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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00130468
		Study Code:	L_9385
Generic drug name:	Sodium Hyaluronate	**Date:**	02/Sep/2008

Title of the study: A Double Blind, Randomized Trial of Intra-articular Injections of 20 mg of HYALGAN® for the Treatment of Knee Pain due to Osteoarthritis

Investigators: 14 investigators in total

Study centers: 13 study centers in total, all located in the United States of America

Publication (reference): none

Study period: Date first patient enrolled: 17-Nov-2004 Date last patient completed: 21-Apr-2006	**Phase of development:** IV

Objectives:

The primary objective was to:

1. Demonstrate whether 3 intra-articular (IA) injections of HYALGAN 20 mg/2 mL provided significant pain relief assessed by a 100-mm Visual Analog Scale (VAS) after a 50-FT walk through 6 months after baseline, compared to phosphate buffered saline (PB-Saline).

The secondary objectives of the study were to demonstrate whether 3 IA injections of HYALGAN could:

2. Provide significant pain relief evaluated by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (consisting of pain, stiffness and function domains) due to OA for up to 6 months from baseline compared to PB-Saline.
3. Provide clinical benefits as assessed by improvement in the WOMAC pain subscore for up to 6 months from baseline compared to PB Saline.
4. Elicit a superior clinical response as assessed by responder analyses (20%, 50%, or 70% improvement from baseline [BL]) of VAS pain (after a 50-FT walk on a flat surface) for HYALGAN compared to PB-Saline.
5. Provide significant subject benefit as evaluated by Patient's Global Assessment for up to 6 months from baseline compared to PB-Saline
6. Provide a benefit with respect to onset of action of pain relief assessed by VAS after a 50-FT walk on a flat surface for HYALGAN compared to PB-Saline.
7. Provide an improvement in the subjects' general health, daily living, quality of life (QoL) assessments, health utility and pharmaco-economic scores (EuroQoL–5D) for up to 6 months from baseline compared to PB Saline.
8. Improve various clinical parameters (amount and frequency of joint effusion, flexion, and extension, etc) based upon clinical knee examinations for up to 6 months from baseline compared to PB-Saline.\
9. Reduce the requirement for rescue analgesic medication (i.e., acetaminophen) for pain relief of the target knee throughout the study compared to PB-Saline and to assess the requirement for any analgesic medication between groups for pain relief of the target knee.

Furthermore, the clinical safety following a single course of 3 IA injections of HYALGAN was to be assessed and compared to PB Saline.

Methodology:

This was a parallel design, double-blind (masked observer), and multicenter, randomized, PB-Saline controlled clinical study.

There were 2 randomized treatment groups. Subjects received a single weekly injection in the knee for a total of 3 IA injections over 2 weeks of either:

- PB-Saline (2 mL)
- HYALGAN (20 mg total in 2 mL)

Prior to each treatment, 1% lidocaine was administered subcutaneously after which the PB-Saline and HYALGAN were administered into the knee joint space. As a rescue medication, only acetaminophen, up to 1000 mg four times a day (qid) for knee pain, (maximum 8 tablets or 4 grams per day) was permitted. However, acetaminophen, or any other analgesic, was not permitted within 24 hours prior to any study visit.

Number of patients:

150 subjects were planned for enrollment; a total of 159 subjects were enrolled (79 HYALGAN and 80 PB-Saline subjects) and 139 subjects were included in the analysis of the modified Intent to Treat Population (69 HYALGAN and 70 PB-Saline subjects).

Diagnosis and criteria for inclusion:

Male and female subjects (≥40 years of age) with OA of the knee associated with moderate to severe knee pain were enrolled into this study. At screening, subjects had to demonstrate a VAS pain score of ≥30 mm and ≤90 mm after a 50-FT walk on a flat surface if receiving any analgesic medications, and ≥40 mm and ≤90 mm if not taking any analgesic medications. Similarly, the contralateral knee from the target knee had to have a VAS pain score of <30 mm on or off pain medication. The target knee for subjects with contralateral involvement of OA was to be considered the knee demonstrating the greatest VAS pain at baseline.

Diagnosis and clinical evaluations of OA of the knee were made according to American College of Rheumatology (ACR) criteria based upon a standing weight bearing knee radiogram at screening or an X-ray performed within 6 months prior to screening. The radiograms were classified as a Kellgren and Lawrence Grade I, II, or III for OA of the knee.

All analgesic and anti-inflammatory drugs were to be discontinued for 2 weeks prior to baseline except for acetaminophen. The rescue medication, acetaminophen (maximum of 1000 mg qid), or any other analgesic was not permitted within 24 hours prior to any study visit.

Test product, dose and mode of administration: HYALGAN (sodium hyaluronate): 20 mg/2 mL of avian derived hyaluronic acid administered IA.

Reference therapy, dose and mode of administration: PB-Saline (2 mL) administered IA

Duration of treatment:

The study consisted of 2 weeks screening period and 2 weeks treatment period and 24 weeks of double-blind follow-up period. The total duration of the study was 28 weeks. Subjects had up to a 2-week washout from previous non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) selective inhibitors, and other analgesics. At baseline and at Week 1 and Week 2, randomized subjects received weekly injections of HYALGAN or PB-Saline, with follow-up at 1, 2, 3, 4, 5, and 6 months after baseline (Week 0) for a total of 10 visits.

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the improvement in pain due to OA of the knee after 50-FT walk on a flat surface based upon a 100-mm VAS score through 6 months after baseline for the HYALGAN-treated group compared to the PB-Saline group.

The modified intent-to-treat (mITT) population was used for the evaluation of the primary efficacy variable and consisted of all randomized subjects who received at least 1 dose of study medication and who provided sufficient efficacy data for at least 1 analysis.

Secondary efficacy variables were improvement in WOMAC total score, every domain scores and pain subscore at all evaluable timepoints up to 3 and 6 months compared to PB-Saline; the percentage of subjects reporting a significant response to treatment as measured by the baseline improvements in pain of 20% (BL_{20}), 50% (BL_{50}), and 70% (BL_{70}), response criteria; time of onset and maintenance of improvements compared to PB-Saline at all time points, Patient's Global Assessment, EuroQoL-5D, knee examination parameters, and use of rescue pain medication through 6 months after baseline of HYALGAN-treated subjects compared to PB-Saline.

Safety: The safety variables in this study were recorded adverse effects (AEs), laboratory abnormalities as evaluated by the investigator, vital signs, and physical examination findings.

Statistical methods:

The primary efficacy analysis of improvement in the pain score after the 50-FT walk on a flat surface was performed on the mITT using all subjects who had both a baseline and at least 1 follow-up evaluation by 100-mm VAS. Longitudinal data analysis methods based on mixed model repeated measures (MMRM) were used to test for a treatment effect. All follow-up observations were utilized; missing values remained as missing, and only observed values were used in the data analysis. The model included terms for treatment group (HYALGAN, PB-Saline), baseline VAS value, investigational center, month, treatment by month interaction, and the baseline prognostic factors: age, gender, body mass index, Kellgren-Lawrence grade of OA (Grade I or II and Grade III as 2 categories), VAS pain score in the contralateral knee, and analgesic medication and NSAID usage. Similar analysis was performed on the per-protocol (PP) population (defined as all subjects without any significant protocol violations and completing all visits).

All secondary efficacy variables were analyzed using the mITT population only. Continuous efficacy variables, such as improvement in WOMAC total score, WOMAC pain subscore, WOMAC domain scores, EuroQoL–5D Health Utility Index, and VAS for overall actual health state were analyzed using the MMRM with terms for treatment group, baseline value, center, month, treatment by month interaction and other prognostic factors found significant in the primary efficacy analysis. All statistical tests were 2sided and performed at the 5% significance level.

Dichotomized pain reduction measures, such as response and sustained response, were analyzed with a logistic regression model containing terms for treatment group and the baseline prognostic factors found significant in the primary efficacy analysis. Treatment effects were estimated using predicted percents from the model evaluated at the overall mean for continuous covariates (e.g., age) and the overall distribution of patients for categorical covariates (e.g., gender). Comparisons for ordinal categorical variables, such as patient global assessment, categorical response scales based on VAS % reduction and EuroQoL–5 D scores were performed by Cochran-Mantel-Haenszel tests for row mean scores, stratified by investigational center.

Time to onset of pain relief, time to discontinuation due to lack of efficacy, and time from the third injection to the end of first response for BL_{20}, BL_{50} and BL_{70} were compared between the 2 treatment groups using the Kaplan-Meier procedure and the log-rank test. Subjects completing the study without onset of pain relief or discontinuation due to lack of efficacy were considered censored observations for those endpoints with time equal to the total study time. Subjects who discontinued prematurely for reasons other than lack of efficacy were also considered censored for onset of pain relief and time to discontinuation due to lack of efficacy endpoints. For the time from the third injection to the end of first response endpoints, only subjects achieving a response were included in the analyses. Subjects completing the study or discontinuing from study while still maintaining a response were considered censored observations with time equal to (last visit date) – (third injection date) + 1.

All AEs were coded and tabulated by system/organ class using the Medical Dictionary of Regulatory Activities (MedDRA) dictionary. Serious AEs (SAEs) were also summarized. Appropriate tables were produced to summarize discontinuations due to AEs, changes in vital signs, laboratory parameters, and physical examination findings.

Results:

Subject Disposition and Analysis Sets:

A total of 159 subjects were randomized to either HYALGAN (N = 79) or PB-Saline (N = 80). All PB-Saline subjects and all but 2 HYALGAN subjects completed all 3 injections of treatment

There were 159/159 subjects in the adverse effects population (79 HYALGAN and 80 PB-Saline subjects), 139/159 subjects in the mITT population (69 HYALGAN and 70 PB-Saline subjects), and 83/159 subjects in the PP population (41 HYALGAN and 42 PB-Saline subjects).

Efficacy results:

For the primary efficacy endpoint, there was no statistically significant difference between treatment groups in overall improvement through 6 months in the mITT population. However, treatment groups were significantly different at the Month 5 and Month 6 time points. Results in the PP population showed significant differences at Month 5 and Month 6, as well as a statistically significant difference between treatment groups for overall improvement.

Most secondary efficacy endpoints did not show statistically significant differences between treatment groups. Exceptions included a statistically significant difference between treatment groups at Month 6 for change from baseline in the WOMAC pain subscore and significant differences between treatment groups in the time from the third injection to the end of the first response of a 50% and 70% improvement in the VAS score.

Safety results :

There were no deaths reported in this study. A total of 81/159 subjects (50.9%) reported at least 1 treatment-emergent adverse effect (TEAE), 40/79 HYALGAN subjects (50.6%) and 41/80 PB-Saline subjects (51.3%). A total of 9/159 subjects (5.7%) reported at least 1 treatment-related TEAE, 5/79 HYALGAN subjects (6.3%) and 4/80 PB-Saline subjects (5.0%).

The majority of AEs were assessed as mild or moderate in severity, with only 12 subjects reporting an AE assessed as severe (5 HYALGAN and 7 PB-Saline subjects). The most commonly reported TEAEs were arthralgia, nasopharyngitis, upper respiratory tract infection, back pain, diarrhea, pain in extremity, sinusitis, and headache and injection site pain. No trend in the number or severity of TEAEs was noted between treatment groups, with the exceptions of nasopharyngitis (12.7% in HYALGAN subjects compared with 3.8% in PB-Saline subjects), upper respiratory tract infection (10.1% in HYALGAN subjects compared with 3.8% in PB-Saline subjects), and diarrhea (1.3% in HYALGAN subjects compared with 5.0% in PB-Saline subjects).

Eight subjects experienced SAEs: 2 subjects in the HYALGAN group and 6 subjects in the PB-saline group; none of the SAEs were considered device related. Four subjects experienced AEs that led to study discontinuation: 2 HYALGAN subjects for moderate arthralgia; 1 HYALGAN subject for myocardial infarction; and 1 PB-Saline subject for knee arthroplasty.

Analysis of laboratory measurements, vital signs, and physical examination findings showed minor but not clinically relevant changes between baseline and last observation for both treatment groups..

Date of ACSRS: 19-Aug-2008