing OA increases with age.<sup>4,5</sup> In addition to gender and age, obesity, joint malalignment, joint injury, and other diseases may increase the risk of OA of the knee.<sup>3</sup>

OA is a degradative disease of the articulating joint, caused by a cascade of events that can ultimately lead to joint destruction. The traditional view of osteoarthritic pathology is that of cartilage destruction. In advanced OA, the osteoarthritic knee is in fact characterized by thin and fragmented cartilage, disrupting the “cushion” between

the bones in the joint. Extensive cartilage erosion can lead to symptoms including pain, grating, or catching when moving the knee, and the sensation of the knee locking. Patients typically report discomfort during standing or walking, and may be limited in their daily activities such as dressing and bathing.<sup>6</sup> The subsequent reduction in physical activity can lead to weakening of the thigh muscles, thereby increasing the load on the degraded joint and exacerbating disability.<sup>6</sup>

While cartilage erosion is the ultimate result of osteoarthritis, other tissues in the joint are affected during the early progression of the disease. In particular, the synovial fluid and synovial membrane play key roles in joint health and can be severely impacted by osteoarthritis. Synovial fluid is responsible for several functions in the joint, including lubrication of articular cartilage, shock absorption, and dampening of inflammation. Healthy synovial fluid is distinguished by a high concentration of **hyaluronic acid (HA)**, a polysaccharide produced by synoviocytes that is also an important structural component of articular cartilage. In healthy synovial fluid, the high molecular weight of HA imparts the fluid with its characteristic viscoelasticity and lubricity.<sup>7</sup>

In many OA patients, synovial inflammation is an important component of the osteoarthritic cascade. In osteoarthritic joints, synovial inflammation can lead to swelling, effusion, and pain. Synovitis is now recognized as being a prominent component of OA, with as many as 70% of OA patients showing evidence of synovitis.<sup>8,9</sup> Osteoarthritic synoviocytes produce less HA, with a lower molecular weight compared to healthy joints. They also produce increased levels of inflammatory cytokines and degradative enzymes that can perpetuate the osteoarthritic cascade and accelerate cartilage destruction.<sup>10-14</sup>

For patients diagnosed with knee OA, a number of treatment options are available to control pain, improve function, and potentially slow disease progression. Although weight loss and an appropriate exercise program often are recommended as initial treatments, pharmacologic agents to alleviate pain and inflammation are usually required for meaningful pain relief. Pharmacological treatment options include non-narcotic and narcotic analgesics, NSAIDs, glucosamine and/or chondroitin sulfate, and intra-articular corticosteroids. When patients have inadequate response to pharmacologic therapy, the use of intra-articular injections of hyaluronic acid may be used to relieve pain and restore joint mobility.

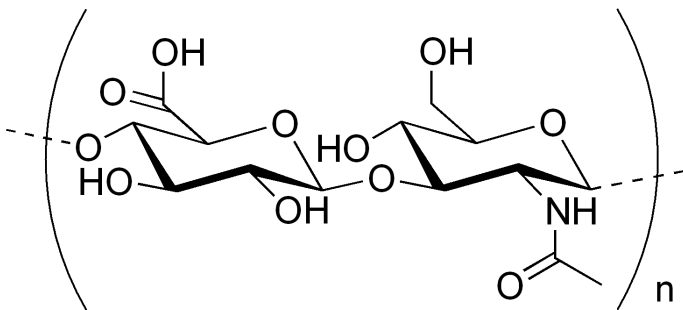
## Intra-articular hyaluronic acid injections for OA

The development of intra-articular HA therapy was driven by the need for OA treatments that relieve symptoms through local action in the joint without systemic side effects. While the mechanisms by which HA reduces pain

associated with OA are not entirely understood, several mechanisms of action have been proposed, including improvement of the viscoelastic properties of the synovial fluid, protection of the surface of articular cartilage, inhibition of synovial inflammation, upregulation of native HA production, and direct interaction of HA with joint nociceptors.<sup>10,15-20</sup>

Hyaluronic acid, also referred to as sodium hyaluronate or hyaluronan, was originally isolated and characterized from the vitreous humor of a bovine eye<sup>21</sup>. As shown in Figure 1, HA is a polysaccharide. Its disaccharide repeating units comprise of D-glucuronic acid and D-N-acetylglucosamine linked in alternating  $\beta$ -1,4- and  $\beta$ -1,3-glycosidic bonds.<sup>22</sup> HA is found throughout the body, including the eye, skin and articular cartilage. In healthy synovial fluid, high molecular weight HA imparts viscoelasticity and lubricity, helping the joint to absorb shock and contributing to the biomechanical stability of the joint.<sup>7</sup>

**FIGURE 1: CHEMICAL STRUCTURE OF HYALURONIC ACID**

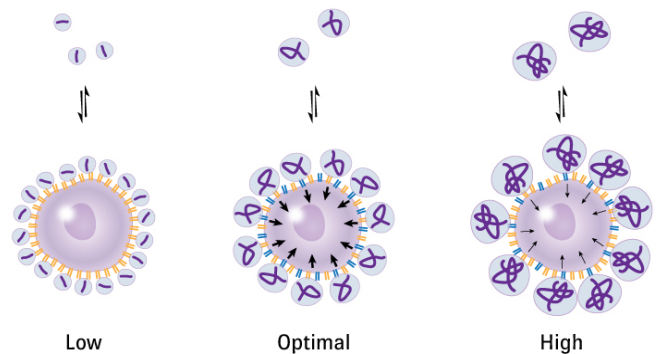


In its earliest commercial use, HA was extracted from rooster combs. More recently, bacterial fermentation processes have been developed to produce high purity HA with high molecular weights comparable to those from animal tissue.<sup>23</sup>

Numerous clinical trials and meta-analyses have confirmed the efficacy of intra-articular HA injections in providing symptomatic relief from knee OA.<sup>24-28</sup> A number of in vitro and in vivo studies have shown that introduction of exogenous, high molecular weight HA into the joint can interrupt the osteoarthritic cascade by downregulating the production of inflammatory cytokines and enzymes, restoring production of native HA, and slowing the progression of OA. These effects have been shown to be molecular weight dependent.<sup>10,16,29</sup> As shown in Figure 2, research suggests that there is an optimum molecular

weight range that maximizes the ability of HA to interact with cell surface receptors on synoviocytes, thereby maximizing the synthesis of native HA.<sup>10</sup>

**FIGURE 2: EFFECT OF HA MOLECULAR WEIGHT ON ITS INTERACTION WITH CELL SURFACE RECEPTORS ON OSTEOARTHRITIC SYNOVIOCYTES**



- Low molecular weight molecules of HA bind only weakly to surface receptors, resulting in little to no stimulation of native HA biosynthesis by osteoarthritic synoviocytes.
- Excessively high molecular weight molecules of HA (greater than 4 million Daltons) cannot bind strongly to cell surface receptors due to steric hindrance, inhibiting their ability to stimulate HA biosynthesis.
- Optimal molecular weight molecules (between 500,000 and 4 million Daltons) bind strongly to cell surface receptors, maximizing the stimulation of native HA biosynthesis.

Such cellular level effects of HA have been shown to be concentration dependent.<sup>10,16,29</sup> Moreover, there are no studies in the scientific literature suggesting that the osteoarthritic joint can be overdosed with intra-articular HA. As such, the ideal HA formulation would contain an optimum molecular weight, a very high concentration of HA, while maintaining an injection volume that could be tolerated by most patients.

### Development of single injection HA therapies

First generation HA treatments for the treatment of OA

were relatively low in molecular weight and required multiple (3-5) weekly injections for optimal efficacy. While effective for many patients, multiple injection therapies are not ideal in patients for whom consecutive weekly physician visits are impractical. To provide an HA therapy option for such patients, single injection HA products were developed. Three such products are now approved by FDA for the treatment of knee pain due to osteoarthritis (Synvisc One, Gel-One and MONOVISC). These products seek to provide safe and durable pain relief with the convenience of a single treatment.

One approach to the formulation of single injection HA is chemical cross-linking. This technique increases the molecular weight of the HA molecules via covalent crosslinks, thereby prolonging their residence time in the joint following injection. However, highly crosslinked HA may be outside the molecular weight range that has been proposed for optimum interaction with synoviocytes.<sup>10</sup> Moreover, crosslinking of avian-derived HA has been proposed as an explanation for pseudoseptic reactions.<sup>30-32</sup>

Another approach to single injection HA formulation is to significantly increase the concentration of HA, while maintaining an optimum molecular weight. MONOVISC is formulated with a high concentration of HA (22 mg/ml). This HA concentration, the highest of any FDA approved product, is intended to prolong its presence in the joint, while maintaining a molecular weight that is similar to that of ORTHOVISC® High Molecular Weight Hyaluronan, a multi-injection therapy with proven efficacy. Moreover, a high HA concentration maximizes the potential opportunity for stimulation of native HA synthesis by osteoarthritic synoviocytes.<sup>29</sup> An overview of FDA approved single injection HA products is presented in Table 1.

**TABLE 1. FDA-APPROVED SINGLE INJECTION HA PRODUCTS\***

MONOVISC® High Molecular Weight Hyaluronan – Product Comparison Table			
	MONOVISC	SYNVISC-ONE®	GEL-ONE®
Company	Anika Therapeutics	Sanofi Aventis	Seikagaku Corp
FDA Approval	2/25/2014	2/26/2009	3/22/2011
Directions for Use	1 injection	1 injection	1 injection
Duration of Pain Relief	Up to 6 months	26 weeks	13 weeks
# of Patients Treated in Trials	369	253	377
Retreatment (one-time)	Safety comparable to first injection	Device related AEs 5.2%	Not established
HA Source	Bacterial Fermentation Lightly crosslinked	Avian Chemically crosslinked Hylans A&B	Avian Highly crosslinked
HA Concentration mg/mL	22	8	10
Injected Volume	4 mL	6 mL	3 mL
Total HA Content	88 mg	48 mg	30 mg
Molecular Weight (Daltons)	1.0–2.9M High MW	6M (Hylan A) ∞ (Hylan B)	∞

\*INFORMATION FROM MONOVISC, SYNVISC-ONE® & GEL-ONE®  
FULL PRESCRIPTION INFORMATION

SYNVISC One is composed of cross-linked HA extracted from rooster combs. The Hylan A component of SYNVISC comprises HA that is crosslinked with formaldehyde during the tissue extraction process. Hylan B is an insoluble HA gel that is further crosslinked with vinyl sulfone. SYNVISC One is supplied in a 6 ml syringe contained 8 mg/ml of hylan polymers, for a total hylan content of 48 mg per injection.<sup>33</sup>

Gel-One® contains a crosslinked gel produced from rooster comb derived HA. To produce the gel, the HA in Gel-One® is highly crosslinked with cinnamic acid. Gel-One® is supplied in a 3 mL syringe containing 10mg/mL of HA, for a total HA gel content of 30 mg per injection.<sup>34</sup>

MONOVISC is composed of HA that is lightly crosslinked with bis(ethylcarbodiimide) (BCDI). The HA in MONOVISC, like that of ORTHOVISC, is derived from bacterial fermentation. MONOVISC is delivered as a 4 mL injection with an HA concentration of 22 mg/mL, for a total HA content of 88 mg per injection per injection.<sup>35</sup>

### Importance of injection volume

Synovial inflammation is very common in OA patients<sup>8-9</sup>. As with any inflamed tissue, pressure exerted on the tissue can be painful. As a result, the injection of a high volume of fluid into an osteoarthritic joint can be painful for many patients, as the injected fluid can exert substantial outward pressure on the synovium. MONOVISC is formulated in a 4 ml volume to minimize injection site discomfort.

### Terminal sterilization

The crosslinking process used in MONOVISC provides a unique advantage among HA products, namely terminal sterilization. All other HA products are manufactured using aseptic processing, in which only the HA solution inside the syringe is sterilized. Following HA solution sterilization, careful aseptic processing procedures must be followed to ensure that the final package product is sterile. With MONOVISC, the entire final package and its contents are heat sterilized. This process is enabled by the chemical stability imparted to HA molecules by the crosslinking of MONOVISC, which limits heat-induced degradation of HA during the sterilization process.

### 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 comparable magnitude and duration of pain relief as ORTHOVISC. ORTHOVISC delivers a total of 90 mg of HA in three (or four) weekly

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.

MONOVISC performance was 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.<sup>36</sup> Inclusion criteria included subjects 40-80 years of age, with BMI 20-35 and 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.

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 WOMAC Pain score from their baseline assessments.

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

The pilot study described previously 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. The protocol was reviewed by FDA prior to study initiation. A total of 184 patients received MONOVISC, and 185 received saline as placebo. The primary endpoint was the proportion of treatment successes in the MONOVISC and the placebo groups, where 'Patient Success' was defined as a patient who achieved  $\geq 40\%$  improvement in WOMAC Pain score and a  $\geq 15\text{mm}$  improvement as compared to baseline. Assessments were made at 2, 4, 8, 12, 20 and 26 weeks post-injection. Secondary outcomes included patient and evaluator global assessments, WOMAC physical function subscale, 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. The ITT population comprised 365 (4 patients did not attend any follow-up visits); 334 patients were included in the per-protocol (PP) population.

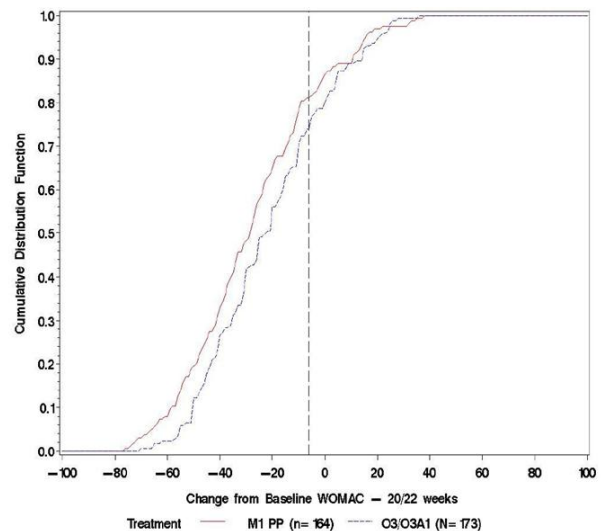
### Comparison of MONOVISC with ORTHOVISC

Despite the strong patient response to the MONOVISC treatment, the ability to demonstrate statistically significant improvement versus saline placebo over the 26-week trial was challenged by the unanticipated strength of the saline group response. Based on the strength of the patient response to MONOVISC, a non-inferiority analysis was conducted and submitted to FDA. This analysis compared patient responder rates for MONOVISC to those for multiple injections of ORTHOVISC as studied in previous clinical trials.

The non-inferiority analysis was enabled by the similarity in clinical trial designs between the MONOVISC and ORTHOVISC studies, including patient demographics, disease severity, inclusion/exclusion criteria, and standard of care at the time of the trials. The analysis compared the distribution of patient responder rates for each time point in the MONOVISC and ORTHOVISC trials. A typical result is illustrated in Figure 3, which shows a comparison of the Cumulative Distribution Function (CDF) plots for both products at the 20-22 week time period.

Similar results were found for all other time points in the analysis. Because of the close overlap in patient responder rate distributions, the efficacy of one single injection of MONOVISC was determined to be *substantially equivalent* (i.e. non-inferior) to that of three injections of ORTHOVISC with an additional arthrocentesis procedure.

**FIGURE 3: CDF PLOTS FOR CHANGE IN WOMAC PAIN SCORES: MONOVISC-1 VS. ORTHOVISC-3 AT 20-22 WEEKS. THE CLOSE OVERLAP OF PLOTS INDICATES SUBSTANTIAL EQUIVALENCE OF THE TWO THERAPIES**



Moreover, MONOVISC was found to be superior to the three-injection saline placebo groups from the previous ORTHOVISC trials. *Based on the non-inferiority analysis, MONOVISC is indicated for knee OA pain relief for up to six months.*

In addition, the non-inferiority between MONOVISC and ORTHOVISC-3 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 administered with either a 4 mL single injection of MONOVISC or three or four weekly injections of 2 mL of ORTHOVISC.<sup>37</sup> 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 difference was noted between the single or three-injection regimens for WOMAC or patient's and physician's global assessment scores.

### **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 the treatment group (2.2%) and one patient in the 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 of 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".

### **Safety comparison of HA to saline injections**

Intra-articular HA injections typically decrease OA knee pain by 30% or more on average compared to baseline pain levels. However, when compared with saline injections, the efficacy of intra-articular HA 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 marked placebo response, due in part to the invasiveness of the procedure and patient expectations of pain relief. Saline injections may also have a direct impact on knee OA pain.<sup>38-40</sup> For example, saline injections given with arthrocentesis can reduce inflammation and swelling. The injection of a diluting fluid may also decrease the concentration of pro-inflammatory and pain-inducing factors. Effects such as these are believed to have contributed to the unusually high response of the saline arm in the MONOVISC pivotal trial.

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

Direct comparison between single injection products has not been conducted in a single study. Pre-market approval (PMA) studies, which are typically large and well-controlled, tend to have similar designs and endpoints. Therefore, reasonable comparisons are possible between the clinical results for different HA products. The following products are chosen due to the availability of publicly available PMA study results.

#### **Synvisc-One®**

Synvisc-One® combines three 2 mL SYNVISIC® (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.<sup>41</sup> 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 significant improvements in WOMAC A pain scores vs. saline.

#### **Gel-One®**

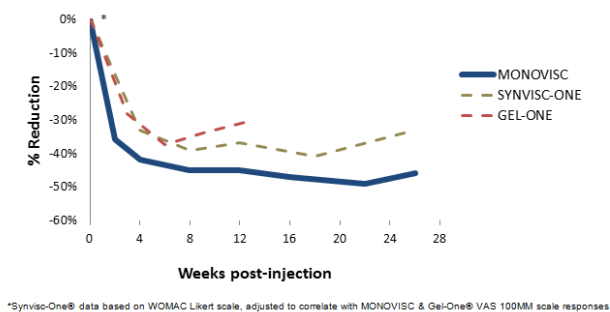
A 2:1 randomized controlled study testing the safety and effectiveness of a single intra-articular injection of Gel-One® to phosphate buffered saline (PBS) was conducted in 377 patients.<sup>42</sup> Follow-up was conducted at 1, 3, 6, 9, and 13 weeks using the WOMAC Visual Analog Scale (VAS). There 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***

A comparison of pain outcomes from clinical trials of FDA approved single injection HA therapies show that MONOVISC achieved the largest reduction from baseline with a durable effect (Figure 4). The mean pain reduction at 26 weeks for MONOVISC remained at a level greater than that obtained for the other products.

**FIGURE 4. PERCENT REDUCTION IN WOMAC PAIN FOR FDA APPROVED SINGLE INJECTION HA PRODUCTS OVER THE LENGTHS OF THEIR PIVOTAL STUDIES** <sup>36,37,41,42</sup>



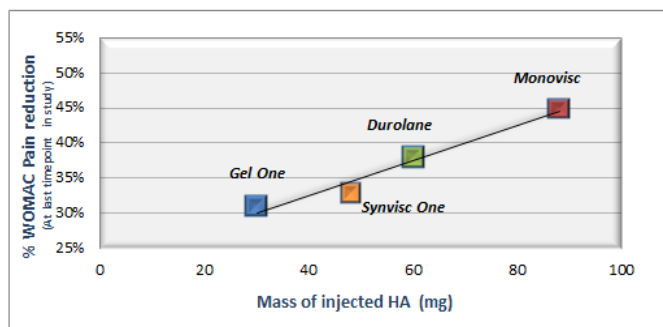
**Early Pain Relief: a significant outcome of single injection therapy**

In addition to providing pain relief up to six months, the onset of pain relief with MONOVISC was rapid. The mean improvement in WOMAC Pain from baseline by the earliest time point, week 2, for the MONOVISC ITT population was 36%. MONOVISC is the only single injection HA for which early pain relief has been measured in a clinical study.

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

As with any therapy, not all patients respond to HA injections. However, the response to MONOVISC is impressive in terms of the proportion of patients who achieve clinically meaningful levels of pain reduction. At 6-month time points, more than 50% of MONOVISC patients achieved longer lasting pain reduction from baseline of 50% or higher – a result not reported for other products.

**FIGURE 5. REDUCTION IN BASELINE WOMAC PAIN AS A FUNCTION OF MASS OF HA INJECTED INTO JOINT**



\*Durolane is not approved for use in the United States.

The relationship between pain reduction and the amount of HA injected into the joint is graphically depicted in Figure 5. These data (which include Durolane, a single injection therapy approved in ex-US markets<sup>43</sup>) are consistent with mechanism of action studies which suggest a concentration dependence on cellular level effects of HA on osteoarthritic cells. As such, these clinical data confirm the importance of high HA concentration on the ability of hyaluronic acid to reduce joint pain and restore function.

**Post Market Adverse Events Report**

With data derived from the April 30, 2012 report for Orthovisc, Synvisc, Synvisc-One, Hylan G-F20, etc. In the Manufacturer and User Facility Device Experience (MAUDE) database, the overall safety record for the HA 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.<sup>44</sup> Secondly, while Hylan G-F 20 (SYNVISIC® and Synvisc-One®) only represents an estimated 36% of total injections, they represent 82% of adverse events in the MAUDE database. This may be related to severe acute inflammatory reactions (SAIRs), commonly known as pseudoseptic reactions, that have been specifically linked to the Hylan G-F 20 products.<sup>25-26,45-49</sup>

**Conclusions**

Single injection hyaluronic acid therapies for the treatment of knee pain due to OA reduce the exposure of patients to injection procedures, maximize the probability of treatment completion/compliance, increase convenience for patients and healthcare professionals, MONOVISC provides a single injection HA therapy that is specifically formulated to maximize the amount of injected HA in a volume easily tolerated by patients, while maintaining a proven effective HA molecular weight. Based on the comparisons detailed in this paper, MONOVISC offers patients early pain relief and durable treatment effects that continue up to six months after the first injection.

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**Important Safety Information:**

High Molecular Weight Hyaluronan is indicated in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics, e.g., acetaminophen. In clinical studies, the most commonly reported adverse events for ORTHOVISC were arthralgia, back pain, and headache. Other side effects included local injection site adverse events. In clinical studies, the most commonly reported adverse events for MONOVISC were arthralgia, joint swelling and injection site pain. ORTHOVISC and MONOVISC are contraindicated in patients with known hypersensitivity to hyaluronate formulations or known hypersensitivity (allergy) to gram positive bacterial proteins. ORTHOVISC and MONOVISC should not be injected in patients with infections or skin diseases in the area of the injection site or joint. MONOVISC should not be administered to patients with known bleeding disorders.

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