These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert in the country of prescription*			
Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00377624
		Study Code:	L_8229
Generic drug name:	Hyaluronate sodium	**Date:**	09/Aug/2007

Title of Study: A double-blind, randomized trial of intra-articular injection of HYALGAN® into the glenohumeral articular space for the treatment of chronic painful shoulder with limitation of motion due to glenohumeral joint osteoarthritis, rotator cuff tear (partial or complete), and/or primary or secondary adhesive capsulitis (HYALGAN® Use in Painful Shoulder-HUPS)

Investigators: Roy Altman, MD, and the HUPS Clinical Study Group

Study Sites: 79 study sites

Publication (reference): None

Studied Period (years):
First Patient Enrolled: 03 January 2002
Last Patient Completed: 19 August 2004

Phase of Development: III

Objectives:

The primary objective was to demonstrate whether 3 and/or 5 weekly intra-articular (i.a.) injections of HYALGAN® provided significant pain relief upon movement for up to 3 months after Baseline, compared to phosphate-buffered saline (PB-Saline) control injections, in patients with chronic painful shoulder with limitation of motion due to glenohumeral joint osteoarthritis (OA), and/or rotator cuff tear (partial or complete), and/or primary or secondary adhesive capsulitis.

The secondary objective was to demonstrate whether 3 and/or 5 weekly i.a. injections of HYALGAN® maintained or improved pain relief upon movement for up to 6 months after Baseline, compared to PB-Saline injections, in patients with chronic painful shoulder.

The supportive objectives were to:

1. Evaluate the onset of pain relief of HYALGAN® in patients with chronic shoulder pain, compared to PB-Saline.
2. Demonstrate whether 3 and/or 5 i.a. injections of HYALGAN® provided night pain relief for up to 6 months in patients with chronic shoulder pain, compared to PB-Saline.
3. Demonstrate whether 3 and/or 5 i.a. injections of HYALGAN® provided functional improvement (range of motion [ROM], posterior reach) for up to 6 months in patients with chronic painful shoulder compared to PB-Saline.
4. Demonstrate whether 3 and/or 5 i.a. injections of HYALGAN® provided improvement in the patient's daily living and quality of life (patient's global assessment; Shoulder Rating Questionnaire [SRQ], disease specific outcome questionnaire; and 12-Item Short Form [SF-12], general health questionnaire) for up to 6 months in patients with chronic painful shoulder, compared to PB-Saline.
5. Assess the requirement for rescue analgesic medication (simple analgesics, such as acetaminophen) for pain relief of the shoulder throughout the study, in patients receiving HYALGAN® compared to PB-Saline.
6. Assess the clinical safety of HYALGAN® following a single course of i.a. injections in the shoulder, compared to PB-Saline.

Study Design and Methodology: Three-arm, parallel, double-blind (masked observer), randomized PB-Saline-controlled, clinical study. Patients were first stratified into OA or non-OA (rotator cuff tear and/or adhesive capsulitis) groups, based on the Investigator's diagnosis of shoulder pain etiology, and then randomly assigned to one of the 3 treatment groups.

Patients received a single weekly injection (total of 5 injections over 4 weeks) into the glenohumeral articular space of the signal shoulder of 1 of the following treatments:

- Five HYALGAN® i.a. injections (20 mg total in each 2 mL injection)
- Three HYALGAN® i.a. injections (20 mg total in each 2 mL injection) followed by 2 sterile phosphate-buffered 0.85% sodium chloride control solution (PB-Saline) i.a. injections (2 mL in each injection).
- Five PB-Saline i.a. injections (2 mL in each injection).

Prior to each double-blind treatment with HYALGAN® or PB-Saline, 1% lidocaine was administered subcutaneously.

HYALGAN®: A subcutaneous injection of 1% lidocaine followed by an i.a. injection of 2 mL (20 mg) sterile sodium hyaluronate (HYALGAN®) in a PB-Saline solution.

PB-Saline: A subcutaneous injection of 1% lidocaine followed by an i.a. injection of 2 mL of sterile phosphate-buffered 0.85% sodium chloride solution.

Rescue Pain Medication: All patients were permitted access to 500 mg x 1-2 tablets of acetaminophen 4 times a day (q.i.d.), as needed (p.r.n.) (maximum 8 tablets or 4 g per day).

Number of Patients (planned and analyzed): Planned: 603; Intent-to-Treat (ITT): 602; Per Protocol (PP): 449; Safety: 660.

Diagnosis and Main Criteria for Inclusion: Patients (≥35 years of age) with chronic shoulder pain and limitation of the glenohumeral joint due to OA, partial or complete rotator cuff tear, or adhesive capsulitis of at least 6 months, but not greater than 5 years' duration; pain present for at least 50% of the days during the previous month and showed no significant improvement in the past month; had failed conventional therapy, including 1 or more i.a. or local steroid injection(s), nonsteroidal anti-inflammatory drugs (NSAIDs), and physiotherapy; pain upon shoulder movement in the previous 24 hours with a 100-mm Visual Analog Scale (VAS) pain score of ≥40 mm and ≤90 mm at Baseline; and not taking any analgesic/anti-inflammatory medications (with the exception of acetaminophen, the rescue medication) 2 weeks prior to Baseline. Acetaminophen was not permitted within 24 hours of any visit.

Within the previous 6 months, patients must have had: an X-ray of the shoulder to diagnose if OA was the cause of the chronic painful shoulder and to rule out any exclusionary criteria; and magnetic resonance imaging (MRI) to demonstrate soft tissue and bony pathology and to confirm rotator cuff tear. All X-ray and MRI films were read by a radiologist.

Baseline assessments of ROM of the signal shoulder joint were recorded. Limitation of active ROM in at least 1 of the following directions was required: abduction with scapula fixed of ≤80°, internal rotation of ≤55°, and/or external rotation of ≤80°. Maintenance of ROM of ≥30% in all these directions was required to rule out frozen shoulder (≥30° for abduction with scapula fixed, ≥30° for external rotation, and ≤20° for internal rotation).

Test Product, Dose and Mode of Administration: Three mL syringes contained 20 mg/mL of HYALGAN® (sodium hyaluronate) in 2 mL PB-Saline, administered i.a.

Duration of Treatment: Duration of treatment was up to 4 weeks (a total of 5 injections). Total study duration was up to 26 weeks (not including the 2- to 4-week Screening period).

Reference Therapy, Dose and Mode of Administration: Three mL syringes contained 2 mL PB-Saline, administered i.a..

Rescue Medication, Dose and Mode of Administration: Acetaminophen, 500 mg tablets, 1-2 tablets q.i.d., p.r.n., administered orally (maximum 8 tablets or 4 g per day)..

Criteria for Evaluation:

Randomized patients received a single weekly injection (total of 5 injections over 4 weeks) into the glenohumeral joint space of the signal shoulder of one of the following treatments: 5 i.a. HYALGAN® injections; 3 i.a. HYALGAN® injections followed by 2 i.a. PB-Saline injections; or 5 i.a. PB-Saline injections. Assessments were performed at 11 scheduled visits during the study: at Weeks -4 to -2 (Screening Visit) and at Weeks 1, 2, 3, 4, 5, 7, 9, 13, 17, and 26.

Efficacy:

Primary Endpoint: Reduction in pain at 3 months after Baseline, assessed by the patient evaluation of VAS (100-mm scale) shoulder pain upon movement in the past 24 hours for the 3 i.a. and/or 5 i.a. HYALGAN® injection regimens, compared to PB-Saline control.

Secondary Endpoint: Maintenance or improvement in the reduction in pain upon movement up to 6 months after Baseline, assessed by patient evaluation of VAS (100-mm scale) shoulder pain upon movement in the past 24 hours for the 3 i.a. and/or 5 i.a. HYALGAN® injection regimens, compared to PB-Saline control.

Supportive Endpoints:

1. Improvement in VAS night pain through 6 months
2. Sustained response (ie, maintenance of improvement at all time points).
3. Time to onset of reduction in pain upon movement assessed by patient evaluation of VAS (100-mm scale) shoulder pain upon movement in the past 24 hours
4. Categorical response based on percent reduction in VAS.
5. Response to treatment based on relative and absolute reduction in VAS.
6. Patient's global assessment
7. Functional improvement and improvement in other assessments through 6 months in:
   a. ROM (quantitative measure of shoulder function)
   b. SRQ (disease specific outcome questionnaire)
   c. SF-12 (general health questionnaire)
8. Rescue medication use

Safety: Safety variables included adverse effects (AEs), complete physical examinations (including blood pressure), clinical laboratory tests (hematology and blood chemistry), and urine pregnancy tests.

Statistical Methods:

Two-sided superiority tests were performed comparing HYALGAN® treatment groups to PB-Saline for the primary and secondary efficacy parameters.

Primary Efficacy Analysis: Reduction in VAS shoulder pain score upon movement in the past 24 hours at 3 months from Baseline in the Intent-to-Treat (ITT) population was the primary efficacy parameter. Longitudinal data analysis based on Mixed Model Repeated Measures (MMRM) methods was used to test for a treatment effect, with the change in VAS from Baseline to Month 3 (Week 13) as the dependent variable. The model included terms for treatment group, week, treatment-by-week interaction, Baseline VAS pain score, etiology, and site. The primary efficacy analysis was also performed for subgroups defined by etiology.

Secondary Efficacy Analyses: Each secondary and supportive analysis was conducted in an exploratory fashion. As part of the secondary analyses, the primary analysis was performed on the Per Protocol (PP) population. For the ITT and PP populations, reductions in VAS pain scores were also analyzed and the longitudinal analysis methods, as well as associated SAS® code, were also applied to these analyses at each time point up to and including 6 months post-baseline. Larger models were constructed with additional covariates that were strongly associated with VAS outcome and treatment. Continuous supportive efficacy variables, such as VAS night pain score, SRQ Total score, SRQ domain scores, SF-12 summary scores (Physical Component Score [PCS-12], Mental Component Score [MCS-12]), and ROM scores were analyzed using longitudinal methods with terms for treatment group, week, treatment-by-week interaction, Baseline value of the outcome variable, etiology, site, and any additional covariates found to be significant in the larger model of the longitudinal analysis of VAS pain score. Least square (LS) means from the models were used to estimate treatment effects.

Median time to onset of pain relief was estimated by the method of Kaplan and Meier for each treatment group. The treatment comparison of time to onset of pain relief was performed using the log-rank test. Dichotomized pain reduction measures, such as response and sustained response, were analyzed with a logistic regression model containing terms for treatment group, etiology, and additional covariates chosen using forward selection techniques. Treatment comparisons for patient's global assessment were performed using a Cochran-Mantel-Haenszel (CMH) test for row mean scores.

Summary.

Efficacy Results:

The patients enrolled in this study were chronic shoulder pain patients who were refractory to standard non-surgical clinical interventions. At Screening, patients were stratified by etiology of shoulder pain (OA or non-OA) by the physician's diagnosis.

VAS Shoulder Pain Score

- For the primary efficacy endpoint, reduction from Baseline in VAS shoulder pain score at 3 months (Week 13) for the ITT population, both HYALGAN® treatment groups showed larger reductions from Baseline (ie, improvement) compared to PB-Saline (LS mean reductions from Baseline were 26.26 mm, 26.38 mm, and 23.01 mm for the HYALGAN® 3, HYALGAN® 5, and PB-Saline groups, respectively); however, the differences were not statistically significant ($p>0.025$).
- Although assessment of improvement at a single time point is of value, the true clinical value of HYALGAN® can be demonstrated through a repeated and sustained response over time. The results of secondary analyses for all patients in the ITT population showed notable improvements in VAS shoulder pain score at other post-treatment time points during the study (up to Week 26), as well as significant observed overall treatment effects averaged over all post-treatment time points for each of the HYALGAN® groups.
  - In contrast to Week 13, the test comparing the reduction in VAS pain score for all patients in the ITT population exhibited p-values <0.05 in the HYALGAN® 3 group at Weeks 17 and 26 ($p=0.025$ and $p=0.005$, respectively) and in the HYALGAN® 5 group at Weeks 7 and 17 ($p=0.011$ and $p=0.001$, respectively) compared to PB-Saline. The LS mean difference in reduction from Baseline in VAS score for all post-treatment time points ranged from 2.40 to 7.23 mm for the HYALGAN® 3 group vs. PB-Saline and from 3.37 to 7.97 mm for the HYALGAN® 5 group vs. PB-Saline. From Weeks 7 to 26, in the HYALGAN® 3 group, the reduction from Baseline in VAS shoulder pain score steadily increased, indicating continued improvement during the study compared to Baseline. There was a similar trend in the HYALGAN® 5 group, but not in the PB-Saline group.
  - The observed overall treatment effect averaged over all post-treatment time points for all patients in the ITT population suggested that the HYALGAN® 3 and HYALGAN® 5 groups had greater reductions from Baseline in VAS shoulder pain score ($p=0.036$ and $p=0.012$, respectively), compared to PB-Saline. Both HYALGAN® treatment groups had larger overall reductions from Baseline in VAS shoulder pain score. The overall LS mean difference in reduction from Baseline in VAS shoulder pain score was 4.24 mm for HYALGAN® 3 and 5.05 mm for HYALGAN® 5, compared to PB-Saline.
- Based on historical data, etiology (OA vs. non-OA) is a key factor in the therapeutic effect of HYALGAN® and was included as a covariate in the model. Since the etiology is clinically important and was also statistically significant in the model for reduction in VAS pain score, separate secondary analyses of the OA and non-OA groups were performed. The secondary analyses showed significant improvements in VAS shoulder pain score during the study, as well as observed overall treatment effects in OA patients.

Summary –.(continued):

Efficacy Results (continued):

VAS Shoulder Pain Score (continued):

- For OA patients in the ITT population, the reduction from Baseline in VAS shoulder pain score during the study showed more improvements in both the HYALGAN® 3 and HYALGAN® 5 groups vs. PB-Saline at all time points except Week 13 (all p values ≤0.034). At Week 13, the p-values were 0.051 and 0.058 for the HYALGAN® 3 and HYALGAN® 5 groups, respectively, compared to PB-Saline. The LS mean difference in reduction from Baseline in shoulder pain VAS score during the study ranged from 5.76 to 11.45 mm for the HYALGAN® 3 group vs. PB-Saline and from 5.76 to 9.24 mm for the HYALGAN® 5 group vs. PB-Saline. In OA patients receiving HYALGAN® 3, the LS mean reduction from Baseline in VAS shoulder pain score steadily increased from Weeks 7 to 26, while this trend was not seen in patients receiving HYALGAN® 5 or PB-Saline.
- For OA patients in the ITT population, there were better overall treatment effects across all post-treatment visits for both HYALGAN® groups compared to PB-Saline (p=0.003 and p=0.002 for HYALGAN® 3 and HYALGAN® 5, respectively). Both HYALGAN® treatment groups had larger overall reductions from Baseline in VAS shoulder pain score; the overall LS mean differences were 7.49 mm for HYALGAN® 3 and 7.75 mm for HYALGAN® 5, compared to PB-Saline.
- For OA patients in the ITT population, both the HYALGAN® 3 and HYALGAN® 5 groups, compared to PB Saline, had notably larger LS mean differences in VAS shoulder pain (ranges 5.76 to 11.45 mm and 5.76 to 9.24 mm, respectively) compared to all patients in the ITT population (ranges: 2.40 to 7.23 mm and 3.37 to 7.97 mm, respectively). The overall difference in reduction from Baseline in VAS shoulder pain in both the HYALGAN® 3 and HYALGAN® 5 treatment groups, compared to PB-Saline, were also notably larger in the OA etiology subgroups (7.49 and 7.75 mm, respectively), compared to all patients in the ITT population (4.24 and 5.05 mm, respectively).
- For the non-OA etiology subgroup, although the differences between both HYALGAN® treatment group and PB-Saline had p-values >0.05, it should be noted that in non-OA patients treated with HYALGAN®, the magnitude of the reductions from Baseline in VAS shoulder pain score were similar to those reported by OA patients. However, the PB-Saline treatment group had much larger reductions from Baseline in VAS score (range 24.00 to 31.15 mm) in non-OA patients compared to OA patients (range 16.65 to 19.35 mm). Thus, the differences between the HYALGAN® groups and PB-Saline, in non-OA patients, were smaller and the p-values were >0.05.

- Both HYALGAN® treatments resulted in improvements in VAS shoulder pain score at the first post-treatment time point assessed, Week 7 (3 weeks after the last injection) and the effects persisted until Week 26, the last time point assessed.
- The reduction from Baseline in VAS night pain score in the ITT population was better in the HYALGAN® 3 group vs. PB-Saline at Weeks 17 and 26 (p=0.026 and p=0.009, respectively), and in the HYALGAN® 5 group vs. PB-Saline at Weeks 7 and 17 (p=0.015 and p=0.001, respectively).

Summary –.(continued):

Efficacy Results (continued):

VAS Shoulder Pain Score (continued):

- The reduction from Baseline VAS in night pain score for OA patients in the ITT population was better in the HYALGAN® 3 group vs. PB-Saline at Weeks 17 and 26 (p=0.009 and p=0.003, respectively), and in the HYALGAN® 5 group vs. PB-Saline at Weeks 7, 9, and 17 (p<0.001, p=0.002, and p=0.003, respectively).
- The reduction from Baseline VAS in night pain score for non-OA patients in the ITT population was smaller (ie, less improvement) in the HYALGAN® 3 group vs. PB-Saline at Week 9 (p=0.023).
- Treatment response based on the adopted ACR20 criterion was reported in a higher percentage of patients (ITT population) in the HYALGAN® 5 group, compared to PB-Saline (p=0.043).
- A higher percentage of OA patients in the ITT population responded to treatment based on the adopted ACR50 criterion in the HYALGAN® 5 group, compared to PB-Saline (p=0.046).
- The percent reduction in VAS by Baseline VAS pain score in the ITT population was better in the HYALGAN® 5 group vs. PB-Saline at Weeks 7 and 9 (p=0.024 and p=0.049, respectively), using the ordinal scale: <0%, 0% to <20%, and ≥20%.

ROM Assessments

- Although some of the ROM analyses (active external rotation, active backward extension, and active full neutral abduction) reached p-values <0.05, the differences between the HYALGAN® groups and PB-Saline were less than 10°; a difference that would generally not be considered clinically significant.

SRQ Assessments

- The change from Baseline in SRQ global assessment domain scores in the ITT population was better in the HYALGAN® 3 group vs. PB-Saline at Week 26 (p=0.027).
- The change from Baseline in SRQ work domain scores in the ITT population was smaller (ie, less improvement) in the HYALGAN® 5 group vs. PB-Saline at Week 13 (p=0.015).
- A slightly lower percentage of patients (ITT population) in the HYALGAN® 3 and HYALGAN® 5 groups (56.8% and 66.7%, respectively) ranked pain as the most important domain for improvement at Week 26, compared to PB-Saline (69.2%).

Patient Global Assessment

- The patient's global assessments for all patients in the ITT population was better in the HYALGAN® 3 group at Week 17 (p=0.030) and in the HYALGAN® 5 group at Week 7 (p=0.023), compared to PB-Saline.
- The patient's global assessments for OA patients in the ITT population were better in the HYALGAN® 3 group at Week 26 (p=0.019) and in the HYALGAN® 5 group at Week 7 (p=0.012), compared to PB-Saline.

Summary –.(continued):

Efficacy Results (continued):

Rescue and Analgesic Medications

- Although the use of rescue analgesic medication declined beginning at Week 13, compared to Baseline, there were no notable differences between the 3 treatment groups.
- Although analgesic and NSAID medication use declined during the study, compared to Baseline, there were no notable differences between the 3 treatment groups. The results were similar for OA and non-OA patients.

In general, the results for the PP population supported those of the ITT population.

Safety Results:

- There were no deaths reported during the study.
- There was no imbalance seen in TEAEs among the 3 treatment groups. The incidence of TEAEs by system organ class and preferred term were similar between the 3 treatment groups. The incidence of serious adverse effects (SAEs) and discontinuations due to TEAEs were lower in both HYALGAN® treatment groups compared to PB-Saline.
- A total of 54.2% (358/660) of patients reported TEAEs during the study. The incidence of TEAEs was similar in the 3 treatment groups (55.0% of patients in the HYALGAN® 3 group, 53.8% of patients in the HYALGAN® 5 group, and 53.8% of patients in the PB-Saline group).
- Most TEAEs were mild or moderate in severity and were considered probably not related to the study product by the Investigator.
- A total of 27 patients (6 in the HYALGAN® 3 group, 7 in the HYLAGAN® 5 group, and 14 in the PB-Saline group) experienced 40 SAEs during the study. None of the SAEs were considered related to the study product.
- A total of 10 patients (2 in the HYALGAN® 3 group, 3 in the HYALGAN® 5 group, and 5 in the PB-Saline group) terminated early from the study due to an AE.
- The most frequently reported TEAEs occurred in the following system organ classes: musculoskeletal and connective tissue disorders (25.0% of all patients); and respiratory, thoracic, and mediastinal disorders (11.2% of all patients). The most frequently reported TEAEs by preferred term were aggravated arthralgia and arthralgia (7.4% of all patients each).
- The most frequently reported TEAE considered related to study product by the Investigator was injection site pain (2.0% of all patients), occurring in 3.2% of patients in the HYALGAN® 5 group and 1.4% of patients in both the HYALGAN® 3 and PB-Saline groups.
- The most frequently reported related TEAEs that were severe in intensity were arthralgia, aggravated arthralgia, and injection site pain, all occurring in <1% of patients in any treatment group.
- There were no notable effects of HYALGAN on hematology and chemistry clinical laboratory results or vital signs

Date of the Report: 21 June 2005