Clinical Trial Results Summary
Study AUX-CC-854

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| **Name of Sponsor/Company:** Auxilium Pharmaceuticals, Inc. | |
| **Name of Finished Product:** AA4500 | |
| **Name of Active Ingredient:** Collagenase clostridium histolyticum | |
| **Title of Study:** A Phase 3, Open-Label Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Advanced Dupuytren's Disease | |
| **Investigators:** Multicenter | |
| **Study center(s):** 20 sites in the United Kingdom, Switzerland, Australia, Sweden, Denmark, and Finland participated in the study. | |
| **Publications (reference):** None. | |
| **Studied period:** 9 months<br>Date first subject enrolled: 21-Sep-2007<br>Last subject completed: 19-Dec-2008 | **Phase of development:**<br>Phase 3 |
| **Objective:** The objective of this study was to evaluate the efficacy and safety of up to five injections of AA4500 0.58 mg (maximum three injections per joint) in reducing the degree of contracture (flexion deformity) in multiple joints of subjects with Dupuytren's contracture. | |
| **Methodology:** This nine-month, open-label study investigated subjects who had a diagnosis of advanced Dupuytren's disease that resulted in a fixed-flexion deformity of at least one finger, other than the thumb, that was ≥ 20° as measured by finger goniometry and was suitable for injection and evaluation. Before treatment, the investigator evaluated all fingers (excluding thumb) of both hands and prioritized the joints to be treated.<br>The 386 subjects enrolled in this study were eligible to receive a maximum of five injections of AA4500 0.58 mg, with individual joints receiving a maximum of three injections. During the study, subjects were followed for efficacy and safety on Days 1, 7, and 30 after each injection, with injections separated by 30 days. All subjects had follow-up visits for the determination of efficacy and safety on Day 90, Month 6, and Month 9. | |
| **Number of subjects (planned and analyzed):** 240 subjects were planned; 386 subjects were analyzed. A total of 589 Dupuytren's cords were treated in this study. | |
| **Diagnosis and main criteria for inclusion:** Healthy male or female subjects ≥ 18 years of age with a diagnosis of Dupuytren's contracture with a fixed-flexion (ie, ≥ 20º but ≤ 80º for PIP joint; ≥ 20º but ≤ 100º for MP joint) deformity of at least one finger, other than the thumb, which was caused by a palpable cord. | |
| **Test product, dose and mode of administration, batch number:** AA4500 0.58 mg injected directly into the Dupuytren's cord, after reconstitution with sterile diluent (0.9% NaCl containing 2 mM calcium chloride). The volume of injection was 0.25 mL for MP joints and 0.20 mL for PIP joints. Lot numbers were FIN-0355, FIN-0366 and FIN-0358 for AA4500 and FIN-0322 and FIN-0265 for diluent. | |
| **Duration of treatment:** Subjects could have received up to five injections (Days 0, 30, 60, 90, and 120). Each joint could have received up to three injections. | |
| **Reference therapy, dose and mode of administration, batch number:** None. | |
| **Criteria for evaluation:**<br>**Efficacy:** The following parameters were measured in order to establish clinical effectiveness of AA4500: reduction in contracture to 5° or less, category of time to reach reduction in contracture to 5° or less, | |

clinical improvement, percentage change from baseline contracture, range of motion (ROM), physician and subject global assessments, and investigator-determined recurrence.

**Safety:** Safety was evaluated through the monitoring of adverse events (AEs), clinical laboratory evaluation, vital signs, immunogenicity, and hand grip strength.

**Statistical Methods:**

**Efficacy:**

Population: The intent-to-treat (ITT) population was defined as all subjects who received ≥ 1 injection. All efficacy and safety analyses were based on the ITT population.

*Definitions:*

Reduction in contracture to 5° or less: Reduction in contracture to 5° or less was measured by finger goniometry (neutral zero method) at the visit 30 days after an injection. If the Day 30 visit was missing, the last evaluation carried forward completed post-injection (Day 1 or Day 7) was used to determine reduction in contracture to 5° or less.

Category of time to reduction in contracture to 5° or less: Nominal visit day which was the first visit for which reduction in contracture to 5° or less was achieved and maintained through Day 30 of the injection.

Clinical improvement: A clinical improvement was defined as a ≥ 50% reduction from baseline in contracture after an injection.

Finger range of motion: Difference between the finger extension angle and finger flexion angle expressed in degrees.

Recurrence: Recurrence was evaluated for joints that achieved a reduction in contracture to 5° or less as measured by finger goniometry within 30 days after an injection during the nine-month study period. The investigator determined there was recurrence when the joint contracture increased to at least 20° and had a palpable cord. The recurrence was recorded as an AE.

The following were measured for each efficacy parameter:

- Reduction in contracture to 5° or less (number and percentage achieving by joint type and joint injection number; average number of injections per joint and average number of injections per successful joint [mean, median, standard deviation [SD], minimum, and maximum]);
- Category of time to reach reduction in contracture to 5° or less (number and percentage by success day and joint type);
- Clinical improvement (number and percentage improving by joint type and joint injection number);
- Percentage change from baseline in contracture (N, mean, median, SD, minimum and maximum) within joint type by joint injection number (first and last injections only);
- Change from baseline in ROM (N, mean, median, SD, minimum and maximum) within joint type by joint injection number (first and last injections only)

Summaries of joints not achieving reduction in contracture to 5° or less and the number of finger extensions (n, %) were provided.

At screening, a frequency summary was presented of the physician's and subject's assessment of overall severity of the subject's Dupuytren's disease. At Month 9, a frequency summary by total number of joints treated and overall was presented for the physician's assessment of overall severity and improvement relative to baseline, subject's satisfaction with treatment, as well as subject's assessment of degree of improvement.

All fixed flexion contracture measures for the joint from the first injection into the joint until the last joint measurement and the number of days from the Day 30 visit where the joint was a success until the first visit where the recurrence was measured were listed.

**Safety:**

Treatment-emergent AEs (TEAEs) are AEs with a start date equal to or after the first injection of study drug. Treatment-emergent AEs are presented by frequency, severity, and relationship to study drug. Treatment-emergent AEs are presented overall (first injection until the end of the study), by treatment period (ie, first injection until the Day 30 visit after the last injection), and by post-treatment period (ie, form the day after the Day 30 visit after the last injection until the end of the study).

Adverse events of interest were those considered related to study drug occurring within 30 days of injection, and were determined by the medical monitor. These AEs of interest were summarized by injection number, frequency, duration, and injection cycle study day (injection day, manipulation day, and post-manipulation day).

Vital signs were summarized with descriptive statistics (N, mean, median, SD, minimum, and maximum) for actual and change from baseline. Vital signs taken on the injection day were summarized across the different time points (immediately post-dose, five minutes, 10 minutes, 20 minutes, 30 minutes, 60 minutes, and pre-discharge). The baseline value was the vital sign measure immediately pre-dose for that injection. The summary was done by time point for each injection number. Vital signs were also summarized at Day 90, Month 6, and Month 9.

Clinical laboratory data (chemistry and hematology) were summarized with descriptive statistics (N, mean, median, standard deviation, minimum, and maximum) at Month 9 for actual and change from baseline. Clinically significant laboratory values were summarized by treatment group (number and percentage) and listed.

Hands were identified as primary for the first hand injected and secondary for the second hand injected (if necessary). The summary included the grip strength (n, mean, median, SD, minimum, and maximum) and the change from baseline.

**SUMMARY**

**EFFICACY RESULTS:**

**Primary Measure of Efficacy, Reduction in Fixed-Flexion Contracture to 5° or Less**

- After the first injection of AA4500, 48.2% of all joints (ie, 59.2% of MP joints and 32.8% of PIP joints) had a reduction in contracture to 5° or less. After the last injection of AA4500, 58.4% of all joints (ie, 70.8% of MP joints and 41.0% of PIP joints) had a reduction in contracture to 5° or less.
  - In this study, 23.0% of MP joints and 49.2% of PIP joints did not have a reduction in contracture to 5° or less and did not receive up to three injections of AA4500. The reason most commonly cited by the investigator was “no palpable cord to inject.” The most common reasons for residual contracture were joint stiffness and adjunct cords.
- MP and PIP joints of lesser baseline severity (ie, ≤ 50° and ≤ 40°, respectively) showed a greater response to treatment with AA4500 than did more severely contracted joints (reduction in contracture: MP-low, 84.9% and MP-high, 35.7%; PIP-low, 56.4% and PIP-high, 28.4%).
- AA4500 was effective in reducing contractures to 5° or less in MP joints of both the ring (71.3%) and little (68.2%) fingers, both of which are the most commonly affected fingers among subjects with advanced Dupuytren’s disease.

**Other Measures of Efficacy**

- After the last injection of AA4500, 91% of MP joints had a reduction in contracture to ≤ 25°, a benchmark for consideration of surgery, which would make the contracture ineligible for surgery. Approximately 70% of PIP joints had a reduction in contracture to ≤ 25° after the final injection of AA4500, again possibly negating the need for surgery.

- The majority of MP (90.1%) and PIP (63.1%) joints showed clinical improvement within 30 days after the last injection of AA4500.
- On average, contracture had been reduced from 41.8° to 7.7° (mean percent reduction of 85.2%) for MP joints and from 46.4° to 18.9° (mean percent reduction of 61.6%) for PIP joints after the final injection of AA4500.
- Full flexion, which ranged from 25° to 130° at baseline, was virtually unaffected by AA4500. The improvement in ROM in both MP and PIP joints after treatment with AA4500 resulted from the improvement in the full extension angle, which allowed for greater extension of the affected finger.
- At the end of the treatment, Dupuytren's contracture was very much improved or much improved in the majority of subjects (78.5%), as determined by the investigator.
- At the end of treatment, the majority of subjects (87.3%) were very or quite satisfied with their treatment.
- Eight (2.3%) of the 343 joints that achieved a reduction in contracture to 5° or less had a recurrent contracture. Five of the eight recurrences affected PIP joints.

**SAFETY RESULTS:**

- Most TEAEs were related to injection of AA4500 or to the finger extension procedure to facilitate cord disruption (ie, TEAEs of interest) and were moderate in severity.
- Overall, 97.9% (378/386) of subjects treated with AA4500 reported at least one TEAE during the treatment period (first injection to 30 days after the last injection of AA4500).
- Approximately 39% of subjects reported TEAEs during the posttreatment period; less than 10% of these events were related to study drug.
- Treatment-emergent AEs of interest that occurred in approximately one quarter or more subjects included edema peripheral, contusion, pain in extremity, injection site pain, injection site hemorrhage, injection site swelling, and tenderness.
- The majority of TEAEs of interest reported by subjects either began on the day of injection or on the day of the finger extension procedure to facilitate cord disruption and resolved without intervention before the next scheduled injection of AA4500.
- No increase in the frequency or duration of any reported TEAE of interest was observed as the number of injections increased from one to five.
- Subjects who received multiple injections of AA4500 usually reported specific TEAEs of interest only once or twice across injections. The exception was edema peripheral, which tended to occur after each injection of AA4500.
- One subject died during the study due to acute myocardial infarction that was considered by the reporting investigator to be not related to study drug.
- Thirty-nine subjects experienced treatment-emergent SAEs during the study, only two of which were considered by the reporting investigators to be related to study drug (deep vein thrombosis and tendonitis).
- Two subjects had SAEs of prostate carcinoma and gastrointestinal carcinoma, respectively, which led to discontinuation from the study.
- Mean changes in laboratory and vital sign parameters were small and not considered clinically meaningful.
- Hand grip strength was unaffected by treatment with up to five injections of AA4500. No adverse trends were observed for the primary or secondary hand.

- Although most subjects had positive antibodies to AUX-I and AUX-II after receiving up to five injections of AA4500, no subject reported an AE that was indicative of a significant systemic immunological response to AA4500.