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	ClinicalTrials.gov Identifier:	NCT00830830
		Study Code:	L_9385EXT
Generic drug name:	Sodium Hyaluronate	Date:	17/Mar/2009

Title of Study: An Extension Trial to TREAD-20 to Evaluate the Duration of Efficacy of a Single Course of Intra-articular Injections of 20 mg of HYALGAN® or PB-Saline in Responders and the Effects of a Second Course of Injections (20 mg of HYALGAN®) in Non-responders to the Initial TREAD-20 Injections for the Treatment of Knee Pain due to Osteoarthritis: 6-month Extension Follow-up

Investigators: 9 investigators in total.

Study centers: 8 study centers in total, all located in the United States of America

Publication (reference): None

Phase of development: 4

Study period:

Date of First Patient First Visit: 27 December 2005

Date of Last Patient Last Visit: 24 October 2006

Objectives:

The primary objective for responders (subjects with ≥ 20% pain relief based on a visual analog scale [VAS]) was to:

- Evaluate whether 3 intra-articular (IA) injections of HYALGAN® (20 mg/2 mL) provided significant pain relief for subjects with osteoarthritis (OA) of the knee, as assessed by the 100-mm VAS after a 50-foot (FT) walk, for up to 9 months from the base study (TREAD-20) BL compared with phosphate-buffered saline (PB-Saline).

The primary objective for non-responders (subjects with < 20% pain relief based on VAS from BL to final visit for TREAD-20) was to:

- Explore if 3 IA injections of HYALGAN® (20 mg/2 mL), as a repeat treatment 6 months after an inadequate response to an initial course of injections of either HYALGAN® or PB-Saline, provides significant pain relief for subjects with OA of the knee, as assessed by VAS after a 50-FT walk, for a duration of up to 3 months and 6 months from retreatment with HYALGAN®.

The secondary objective for responders was to:

- Evaluate whether 3 IA injections of HYALGAN® (20 mg/2 mL) provided significant pain relief for subjects with OA of the knee as assessed by VAS after walking on a flat surface for up to 12 months (from TREAD-20 BL) compared with PB-Saline.

The secondary objective for non-responders was to:

Explore if 3 IA injections of HYALGAN® (20 mg/2 mL), as a repeat treatment 6 months after an inadequate response to an initial course of injections of either HYALGAN® or PB-Saline, provided significant pain relief for subjects with OA of the knee as assessed by VAS after a 50-FT walk for up to 6 months.

Methodology:

This was a 2-part study:

Responders (subjects who had demonstrated a clinical benefit at 6 months [i.e., completion of TREAD-20]) were enrolled into a parallel, 2-arm (HYALGAN® or PB-Saline) follow-up clinical study that extended the duration of TREAD-20 subjects for up to 12 months from the original BL.

Non-responders to the initial series of injections (HYALGAN® or PB-Saline) at 6 months (i.e., completion of TREAD-20) were enrolled into an open-label extension (EXT) evaluating an additional 3 IA injections of HYALGAN® (20 mg/2 mL).

Subjects who had met the inclusion criteria of an improvement of ≥ 20% from BL on VAS pain score at the 6-month Final Visit of TREAD-20 and had successfully completed the study protocol with no major violations were permitted to enter EXT and were followed for an additional 6 months (12 months after TREAD-20 BL). These subjects were defined as responders.

Subjects who had not met the inclusion criteria of an improvement of ≥ 20% from BL on VAS pain score at the 6-month Final Visit of TREAD-20, but otherwise had completed TREAD-20 with no major violations were permitted to enter EXT as non-responders.

Subjects were enrolled for 26 weeks from the final visit of TREAD-20 or 52 weeks from the TREAD-20 BL. Responders received no additional experimental treatments and returned for efficacy and safety assessments at Month 3 and Month 6 of EXT, for a total of 3 visits. All non-responders received 3 weekly injections of HYALGAN® at Weeks 26, 27 and 28 (for a total of 3 IA injections); and then returned for efficacy and safety assessments at Month 3 and Month 6 of EXT, for a total of 5 visits.

Use of acetaminophen, 500 mg x 1 to 2 tablets 4 times daily (qid) as needed (prn), at a maximum of 8 tablets or 4 grams per day, was permitted as rescue medication for breakthrough knee pain, but could not be taken within 24 hours of a clinic visit.

All the original sites from TREAD-20 that had enrolled at least 1 subject were allowed to participate in EXT. The investigator who had performed the original clinical efficacy assessments during TREAD-20 continued to make the evaluations for the included subjects at the EXT BL.

Number of subjects:

Forty (40) responders and 40 non-responders were planned for enrollment into EXT; however, a total of 40 subjects satisfied the enrollment criteria (17 responders and 23 non-responders).

Diagnosis and main criteria for inclusion:

Subjects who had successfully completed TREAD-20 with no major protocol violations and were of sufficiently good health to complete the additional 6-month follow-up.

Responders were defined as those who at their TREAD-20 6-month visit reported a ≥ 20% improvement from that seen at the TREAD-20 BL (Day 0) on a VAS pain score after a 50-FT walk.

Non-responders were defined as those who at their TREAD-20 6-month visit reported a < 20% improvement from that seen at the TREAD-20 BL (Day 0) on a VAS pain score after a 50-FT walk.

Other criteria regardless of TREAD-20 response included: at enrollment into TREAD-20, if there was bilateral OA of the knee involvement, subjects were to continue to have a VAS pain score after a 50-FT walk of < 30 mm in the contralateral knee on or off any pain medication; performing the 50-FT walk test without the support of crutches or other supportive/assistive devices (except canes if used routinely in daily activities and for all assessments); willingness to continue to refrain from chronic use of all NSAIDs or other analgesic medication with the exception of acetaminophen; willingness to continue using acetaminophen 500 to 1000 mg (1 to 2 tablets) qid prn (maximum 8 tablets or 4 g/day) as rescue medication for knee pain during the 6-month study period and refrain from taking acetaminophen for the 24 hours prior to any study visit; willingness, if using low-dose aspirin (325 mg/day or less) to remain on a stable dose throughout the study and to refrain from any aspirin dose 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 in PB-Saline (2 mL) administered IA.

Reference therapy, dose and mode of administration:
Not applicable

Duration of treatment:

Subjects who fulfilled entry criteria and consented were enrolled for an additional 26-week period following the 6-month Final Visit of TREAD-20. Responders did not receive any additional treatment, but had 2 additional follow-up visits at Month 9 and Month 12 after the TREAD-20 BL visit. Non-responders received 3 IA injections at the TREAD-20 Final Visit (EXT BL), at Week 1 (Week 27 from TREAD-20 BL), and at Week 2, and then returned for a follow-up visit at Month 3 (Week 39 from TREAD-20 BL) and Month 6 (Week 52 from TREAD-20 BL).

Criteria for evaluation:

Efficacy:

The primary efficacy variable for responders was reduction in pain as assessed by the subject's evaluation of VAS (100-mm scale) knee pain after a 50-FT walk at 9 months after TREAD-20 BL (3 months after EXT BL) for the 3 IA injections compared with PB-Saline control.

The primary efficacy variable for non-responders was reduction in pain as assessed by the subject's evaluation of VAS knee pain after a 50-FT walk at 3 months after the EXT BL. The intent-to-treat (ITT) population consisted of all subjects enrolled in EXT.

The secondary efficacy variable for responders was reduction in pain assessed by the subject's evaluation of VAS knee pain after a 50-FT walk up to 12 months after TREAD-20 BL (6 months after EXT BL).

The secondary efficacy variable for non-responders was reduction in pain assessed by the subject's evaluation of VAS knee pain after a 50-FT walk up to 6 months after the EXT BL.

Safety:

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

Statistical methods:

For responders, VAS score and improvement from the EXT BL were summarized for the Month 3 and Month 6 visits (Month 9 and Month 12 from TREAD-20 BL, respectively). Additionally, VAS scores and improvements from the TREAD-20 BL were summarized for the TREAD-20 visits (Month 1 through Month 6) to evaluate the full response profile. These data were also presented graphically.

For non-responders, VAS score and improvement from the EXT BL were summarized for the Month 3 and Month 6 visits. Additionally, VAS scores and improvements from the TREAD-20 BL were summarized for the TREAD-20 visits (Month 3 and Month 6) to compare responses with the 3-injection regimen following initial treatment with HYALGAN®or PB-Saline during TREAD-20 and repeat treatment with HYALGAN® in EXT. These data were also presented graphically.

For the supportive efficacy variables, Western Ontario and McMaster Universities Arthritis Index (WOMAC) values (pain score, domain scores, total score) and improvement from the TREAD-20 BL were summarized for the Month 3 and Month 6 EXT visits. Additionally, WOMAC values and improvements from the TREAD-20 BL were summarized for the Month 3 and Month 6 TREAD-20 visits. Patient's Global Assessment was summarized by visit, including selected TREAD-20 visits. Rescue medication use (average number of tablets per day) was calculated and summarized for the length of each subject's participation in both TREAD-20 and EXT. For responders, the time from the third injection date in TREAD-20 to the end of the first response for 20% improvement from BL (BL_{20}), 50% improvement from BL (BL_{50}), and 70% improvement from BL (BL_{70}) was compared between the 2 TREAD-20 treatment groups using summary statistics and survival plots. For non-responders, the time from the third injection in EXT to the end of the first response for BL_{20}, BL_{50} and BL_{70} was compared between and across the TREAD-20 treatment groups. Subjects completing the study or discontinuing from the study while still maintaining a response were considered censored observations with time equal to (last visit date) – (third injection date) + 1.

After database lock, a per-protocol (PP) population was defined as those subjects who were in the PP population of TREAD-20 and who did not violate the EXT protocol in any fundamental manner. An independent, blinded review of concomitant medication use was conducted by an experienced physician to objectively determine appropriate subjects qualifying for inclusion in the PP population. Description of subject disposition and analysis of the primary efficacy endpoint was conducted on this PP population.

All AEs were coded and tabulated by system/organ class and individual effect within system using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Serious AEs 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 40 subjects were enrolled into the study, 17 responders and 23 non-responders. Among the responders, 9 subjects were treated with HYALGAN® and 8 subjects were treated with PB-Saline during TREAD-20. Among the non-responders, 9 were treated with HYALGAN® during TREAD-20 and 14 were treated with PB-Saline. A total of 22 non-responders completed all 3 injections of treatment. A total of 8 responders completed all follow-up visits; for 8 of 9 subjects who did not complete all follow-up visits, the primary reason for not completing was that the Visit #14 data were not collected due to the delay in implementing the protocol amendment that defined EXT. Among the non-responders, a total of 18 subjects completed all follow-up visits; the primary reasons for not completing all follow-up visits were non-serious AEs and subject withdrawal.

All 40 subjects enrolled in the study were included in both the ITT and Safety populations.

Efficacy results:

For the primary and secondary endpoints, pain relief for responders was similar across treatment groups at Months 9 and 12 from TREAD-20 BL. For non-responders, the pain relief was similar across treatment groups at Months 3 and 6 from retreatment with HYALGAN®. The results for the PP population have very limited usefulness because of the small number of subjects analyzed.

Safety results: The numbers of AEs reported for both responders and non-responders were relatively low and no pattern was evident in the frequency or type of AEs reported within or between responder and non-responder groups. Results of other safety parameters did not indicate any clinically meaningful differences between responder and non-responder groups.
Date of report: 13 November 2008