Treatment of Persistent Shoulder Pain with Sodium Hyaluronate: A Randomized, Controlled Trial
A Multicenter Study

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Background: Presently, there are no approved nonoperative therapies for the ongoing treatment of persistent shoulder pain. Preliminary data suggest that intra-articular sodium hyaluronate injections may be beneficial for the treatment of persistent shoulder pain resulting from various etiologies. The present study evaluated the efficacy and safety of sodium hyaluronate (Hyalgan; molecular weight, 500 to 730 kDa) for these patients.

Methods: Six hundred and sixty patients with persistent shoulder pain and limitation resulting from glenohumeral joint osteoarthritis, rotator cuff tear, and/or adhesive capsulitis who had had a failure of conventional therapy were enrolled in this double-blind, randomized, phosphate-buffered saline solution-controlled study, and 456 patients completed twenty-six weeks of follow-up. Patients were randomized to receive either five weekly intra-articular injections of sodium hyaluronate, three weekly intra-articular injections of sodium hyaluronate followed by two weekly intra-articular injections of saline solution, or five weekly intra-articular injections of saline solution. The main outcomes were improvement in terms of shoulder pain on movement at thirteen weeks after the initiation of treatment (as assessed with use of a 100-mm visual analog scale) and the treatment effect throughout twenty-six weeks.

Results: For the overall intent-to-treat population, patients who were managed with sodium hyaluronate had greater pain relief than controls did; significant differences were noted at Week 7 (for the five-injection hyaluronate group), Week 17 (for the three and five-injection hyaluronate groups), and Week 26 (for the three-injection hyaluronate group). Analysis of the stratified populations clearly established that this effect was due to benefits experienced by the patients with osteoarthritis. The treatment effect through twenty-six weeks was significant in patients with osteoarthritis in the three-injection (p = 0.003) and five-injection (p = 0.002) groups, with no significant difference for either regimen in patients without osteoarthritis. The safety profile was very favorable, with no product-related serious adverse effects and no between-group differences for any reported adverse event.

Conclusions: Although the primary end point of this study (that is, improvement in terms of shoulder pain at thirteen weeks) was not achieved, the overall findings, including secondary end points, indicate that sodium hyaluronate (500 to 730 kDa) is effective and well tolerated for the treatment of osteoarthritis and persistent shoulder pain that is refractory to other standard nonoperative interventions.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Persistent shoulder pain is a highly prevalent problem that is frequently associated with limited range of motion and decreased function. It has several underlying etiologies, including glenohumeral osteoarthritis, rotator cuff tear (full or partial), impingement, tendinitis, adhesive capsulitis, and subacromial bursitis. There is substantial evidence that damage or dysfunction affecting one component of the shoulder can lead to secondary pathological changes, thereby contributing to persistent pain. For example, a rotator cuff tear can lead to mechanical and degenerative structural changes in the glenohumeral joint, which may contribute to and even dominate the resulting symptomatology.

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Nonoperative treatment of persistent shoulder pain generally includes the use of oral analgesics, physical therapy, and/or corticosteroid injections aimed at restoring range of motion and function to the shoulder and rotator cuff mechanism. Simple analgesics and nonsteroidal anti-inflammatory drugs are not universally effective and may be associated with substantial side effects, particularly in elderly patients. Similarly, recent reports regarding the chronic use of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2-selective inhibitors have raised safety concerns.

Hyaluronans are naturally occurring glycosaminoglycans that form the backbone of the proteoglycan aggregates in the extracellular matrix and are integral to the structure and function of articular cartilage. The presence of hyaluronan in the joint cavity directly affects the viscoelasticity of synovial fluid, with reduction of the frictional coefficient, and it helps to protect joints against compressive and shear forces. Hyaluronan is normally synthesized as a $2 \times 10^6$ to $2 \times 10^7$ molecular weight molecule that is subsequently aggregated by proteoglycans (primarily aggregan) to regulate its in situ molecular weight. Commercial hyaluronan products differ in molecular weight depending on their mode of purification and, in some cases, subsequent chemical modification. Intra-articularly injected sodium hyaluronate with a molecular weight of 500 to 730 kDa (Hyalgan [Hyl]; sanofi-aventis, Bridgewater, New Jersey, and Fidia Farmaceutici SpA, Abano Terme, Italy) has proved to be efficacious and well tolerated for the treatment of pain associated with knee osteoarthritis. Several small, open-label studies (baseline pain comparisons) have provided preliminary support regarding the safety and clinical benefit of sodium hyaluronate injections for the treatment of shoulder pain. A number of shoulder pain etiologies were evaluated in those studies, including osteoarthritis, rotator cuff tear, periarthritis, bursitis, and tendinitis; each of these conditions may be associated to some degree with intra-articular disease. On the basis of the findings of this preliminary clinical research, it was postulated that intra-articular injections of hyaluronan would be beneficial for the treatment of persistent shoulder pain due to intra-articular pathological changes.

The objective of the present study was to evaluate the effect of three or five weekly intra-articular injections of sodium hyaluronate (500 to 730 kDa) on the relief of shoulder pain and on movement in patients with persistent shoulder pain. In addition, we evaluated the safety and tolerability of these intra-articular hyaluronan injections in an elderly patient population with pain that was refractory to standard nonoperative therapy.

**Materials and Methods**

**Study Design**

This was a randomized, double-blind (blinded observer), parallel-design, phosphate-buffered saline solution-controlled study that was designed to evaluate the efficacy and tolerability of intra-articular injection of sodium hyaluronate (molecular weight, 500 to 730 kDa) into the glenohumeral articular space for the treatment of persistent shoulder pain associated with limitation of motion due to glenohumeral joint osteoarthritis, rotator cuff tear (partial or complete), and/or primary or secondary adhesive capsulitis. Seventy-nine outpatient study sites in the United States participated in the study after having passed a prequalification evaluation conducted by the clinical research provider (PPD, Wilmington, North Carolina) compensated by the sponsor. This evaluation included standard metrics such as relevant investigator experience, patient population, appropriate facilities, and study staff experience.

At the time of screening, 660 patients were randomized into three treatment groups receiving either five weekly 2-mL injections of phosphate-buffered saline solution (the control group), five weekly 2-mL injections of sodium hyaluronate at a dosage of 10 mg/mL (the five-injection hyaluronate group), or three weekly injections of sodium hyaluronate followed by two weekly injections of phosphate-buffered saline solution (the three-injection hyaluronate group). All investigators were trained in the proper technique for injection into the glenohumeral joint. Posterior and anterior approaches were permitted as long as the same method was used for all injections in each patient. Fluoroscopic guidance was not used. Dosage selection was based on the approved dosing (20 mg in 2 mL) and on published studies on the use of three and five-injection regimens for the treatment of pain due to osteoarthritis of the knee. Patients were evaluated at baseline and at seven, nine, thirteen, seventeen, and twenty-six weeks after the initiation of treatment.

All analgesic and anti-inflammatory drugs had to be discontinued for two weeks prior to the baseline evaluation, with the exception of acetaminophen (which was allowed as rescue medication for shoulder pain at a maximum dosage of 4 g/day). However, acetaminophen was not to be taken within twenty-four hours before any visit, including the baseline visit, in order to mitigate any effect of rescue medication on the evaluation of pain. On the basis of previous studies of the duration of effect observed with sodium hyaluronate in the knee, this criterion was not deemed to subject patients to notable amounts of pain during the twenty-four-hour period prior to each visit. Withdrawal of rescue medication for twenty-four hours prior to evaluation is routinely part of pain studies and was acceptable to the institutional review boards. A radiograph of the shoulder that was made either at the time of screening or within the previous six months was used to confirm the diagnosis of osteoarthritis and to rule out any exclusionary criteria, such as fracture or osteonecrosis. Magnetic resonance imaging of the shoulder was also performed at baseline to serve as the primary tool for the diagnosis of soft-tissue and osseous abnormalities and to confirm the presence or absence of rotator cuff tear pathology. All radiographs and magnetic resonance imaging studies were read, and the diagnosis or diagnoses were confirmed by a radiologist. Osteoarthritis was demonstrated by evidence of osteophytes, cartilage loss, a combination thereof, or focal erosion (subchondral cyst formation). Rotator cuff abnormalities included either high signal intensity within a supraspinatus tendon on T2-weighted images (indicative of tendinitis or, in some cases, a partial tear).
or thinning or frank discontinuity of the infraspinatus or supraspinatus tendon. Characteristic findings of adhesive capsulitis include thickening of the capsule and synovium.

At the time of randomization, patients were stratified into two groups according to the presence or absence of evidence of osteoarthritis in order to ensure equal distribution of patients in the treatment groups. Stratification was based on clinical assessment by the investigator as well as radiographic changes.

**Study End Points**
The primary end point was a reduction, relative to the baseline value, in shoulder pain during movement within the previous twenty-four hours as assessed by the patient with use of a 100-mm visual analog scale at the time of the thirteen-week follow-up visit.

The secondary end point was the maintenance of visual analog scale pain relief through the twenty-six-week period with use of the mixed effects model that considers all of the follow-up visits. Additional end points included improvement in terms of night pain through twenty-six weeks, the presence of a sustained response (i.e., the maintenance of improvement at all time-points), the time to onset of pain reduction, the categorical response based on reduction in the visual analog scale pain score, the global assessment by the patient, the level of functional improvement based on the range of motion, responder analysis (defined as the percentage of patients with a 20% [BL20] and 50% [BL50] reduction in visual analog scores from baseline), the results of the Short-Form Health Survey-12 general health questionnaire, and the use of rescue medication.

Study end points were evaluated in both the stratified population (the groups of patients with and without osteoarthritis) and the unstratified modified intent-to-treat population, which consisted of all randomized patients who received at least one dose of study medication and provided sufficient efficacy data for at least one analysis. This was done in accordance with the "intent-to-treat principle" methodology as acceptable to the United States Food and Drug Administration.

**Study Population**
The patients were thirty-five years of age or older and had had shoulder pain due to glenohumeral joint osteoarthritis, rotator cuff tear (partial or complete), and/or adhesive capsulitis for at least six months but less than five years. Pain with movement of the shoulder had been present for at least 50% of the days during the previous month. In order to be included in the study, the patient had to have persistent shoulder pain that was refractory to standard treatments as defined by a failure to obtain adequate or sustained relief following the use of physical therapy, at least one corticosteroid injection (more than three months prior to entry into the study), and the administration of oral pain medications. The patient was required to have moderate-to-severe pain without analgesic use over the twenty-four hours prior to entry into the study (as indicated by a rating of 40 to 90 mm on a 100-mm visual analog scale). The only permitted concomitant rescue medication was oral acetaminophen, to be taken as needed with a maximum of eight tablets or 4 g/day. Withdrawal of acetaminophen within twenty-four hours before each visit was enforced to obtain accurate assessments of the effect of the study interventions. Patients who were enrolled in this study were not considered to be candidates for surgical intervention, either because it was not indicated, because it was contraindicated, or because of patient preference. Limitation of active range of motion in at least one of several directions (i.e., abduction of ≤80° with the scapula fixed, active internal rotation of ≤55°, and/or external rotation of ≤80°) was required. However, retention of 20% of range of motion in all directions was also required.

Musculoskeletal system-related reasons for exclusion from the study included a major injury (including sports injury) within the past year, chronic pain lasting for more than five years, cervical spine disease that could confound assessments, surgery involving the shoulder within the previous twelve months, inflammatory arthropathy, severe frozen shoulder involving either shoulder (with retention of <20% range of motion), gout or calcium pyrophosphate diseases involving the upper extremities within the previous twelve months, intra-articular corticosteroid injections of any other joint within the previous month, intra-articular hyaluronic therapy within the previous twelve months, radiographic findings indicative of acute fracture of the shoulder, severe loss of bone density, osteonecrosis or severe deformity, or osteoarthritis of the glenohumeral joint equivalent to Kellgren-Lawrence stage IV. General medical conditions (such as pregnancy, malignant disease, or a bleeding diathesis), any condition that might confound the subsequent clinical evaluations, or laboratory abnormalities were also cause for exclusion.

**Sample Size**
Sample-size requirements were based on the effect size used in a placebo-controlled, sodium hyaluronate study of the treatment of pain due to osteoarthritis of the knee (between-group difference of 0.37 at twenty-six weeks)¹⁹. Based on the assumption of a 12.25-mm difference in mean visual analog scale pain scores between the sodium hyaluronate and phosphate-buffered saline solution groups (mean score, 13.5 and 25.75 mm, respectively) with a standard deviation of 33.0 mm, the number of patients required to achieve 80% power and to detect an effect size of 0.37 was 141 patients per treatment group.

**Statistical Methods**
Two-sided t tests were performed to compare the sodium hyaluronate treatment groups with the phosphate-buffered saline (control) solution group in terms of all primary and secondary outcome measures. The overall type-I error rate for the study was 0.05; however, as two two-sided statistical tests were conducted (the three-injection hyaluronate group compared with the control group and the five-injection hyaluronate group compared with the control group), a type-I error rate of 0.025 (Bonferroni correction) was used for the primary comparisons. All secondary and supportive outcomes were...
evaluated in an exploratory fashion with a type-I error rate of 0.05. Longitudinal data analysis based on a mixed-model, repeated-measures method was used to test for overall treatment effect, with the change in visual analog scale from baseline to Week 26 as the primary dependent variable. This model took into account the treatment group, week, treatment group by week interaction, baseline visual analog scale pain score, etiology (for subgroup analyses), and treatment site. The primary and selected secondary analyses were also performed for the stratified subgroups as defined by shoulder pain etiology (that is, for the groups of patients with and without osteoarthritis). Analyses of individual efficacy variables, as well as composite measures, excluded missing data. Non-missing values from a patient’s previous visits, including baseline values, were not carried forward to impute missing items at a given visit.

Safety Assessments
Safety evaluations included all reported adverse events.

Results
Patients
All 660 randomized patients had moderate-to-severe shoulder pain that was refractory to standard treatment. The demographic characteristics were similar in the three treatment groups. The majority (approximately 60%) of the patients in each treatment group had a diagnosis of osteoarthritis as the etiology of shoulder pain (62.4%, 58.4%, and 60.2% in the three-injection hyaluronate group, five-injection hyaluronate group, and phosphate-buffered saline solution group, respectively) (Table I). Approximately 66% of the patients with a diagnosis of osteoarthritis had an additional diagnosis of rotator cuff tear (full or partial) and/or adhesive capsulitis. The population was evenly split with regard to gender. The three treatment groups had similar baseline visual analog scale pain scores, with no meaningful differences between patients with and without osteoarthritis. The population was elderly (mean age, sixty-three years), approximately 37% of the overall population was obese (body mass index, >30.5 kg/m²), and almost all patients (>98%) had at least one medical history abnormality. The most commonly reported abnormalities were musculoskeletal disease (prevalence, 80% to 84%), previous operations other than upper body or shoulder operations (prevalence, 67% to 72%), and cardiovascular disease (prevalence, 67% to 71%).

A total of 456 patients (69.1%) had a follow-up visit at Week 26 (Fig. 1); approximately 20% of the patients had discontinued the study by the thirteen-week time-point. The most common reasons for study discontinuation were lack of efficacy (eighty-two patients), patient withdrawal of consent (fifty-four patients), and loss to follow-up (eleven patients). The percentages of patients and the reasons for withdrawal did not differ significantly among the three groups. The modified intent-to-treat population consisted of 602 patients (including 197 patients in the three-injection hyaluronate group, 201 in the five-injection hyaluronate group, and 204 in the control group).

Primary Efficacy Outcome
At Week 13, all three treatment groups showed significant reductions from baseline (i.e., improvement) in the visual analog scale score for shoulder pain on movement in the previous twenty-four hours. Although both the three-injection and five-injection hyaluronate groups showed larger mean reductions from baseline in comparison with the control group (mean and standard error, 26.3 ± 1.8 for the three-injection hyaluronate group, 26.4 ± 1.8 for the five-injection hyaluronate group, and 23.0 ± 1.8 mm for the control group), the between-group differences compared with control values were not significant at Week 13, the primary end point of the study (difference between the three-injection hyaluronate group and the control group, 3.3 ± 0.8 mm [95% confidence interval, −1.42 to 7.92], p = 0.173; difference between the five-injection

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**TABLE I Demographic and Disease Characteristics (Safety Population)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Three-Injection Sodium Hyaluronate Group (N = 218)</th>
<th>Five-Injection Sodium Hyaluronate Group (N = 221)</th>
<th>Control Group (N = 221)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis* (no. of patients)</td>
<td>136 (62%)</td>
<td>129 (58%)</td>
<td>133 (60%)</td>
<td>0.691†</td>
</tr>
<tr>
<td>Age†</td>
<td>62.3 ± 12.7</td>
<td>63.4 ± 12.4</td>
<td>63.6 ± 12.3</td>
<td>0.523‡</td>
</tr>
<tr>
<td>Male gender (no. of patients)</td>
<td>111 (51%)</td>
<td>114 (52%)</td>
<td>103 (47%)</td>
<td>0.525‡</td>
</tr>
<tr>
<td>Body mass index &gt;30.5 kg/m³ (no. of patients)</td>
<td>75 (34%)</td>
<td>87 (39%)</td>
<td>81 (37%)</td>
<td>&gt;0.05†</td>
</tr>
<tr>
<td>Baseline visual analog scale score† (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>65.7 ± 13.6</td>
<td>65.5 ± 13.3</td>
<td>64.6 ± 12.8</td>
<td>0.475§</td>
</tr>
<tr>
<td>Patients with osteoarthritis</td>
<td>66.5 ± 13.5</td>
<td>65.9 ± 14.0</td>
<td>64.3 ± 13.0</td>
<td>0.463§</td>
</tr>
<tr>
<td>Patients without osteoarthritis</td>
<td>64.2 ± 13.9</td>
<td>65.0 ± 12.5</td>
<td>65.0 ± 12.5</td>
<td>0.918§</td>
</tr>
</tbody>
</table>

*Of the total population with osteoarthritis, 66% also had additional underlying pathological changes (partial or complete rotator cuff tear and/or adhesive capsulitis). †The values are given as the mean and the standard deviation. ‡Based on the Cochran-Mantel-Haenszel test using general association statistic. §Based on an analysis of variance (F-test).
hyaluronate group and the control group, 3.4 ± 2.4 mm [95% confidence interval, −1.28 to 8.02], p = 0.155) (Table II). As is common in studies of knee osteoarthritis, a significant treatment effect was observed in the control group in the present study, with this group having a mean reduction in the visual analog score of 23.0 ± 1.8 mm from baseline to Week 13 (Table II).

Secondary Efficacy Outcomes
At additional individual time-points, significant improvements were seen in the three-injection hyaluronate group at Weeks 17 and 26 (p = 0.025 and p = 0.005, respectively) and in the five-injection hyaluronate group at Weeks 7 and 17 (p = 0.011 and p = 0.001, respectively) (Table II). The two active treatment groups were not significantly different from each other at any time-point.

With use of all data points, the overall treatment effect on pain reduction was found to be significant for both the three-injection hyaluronate group (p = 0.036) and the five-injection hyaluronate group (p = 0.012) in comparison with the control group over twenty-six weeks with use of a mixed-effect model (Table III).

Outcomes for Patients with and without Osteoarthritis
Although both active treatment groups tended to have an improved response to therapy in comparison with the control group, the primary contribution to this overall benefit was revealed in the analysis of the groups of patients with and without osteoarthritis.
osteoarthritis. The treatment benefit was seen in the group of patients with osteoarthritis, 66% of whom also had a partial or complete rotator cuff tear. Among the patients with osteoarthritis, pain reduction was greater in the three and five-injection hyaluronate groups than in the control group at thirteen weeks; these differences approached significance ($p = 0.051$ and $p = 0.058$, respectively). Evaluation of the overall treatment effect for all follow-up visits through twenty-six weeks revealed that pain reduction was significantly better in both the three and five-injection hyaluronate groups than in the control group ($p = 0.003$ and $p < 0.001$, respectively) (Fig. 2-A). Among the patients with osteoarthritis, the five-injection hyaluronate group demonstrated significant pain reduction at Weeks 7, 9, 17, and 26 ($p = 0.001$, $p = 0.018$, $p = 0.006$, and $p = 0.020$, respectively) and the three-injection hyaluronate group also exhibited significant pain reduction at Weeks 7, 9, 17, and 26 ($p = 0.034$, $p = 0.030$, $p = 0.012$, and $p < 0.001$, respectively) (Fig. 2-A). The overall between-group treatment differences in comparison with the control group were 7.49 and 7.75 mm (representing 41% and 42% improvements) for the three and five-injection hyaluronate groups, respectively. In contrast, among the patients without osteoarthritis, neither active treatment group differed significantly from the control group at thirteen or twenty-six weeks (Fig. 2-B, Table III). Therefore, patients with osteoarthritis of the glenohumeral joint, regardless of whether osteoarthritis was the sole abnormality or was concurrent with a rotator cuff tear and/or adhesive capsulitis, benefited significantly from the sodium hyaluronate injections. No difference was noted between the three and five-injection regimens during the twenty-six-week follow-up period.

### TABLE II Mean Reduction from Baseline on Visual Analog Scale for Shoulder Pain with Movement in Previous Twenty-four Hours (Modified Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mean Reduction from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 7</td>
</tr>
<tr>
<td>Three-injection sodium hyaluronate group*</td>
<td>22.9 ± 1.8</td>
</tr>
<tr>
<td>(n = 197)</td>
<td></td>
</tr>
<tr>
<td>Five-injection sodium hyaluronate group*</td>
<td>26.0 ± 1.8</td>
</tr>
<tr>
<td>(n = 201)</td>
<td></td>
</tr>
<tr>
<td>Control group*</td>
<td>20.1 ± 1.8</td>
</tr>
<tr>
<td>(n = 204)</td>
<td></td>
</tr>
<tr>
<td>Difference between three-injection sodium hyaluronate group and control group*</td>
<td>2.8 ± 2.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.228</td>
</tr>
<tr>
<td>Difference between five-injection sodium hyaluronate group and control group*</td>
<td>5.9 ± 2.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*The values are expressed as the mean and the standard error.

### TABLE III Overall Between-Group Differences in Pain Reduction Over Six Months (Modified Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Treatment Group Comparison</th>
<th>Overall Between-Group Difference in Reduction from Baseline on Visual Analog Scale for Shoulder Pain*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-injection hyaluronate group compared with control group</td>
<td>4.2 ± 2.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Five-injection hyaluronate group compared with control group</td>
<td>5.1 ± 2.0</td>
<td>0.012</td>
</tr>
<tr>
<td>Patients with osteoarthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-injection hyaluronate group compared with control group</td>
<td>7.5 ± 2.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Five-injection hyaluronate group compared with control group</td>
<td>7.8 ± 2.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients without osteoarthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-injection hyaluronate group compared with control group</td>
<td>−1.2 ± 3.4</td>
<td>0.720</td>
</tr>
<tr>
<td>Five-injection hyaluronate group compared with control group</td>
<td>1.2 ± 3.2</td>
<td>0.715</td>
</tr>
</tbody>
</table>

*The values are expressed as the mean difference and the standard error.
Supportive Efficacy Outcomes

Night Pain Reduction

The reduction in night pain from baseline (as assessed with the visual analog scale) was significantly better in the three-injection hyaluronate group than in the control group at Weeks 17 and 26 (26.49 ± 1.97 compared with 20.61 ± 1.96 [p = 0.026] and 30.40 ± 2.06 compared with 23.14 ± 2.04 [p = 0.009], respectively), and it was significantly better in the five-injection hyaluronate group than in the control group at Weeks 7, 9, 13, 17, and 26 after the initiation of therapy. Among the patients with osteoarthritis, the pain reduction compared with the phosphate-buffered-saline solution (PBS) control group was significant at Weeks 7, 9, 17, and 26 for both the three-injection (HYL-3) and five-injection (HYL-5) hyaluronate groups.

Bar graphs illustrating the mean improvement from baseline (with the upper limit of the 95% confidence interval) on the 100-mm visual analog scale for pain with movement in the previous twenty-four hours for the patients with osteoarthritis (Fig. 2-A) and those without osteoarthritis (Fig. 2-B) at Weeks 7, 9, 13, 17, and 26 after the initiation of therapy.
injection hyaluronate group than in the control group at Weeks 7 and 17 (21.07 ± 1.82 compared with 21.00 ± 1.80 [p = 0.015] and 29.73 ± 1.93 compared with 20.61 ± 1.96 [p = 0.001], respectively).

Among patients with osteoarthritis, the reduction in night pain was significantly better in the three-injection hyaluronate group than in the control group at Weeks 17 and 26 (26.40 ± 2.37 compared with 17.80 ± 2.51 [p = 0.009] and 29.05 ± 2.46 compared with 19.12 ± 2.58 [p = 0.003], respectively) and was significantly better in the five-injection hyaluronate group than in the control group at Weeks 7, 9, and 17 (28.55 ± 2.32 compared with 17.13 ± 2.25 [p < 0.001]; 28.64 ± 2.41 compared with 18.92 ± 2.36 [p = 0.002], and 27.76 ± 2.51 compared with 17.80 ± 2.51 [p = 0.003], respectively). Among patients without osteoarthritis, other than a significant reduction in night pain from baseline at one time-point (Week 9) in the three-injection hyaluronate group (17.53 ± 3.14 compared with 27.44 ± 3.02, p = 0.023), there was no notable improvement in night pain scores for either active treatment group as compared with the control group.

Range-of-Motion Assessments
Range-of-motion analysis (e.g., active external rotation, backward extension, and full neutral abduction) demonstrated significant differences (p < 0.05) for the hyaluronate groups as compared with the control group at certain time-points and for certain measures. However, the differences between the active treatment and control groups for most range-of-motion measures were generally <10°, which is not considered to be clinically important.

Patient Global Assessments
Patients in the three-injection hyaluronate group had significantly better global assessment scores as compared with controls at Week 17 (p = 0.030), and those in the five-injection hyaluronate group had significantly better global assessment scores as compared with controls at Week 7 (p = 0.023). Similarly, among patients with osteoarthritis, those in the three-injection hyaluronate group had significantly better global assessment scores as compared with controls at Week 26 (p = 0.019) and those in the five-injection hyaluronate group had significantly better global assessment scores as compared with controls at Week 7 (p = 0.012).

Response Analysis Based on Improvement from Baseline
A higher percentage of patients in the five-injection hyaluronate group responded to treatment on the basis of the BL50 criterion (at least a 50% improvement from baseline) as compared with controls (65.22% compared with 52.46%; p = 0.046). This was further supported by the within-group homogeneity for the groups of patients with and without osteoarthritis in terms of both primary and secondary efficacy analyses, safety, and rescue medication use during the study.

Safety
Overall, all treatments were well tolerated in the present study. The rates of treatment-emergent adverse events were similar in the three treatment groups (55%, 54%, and 54% in the three-injection hyaluronate group, the five-injection hyaluronate group, and the control group, respectively). The most common adverse events in the three-injection hyaluronate group, the five-injection hyaluronate group, and the control group were arthralgia (thirty-two patients [15%], twenty-eight patients [13%], and thirty-eight patients [17%], respectively), nasopharyngitis (ten patients [4.6%], nine patients [4.1%], and eleven patients [5.0%], respectively), headache (eight patients [3.7%], nine patients [4.1%], and five patients [2.3%], respectively), and back pain (five patients [2.3%], six patients [2.7%], and nine patients [4.1%], respectively). The rates of serious adverse events were lower in both hyaluronate groups (2.8% and 3.2% for the three and five-injection groups, respectively) than in the control group (6.3%). The most frequently reported adverse event considered to be related to study treatment was injection-site pain, which occurred in seven patients (3.2%) in the five-injection hyaluronate group, three patients (1.4%) in the three-injection hyaluronate group, and three patients (1.4%) in the control group.

Discussion
The primary objective of the present study was to evaluate the safety and efficacy of three and five-injection regimens of intra-articular sodium hyaluronate for the treatment of persistent shoulder pain. Although the primary end point of the study was not achieved, significant improvements occurred in several secondary end points. In all of the patients in the present study, the pain was considered to be refractory to current standard nonoperative clinical interventions, including physical therapy, at least one intra-articular corticosteroid injection, and various oral pain medications. Stratification of the treatment groups according to the presence or absence of underlying glenohumeral osteoarthritis, regardless of whether or not rotator cuff disease and/or adhesive capsulitis was also present, revealed a higher-than-expected prevalence of glenohumeral osteoarthritis (present in 60% of all patients). Two-thirds of these patients had concurrent shoulder abnormalities (a partial or complete rotator cuff tear and/or adhesive capsulitis). Although it is impossible to discern which of the abnormalities was primary, these findings suggest that the presence of osteoarthritis of the glenohumeral joint may be underappreciated in the setting of rotator cuff pathology.

Patients with osteoarthritis demonstrated significantly better visual analog scale shoulder pain scores after hyaluronate treatment as compared with those without osteoarthritis, supporting historical reports that etiology (that is, the presence or absence of osteoarthritis) is a key factor in the therapeutic effect of hyaluronans31. This was further supported by the within-group homogeneity for the groups of patients with and without osteoarthritis in terms of both primary and secondary efficacy analyses, safety, and rescue medication use during the study.
Both the three and five-injection hyaluronate regimens resulted in improvements in visual analog scale shoulder pain scores for patients with osteoarthritis at the earliest post-treatment time-point assessed (Week 7). The benefits persisted at the last time-point assessed (Week 26), but not for all of the intermediary time-points. As the patients were not followed beyond twenty-six weeks, it is unclear how long the clinical benefit would have been maintained.

As previously demonstrated in a comparison of these injection regimens in the knee\textsuperscript{9}, the present study showed a similar response to both three and five-injection regimens in the shoulder. Since the three-injection option may decrease patient time expenditure and discomfort associated with the injection process, many prefer it. However, additional work is needed to determine those who might benefit more from one regimen over the other and whether these regimens may be associated with variable outcomes not fully evaluated in this study (e.g., longer-term duration of benefit).

Both injection regimens were well tolerated. No safety concerns arose during the study, which was especially important from a clinical perspective as the eligible patient population had complex morbidities associated with advanced age and a high prevalence of concurrent diseases and, accordingly, concomitant medication use prior to entry into the study.

The sustained 28% positive effect of intra-articular injection of phosphate-buffered saline solution in the group of patients without osteoarthritis raises the benchmark for active treatments to demonstrate superior efficacy compared with control. The lack of significance in pain reduction seen at the thirteen-week time-point following treatment with either hyaluronate regimen may be in part due to this robust and sustained effect of phosphate-buffered saline solution. Differences in placebo effect observed between the groups of patients with and without osteoarthritis were of interest and may reflect differences in response for different interacting pathologies.

The lack of fluoroscopic guidance may be considered a limitation of the study, however, many investigators were already comfortable with shoulder injections on the basis of their previous experience. Regardless of previous experience or comfort with glenohumeral injections, all investigators were thoroughly trained in proper shoulder-injection technique in accordance with the study protocol.

In summary, osteoarthritis may be underdiagnosed in patients presenting with persistent shoulder pain, regardless of the presence of rotator cuff abnormality or other pathological changes. Many patients with shoulder pain who do not achieve adequate relief with analgesics, nonsteroidal anti-inflammatory drugs, or corticosteroids and who are not candidates for surgical intervention may benefit from intra-articular injection of hyaluronan. Although the primary end point was not met in the present study of a population of patients with persistent shoulder pain that was refractory to other standard nonoperative therapies, our data demonstrate the safety and efficacy of three and five-injection sodium hyaluronate (500 to 730 kDa) regimens for the treatment of persistent shoulder pain due to osteoarthritis alone or associated with other shoulder conditions such as rotator cuff disease. □

\textbf{References}


