Study Number: AUX-CC-860 Year 5

Title of Study: Year 5 Final Annual Report of A Long-Term Follow-Up of Subjects Treated With AA4500 in Studies AUX-CC-854, AUX-CC-856, AUX-CC-857/AUX-CC-858, and AUX-CC-859

Investigators: Multicenter

Study center(s): United States, Australia, United Kingdom, Denmark, Finland, and Sweden

Publications (reference): None.

Studied period (years): approximately 5 years since first AA4500 injection Date first Year 5 visit: 04 January 2012 Date last Year 5 visit: 09 April 2013	**Phase of development:** Phase 3

Objectives: The objectives of the this study were:

- To assess the recurrence of contracture in joints that had a reduction in contracture to 5° or less at the Day 30 evaluation after the last injection of AA4500 in one of the Auxilium sponsored studies (AUX-CC-854, AUX-CC-856, AUX-CC-857/AUX CC 858, or AUX-CC-859)
- To assess the non-durability of response in joints with measurable improvement in contracture (ie, did not have a reduction to 5° or less at the Day 30 evaluation after the last injection, but did have a reduction in baseline contracture of at least 20° at the Day 30 evaluation after the last injection of AA4500 or at the final evaluation) in one of the Auxilium-sponsored studies (AUX-CC-854, AUX-CC-856, AUX CC 857/AUX-CC-858, or AUX-CC-859)
- To assess the progression of disease in joints that either were not treated or not effectively treated with AA4500 (ie, did not have a reduction in contracture of at least 20° at either the Day 30 evaluation after the last injection or at the final evaluation) in one of the Auxilium-sponsored studies (AUX-CC-854, AUX-CC-856, AUX CC 857/AUX-CC-858, or AUX-CC-859)
- To assess the long-term safety of AA4500.

Methodology: This was a non-treatment Year 2 to Year 5 follow-up of subjects who received AA4500 in the 9-month open-label studies (AUX-CC-854 and AUX-CC-856) or the 12-month double-blind with open-label extension studies (AUX-CC-857/AUX-CC-858 and AUX-CC-859) sponsored by Auxilium Pharmaceuticals, Inc. After completion of 1 of the above mentioned studies, subjects were enrolled into this study and were followed once a calendar year for 4 consecutive years (Years 2 through 5 after injection) with at least 6 months between consecutive visits. The end of the study was defined as the time that the final subject completed the Year 5 follow-up visit, or earlier if the subject discontinued participation before Year 5. Of note, Study AUX-CC-862 started during the Year 4 follow-up period.

Subjects who experienced recurrence of contracture in one or more effectively treated joints may have been enrolled in AUX-CC-862 after the investigator determined subject eligibility and after informed consent was obtained. Once informed consent was obtained for participation in AUX-CC-862, the investigator could have withdrawn the subject from this study.

During the enrollment visit, a complete medical history was recorded for each subject. Before the Year 2 follow-up visit, investigators were provided with the relevant joint measurements for all 16 joints (reference values) and a sponsor-defined joint classification for each joint for subjects in one of the above mentioned studies. At each yearly follow-up visit, joints were assessed for recurrence, non-durability of response, progression of disease, and subject-reported adverse events (AEs) relative to their last assessment. Blood samples for the determination of antibodies to clostridial type I collagenase, *colG* (AUX-I) and clostridial type II collagenase, *colH* (AUX-II) were collected at Year 2 through Year 5.

Number of subjects (planned and analyzed): The sample in this study was limited to subjects who were treated with AA4500 in the AUX-CC-854, AUX-CC-856, AUX-CC-857/858, or AUX-CC-859 studies. A total of 950 subjects met this definition (including the 1 subject randomized to placebo who erroneously received an injection of AA4500). A total of 645 subjects enrolled in the study and 644 subjects had at least one post-enrollment evaluation.
Diagnosis and main criteria for inclusion: Subjects must have received at least 1 injection of AA4500 in one of the Auxilium-sponsored studies (AUX-CC-854, AUX-CC-856, AUX-CC-857/AUX-CC-858, or AUX-CC-859) and had at least one fixed flexion contracture measurement after treatment with AA4500.
Test product, dose and mode of administration, batch number: Any subject may have received commercially available AA4500 (XIAFLEX®) to treat any joints with an already existing Dupuytren's contracture or a recurrent Dupuytren's contracture. A total of 66 subjects received at least 1 injection of XIAFLEX.
Reference therapy, dose and mode of administration, batch number: Not applicable.
Duration of treatment: No study drug was administered in this study.
Criteria for evaluation: **Efficacy:** The primary response variable was the investigator's assessment of recurrence/non-durability of response/progression for a joint. **Safety:** Safety was evaluated through the monitoring of adverse events (AEs) and immunogenicity.
Statistical Methods: **Efficacy:** The 860 Study Population for Year 5 was defined as all subjects enrolled in the current study who had at least one post-enrollment evaluation. The primary response variable was the investigator's assessment of recurrence/non-durability of response/progression for a joint as defined below.

Joint Classification From Previous Study	Criteria for Evaluation	Joint Classification in This Study
Recurrence in previous study	No evaluation required.	Recurrence
Effectively treated with AA4500 (ie, correction to 5° or less at the Day 30 evaluation after the last injection)	The joint contracture increased by at least 20° compared with the reference value and a palpable cord is present, **or** The joint being evaluated underwent medical[a] or surgical[b] intervention primarily to correct a new or worsening Dupuytren's contracture in that joint.	Recurrence
Measurably improved after treatment with AA4500 (ie, did not have a reduction to 5° or less at the Day 30 evaluation after the last injection, but did have a reduction in baseline contracture of at least 20° at the Day 30 evaluation after the last injection or at the final evaluation) *(measurably improved joints are referred to as 'joints with a 20° reduction' in the statistical tables)*	The joint contracture increased by at least 20° compared with the reference value and a palpable cord is present, **or** The joint being evaluated underwent medical[a] or surgical[b] intervention primarily to correct a new or worsening Dupuytren's contracture in that joint.	Non-durability of response
Not effectively treated with AA4500 (ie, did not have a reduction in contracture of at least 20° at either the Day 30 evaluation after the last injection or at the final evaluation)	The joint contracture increased by at least 20° compared with the reference value and a palpable cord is present, **or** The joint being evaluated underwent medical[a] or surgical[b] intervention primarily to correct a new or worsening Dupuytren's contracture in that joint.	Progression
Not treated		
Not previously evaluated	A joint contracture of at least 20° and a palpable cord is present, **or** The joint being evaluated underwent medical[a] or surgical[b] intervention primarily to correct a new or worsening Dupuytren's contracture in that joint.	Progression

[a] Commercially available XIAFLEX
[b] Fasciotomy, fasciectomy, dermofasciectomy, needle aponeurotomy, or amputation

Analyses of worsening of successful joints, worsening of measurably improved joints, and worsening of responsive joints, using a definition of ≥30° increase from baseline in fixed flexion contracture for worsening, were performed.

Safety:

Treatment-related AEs are any AEs with a relationship to study medication given in the predecessor study of possible, probable, or missing. Adverse events were summarized overall, including summaries of treatment-related AEs, SAEs, AEs leading to discontinuation, deaths, and AEs of moderate or severe intensity.

Summaries of preferred terms provided a count of the number of subjects with at least one occurrence of the AE preferred term. A summary of preferred term by maximum severity was also generated. A separate summary of preferred terms was generated for all treatment-related AEs.

AUX-I and AUX-II titer levels were analyzed by yearly visit window. The summary also includes the last available immunogenicity sample from the previous studies (Year 1). If two samples were taken within the same immunogenicity visit window (except for Year 1), then the later sample was used in the analysis.

The immunogenicity analysis summarized the number of subjects with an immunogenicity sample at each visit window, the percentage of subjects with a positive sample, and the average titer level (mean, median, standard deviation, minimum, and maximum) of the positive samples. The titer levels were log transformed prior to being summarized.

An additional analysis of immunogenicity divided subjects into cohorts by the total number of AA4500 injections received and then looked at the average titer level at each visit window for each cohort.

SUMMARY

EFFICACY RESULTS:

The distribution of joint subgroups at the end of the previous studies and at Year 2, Year 3, Year 4, and Year 5 of the current study is summarized below.

Joint Subgroup by Year (860 Study Population)

Parameter	Previous Studies	AUX-CC-860 Year 2	AUX-CC-860 Year 3	AUX-CC-860 Year 4	AUX-CC-860 Year 5
MP+PIP, n (%)	N=15200	N=10256	N=9648	N=8624	N=7216
Successfully treated[a]	838 (5.5)	622 (6.1)	593 (6.1)	527 (6.1)	413 (5.7)
Measurably improved[b]	444 (2.9)	300 (2.9)	271 (2.8)	249 (2.9)	211 (2.9)
Not effectively treated[c]	286 (1.9)	156 (1.5)	144 (1.5)	135 (1.6)	112 (1.6)
Not treated	13632 (89.7)	9178 (89.5)	8640 (89.6)	7713 (89.4)	6480 (89.8)
MP,[d] n (%)	N=7600	N=5128	N=4824	N=4312	N=3608
Successfully treated[a]	618 (8.1)	450 (8.8)	429 (8.9)	381 (8.8)	304 (8.4)
Measurably improved[b]	221 (2.9)	152 (3.0)	141 (2.9)	128 (3.0)	108 (3.0)
Not effectively treated[c]	81 (1.1)	45 (0.9)	41 (0.8)	40 (0.9)	30 (0.8)
Not treated	6680 (87.9)	4481 (87.4)	4213 (87.3)	3763 (87.3)	3166 (87.7)
PIP,[e] n (%)	N=7600	N=5128	N=4824	N=4312	N=3608
Successfully treated[a]	220 (2.9)	172 (3.4)	164 (3.4)	146 (3.4)	109 (3.0)
Measurably improved[b]	223 (2.9)	148 (2.9)	130 (2.7)	121 (2.8)	103 (2.9)
Not effectively treated[c]	205 (2.7)	111 (2.2)	103 (2.1)	95 (2.2)	82 (2.3)
Not treated	6952 (91.5)	4697 (91.6)	4427 (91.8)	3950 (91.6)	3314 (91.9)

[a] Joints previously treated with AA4500 and had a fixed flexion contracture measurement of 0° to 5° on Day 30 after the last injection. This includes joints reported as recurring in a previous study.

[b] Joints previously treated with AA4500 that had a reduction from baseline contracture of at least 20° at either the Day 30 visit after the last injection of AA4500 or at the final visit.

[c] Joints previously treated with AA4500 that were neither successful nor had a 20° reduction.

[d] Percentages based on the total number of MP joints assessed at the yearly visit.

[e] Percentages based on the total number of PIP joints assessed at the yearly visit.

The Year 5 results of this long-term study in subjects with Dupuytren's contracture demonstrate:

- The Year 5 cumulative nominal rate of recurrence through 1825 days of follow-up was 46.7% (291/623) for joints that had a reduction in contracture to 5° or less at the Day 30 evaluation after the last injection of AA4500 in one of the previous studies.

- The rate of increase of recurrence of contracture in joints successfully treated with XIAFLEX in a previous Auxilium-sponsored study slowed over the 5 year follow-up period (Year 2: 19.6%; Year 3: 35% [15.4% increase from Year 2]); Year 4: 42.1% [7.1% increase from Year 3]; Year 5: 46.7% [4.6% increase from Year 4]).
- The Year 5 cumulative nominal rate of recurrence was lower for MP joints than PIP joints (39.5% [178/451] vs. 65.7% [113/172]). PIP joints with low baseline severity had a lower rate of recurrence (62.8% vs. 72.5%) than PIP joints with high baseline severity.
- Recurrent MP joints at Year 5 show an increase in fixed flexion contracture that is still less than baseline degree of contracture (Year 5: 26.7° versus baseline: 37.5°. A similar pattern of results was observed for recurrent PIP joints (Year 5: 34.8° versus baseline: 40.1°).
- The Year 5 cumulative nominal rate of non-durability by 1825 days of follow-up was 59.9% (181/302) for joints with measurable improvement in contracture (ie, did not have a reduction to 5° or less at the Day 30 evaluation after the last injection; but did have a reduction in baseline contracture of at least 20° at the Day 30 evaluation after the last injection of AA4500 or at the final evaluation) in one of the previous studies. The Year 5 cumulative nominal rate of non-durability was lower for MP joints than PIP joints (50.0% [76/152] vs. 70.0% [105/150]).
- The Year 5 cumulative nominal rate of progression by 1825 days of follow-up was 51.9% (81/156) for joints not effectively treated with AA4500 (ie, did not have a reduction in contracture of at least 20° at either the Day 30 evaluation after the last injection or at the final evaluation) in one of the previous studies. The Year 5 cumulative nominal rate of progression was similar for MP joints and PIP joints (53.3% [24/45] vs. 51.4% [57/111]).
- On average, 3 of the 16 joints (18.8%) evaluated in each study subject were affected with Dupuytren's contracture in the Auxilium studies. Thus, the majority of the untreated joints in the study had no evidence of disease. Among all untreated joints in a previous study (N=9179), a new or worsening Dupuytren's contracture with a palpable cord (ie, progression) was observed in 7.9% of joints by 1825 days of follow-up since either the screening measurement or the last measurement in the previous study, whichever was lower. The Year 5 cumulative nominal rate of progression by Day 1825 was similar among MP joints (8.5%) and PIP joints (7.3%).
- Year 5 cumulative nominal rates for worsening of successful joints (31.8%), worsening of measurably improved joints (42.7%), and worsening of responsive joints (35.4%), using a definition of ≥30° increase from baseline in fixed flexion contracture for worsening, were lower than rates utilizing a 20° definition at Year 5. These analyses were performed in an effort to further understand the XIAFLEX recurrence data.
- Of the 623 joints successfully treated in a previous study, only 105 (16.9%) had a medical or surgical intervention by the Year 5 visit.

SAFETY RESULTS:

The percentage of subjects who had at least one AE since the signing of informed consent for this study and prior to the first injection of commercially available AA4500 (pre-XIAFLEX) was 54.3%. Adverse events reported for ≥2.0% of these subjects were osteoarthritis (4.7%), cataract (3.9%), hypertension (3.3%), atrial fibrillation (3.0%), hypercholesterolaemia (2.2%), and basal cell carcinoma (2.0%). These AEs are consistent with and common in the age of the study population.

A total of 66 subjects received at least one injection of commercially available AA4500 (post-XIAFLEX). The percentage of these subjects who had at least one AE after receiving commercially available XIAFLEX was 42.4%. Adverse events reported for ≥10.0% of these subjects were oedema peripheral (12.1%) and contusion (10.6%). These events are consistent with the safety profile of XIAFLEX. The safety profile demonstrated in the subjects who received commercial XIAFLEX following the start of AUX-CC-860 is consistent with that demonstrated in the earlier clinical studies of AA4500.

Most AEs were mild or moderate in severity and none were considered by the investigator to be related to study drug.

Ten subjects (nine pre-XIAFLEX and one post-XIAFLEX) died as of the Year 5 visit. Adverse events leading to death included colorectal cancer (preferred term: colorectal cancer), fatal injuries from a motor vehicle accident (preferred term: accidental death), cerebral hemorrhage (preferred term: cerebral haemorrhage), B cell lymphoma (preferred term: B-cell lymphoma), worsening of small vessel vasculitis (preferred term: vasculitis), hepatic failure (preferred term: hepatic failure), acute myeloid leukemia (preferred term: acute myeloid leukaemia), liver adenocarcinoma (preferred term: hepatic neoplasm malignant), kidney cancer and metastasis to lungs (preferred terms: renal cancer and metastases to lung, respectively), and adenocarcinoma of the gallbladder (preferred term: gallbladder cancer). None of these events were considered by the investigator to be related to study drug.

A total of 103 subjects (100 pre-XIAFLEX and three post-XIAFLEX) experienced at least one SAE (including those with an outcome of death), none of the events leading to death were considered by the investigator to be related to study drug.

The maximum titer level for AUX-I and AUX-II increased with increasing number of injections and reached a plateau at four or more injections. At Year 5, mean log titers for AUX-I and AUX-II were similar to that observed in previous years.