

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125338

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA: 125338

Drug Name: Collagenase Clostridium Histolyticum

Indication: Treatment of advanced Dupuytren's disease

Applicant: Auxilium Pharmaceuticals

Date(s): Stamp Date: 2/27/2009
PDUFA Date: 8/29/2009

Review Priority: Priority

Biometrics Division: DBII

Statistical Reviewer: Jonathan Norton

Concurring Reviewers: Dionne Price
Thomas Permutt

Medical Division: Division of Anesthesia, Analgesia, and Rheumatology Products

Clinical Team: Eric Brodsky
Sarah Okada

Project Manager: Margarita Tossa

Keywords: benefit-risk, clinical studies, Cochran-Mantel-Haenszel, generalizability, multiple endpoints, subgroup analyses

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS.....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES.....	3
1.3 STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION	4
2.1 OVERVIEW	4
2.2 DATA SOURCES	5
3. STATISTICAL EVALUATION	5
3.1 EVALUATION OF EFFICACY	5
3.2 EVALUATION OF SAFETY	17
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	18
4.1 GENDER, RACE AND AGE	18
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	18
5. SUMMARY AND CONCLUSIONS.....	19
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	19
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	20
5.3 REVIEW OF THE PROPOSED LABEL	20
SIGNATURE LIST	28

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Applicant seeks to have collagenase clostridium histolyticum, referred to herein as CCH, approved for treatment of advanced Dupuytren's disease. The results of two pivotal studies strongly support a finding that CCH is efficacious for treatment of this disease. The Applicant submitted an additional Phase 3 study which showed positive results, but I recommend that this study not be included in the labeling.

1.2 Brief Overview of Clinical Studies

DUPY-303 was a double-blind, placebo-controlled study of CCH which enrolled 35 subjects at a single center in the United States. In order to qualify for the study, patients had to have a fixed-flexion contracture of 20° or more in at least one finger. Both metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints could be treated. The investigator examined both hands of each subject and chose a primary joint to treat. The primary joints for the 35 subjects were randomized to the follow treatment arms: 23 in the CCH arm, 12 in the placebo arm. Study medication was then injected into the cord corresponding to the primary joint. The primary efficacy endpoint was clinical success, defined as a reduction in contracture to 5° or less at Day 30 after the last injection. The primary joint could be injected up to three times until clinical success was achieved. It was re-examined one day, one week, two weeks, and one month after each injection. "Supportive" efficacy variables included the change from baseline in contracture, change in range of motion (ROM), and change in grip strength. Other efficacy variables included time to clinical success and duration of effect.

The design of the other two studies was similar to that of DUPY-303. Study AUX-CC-857 enrolled 308 subjects in 16 centers in the United States. Of the enrolled subjects, 204 were randomly assigned to the CCH arm and 104 were assigned to the placebo arm. Study AUX-CC-859 enrolled 66 subjects in five sites in Australia. Of the enrolled subjects, 45 were assigned to CCH and 21 to placebo.

1.3 Statistical Issues and Findings

The three Phase 3 studies provide overwhelming evidence for an effect of treatment with CCH on the primary endpoint. In these studies the success rate of treatment ranged from 44% to 91%; in comparison, the placebo response rate was no more than 5% in any study (excluding patients who were erroneously given active treatment.) Findings from the secondary endpoints were supportive. Although CCH was effective for both MP and PIP joints in two studies, the largest study showed a significantly higher response rate for MP joints.

Dr. Eric Brodsky raised concerns about the conduct of Study 303. He noted that the study was conducted at a single site by investigators who had a substantial financial interest in the outcome. Also, there were no reported protocol deviations. In response to an information request, the

Applicant stated, “No comprehensive review of the database for DUPY-303 was planned nor carried out for determination of protocol deviations...” I share Dr. Brodsky’s concerns and do not consider the study pivotal.

A particular question in regard to this product is whether successful use is related to the specialized training of the physician performing the injections. Unfortunately, the three Phase 3 studies do not provide adequate comparative data to make any conclusions about the effect of training. Of the 272 subjects injected with CCH in the Phase 3 trials, all but 11 were treated by hand or general orthopedic surgeons.

2. INTRODUCTION

2.1 Overview

The Applicant seeks to have collagenase clostridium histolyticum, referred to herein as CCH, approved for treatment of advanced Dupuytren’s disease. In this disease, also known as Dupuytren’s contracture, excess collagen forms a cord connecting the affected joint with a hard node in the palm of the hand. Formation of these cords results in the patient not being able to completely extend the affected fingers. CCH is injected directly into the cord, and is believed to work by breaking down collagen in the cord.

The Applicant had an end-of-phase 2 teleconference with the Center for Biologics Evaluation and Research (CBER) on September 21, 2001. In this meeting, CBER asked the Applicant to assess the effectiveness of repeat dosing and the durability of response out to twelve months.

Following a reorganization within FDA, CCH fell within the purview of the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) in the Center for Drug Evaluation and Research. In a meeting with the Applicant on April 4, 2006, DAARP indicated that last-observation-carried-forward imputation would be acceptable in a proposed Phase 3 study, with a “non-responder” imputation suggested as a sensitivity analysis. DAARP also stated the Applicant would be required to follow patients for 12 months after the first injection to assess safety and efficacy. This requirement is satisfied in the current submission. In a pre-BLA meeting on September 15, 2008, DAARP stated that studies DUPY-303, AUX-CC-857, and AUX-CC-859 appeared to be adequate to support a BLA submission. These studies are summarized in Table 1.

Table 1: Phase 3 Studies (Source: Reviewer)

Study ID	Study Design	Sample Size	Primary Endpoint and Applicant's Results
DUPY-303	Single-center, double-blind, randomized, placebo-controlled	35	Reduction of contracture of primary joint to within 5 degrees of normal Treatment superior to placebo (p < .001)
AUX-CC-857	Multicenter, randomized, double-blind, placebo-controlled	308	Reduction of contracture of primary joint to within 5 degrees of normal Treatment superior to placebo (p < .001)
AUX-CC-859	Multicenter, randomized, double-blind, placebo-controlled	66	Reduction of contracture of primary joint to within 5 degrees of normal Treatment superior to placebo (p < .001)

2.2 Data Sources

The electronic version of this BLA can be found at \\cbsap58\M\CTD_Submissions\STN125338.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

DUPY-303

Study Design and Endpoints

DUPY-303 was a double-blind, placebo-controlled study of CCH in patients with advanced Dupuytren's disease. Thirty-five subjects were enrolled at a single center in the United States.

In order to qualify for the study, patients had to have a fixed-flexion contracture of 20° or more in at least one finger. Both metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints

could be treated. The investigator examined both hands of each subject, chose a hand to treat, and then chose the primary, secondary, and tertiary joints. When both the MP and PIP joints of a finger were affected, the MP joint was chosen as primary. Aside from this criterion, the protocol did not specify how the joints were prioritized. Study medication was injected into the cord corresponding to the primary joint. The joint was re-examined one day, one week, two weeks, and one month after each injection. The primary joint could be injected up to three times until a clinical success (defined within) was achieved. The injections were given four to six weeks apart.

The primary joints for the 35 subjects were randomized to the follow treatment arms: 23 in the CCH arm, 12 in the placebo arm. If the primary joint was treated successfully, then the secondary and tertiary joints could also be treated. Each joint was randomized separately, so the same subject could have different blinded treatments on different joints. This review covers only the data from the primary joint. The randomization was stratified by joint type (MP or PIP) using permuted blocks.

The primary efficacy endpoint was clinical success for the primary joint, defined as a reduction in contracture to 5° or less at Day 30 after the last injection. Contraction was measured by finger goniometry using the neutral zero method. The secondary efficacy endpoint was clinical success on the secondary and tertiary joints. “Supportive” efficacy variables included the change from baseline in contracture, change in range of motion (ROM), and change in grip strength. Other efficacy variables included time to clinical success and duration of effect. No adjustment was used for the multiple non-primary endpoints. Subgroup analyses were planned for the MP and PIP joints. The primary analysis set was the intent-to-treat set, defined as all randomized patients.

Patient Disposition, Demographic and Baseline Characteristics

Thirty-five subjects enrolled in the study, all of whom are included in the ITT population for the primary joint. Two subjects in the CCH treatment group were discontinued, one for “failure to follow the appointment schedule” and another when he/she had hand surgery. Table 2 shows the demographics of enrolled subjects.

Table 2: Demographics of Subjects (Source: Reviewer)

	CCH N=23	Placebo N=12	Total N=35
Age			
Mean (SD)	60 (8)	64 (10)	61 (9)
Min, Max	45, 73	48, 81	45, 81
Gender, N (%)			
Male	20 (87%)	8 (67%)	28 (80%)
Female	3 (13%)	4 (33%)	7 (20%)
Race, N (%)			
White	23 (100%)	12 (100%)	35 (100%)

Protocol Deviations

In the section on protocol deviations in the Clinical Study Report, the Applicant simply stated that all subjects met the exclusion and inclusion criteria. In response to an information request, the Applicant stated in e-mail of June 19, 2009 that, "No comprehensive review of the database for DUPY-303 was planned nor carried out for determination of protocol deviations; and as a consequence, no listing of general protocol deviations was generated for this study."

Statistical Methods

The primary efficacy analysis was a Cochran-Mantel-Haenszel (CMH) test for the effect of treatment on clinical success, stratified by joint type. Any missing data was to be imputed using last-observation-carried-forward (LOCF). Separate analyses were also to be performed for each joint type, using Fisher's exact test. The secondary efficacy variables, clinical success in the secondary and tertiary joints, were to be analyzed the same way. The "supportive" variables were to be analyzed using ANCOVA with the baseline value included in the model.

Results and Conclusions

Table 3 shows the results for the primary endpoint of clinical success. The table was provided by the Applicant, but I was able to reproduce the results from both the tabulation and analysis datasets provided in the submission. As the table shows, there were large treatment effects for both MP and PIP joints. The Applicant also reported significant effects of treatment on median time to clinical success, change in degree of contracture, and change in range of motion for the primary joint.

Dr. Eric Brodsky stated that in his opinion this trial should not be considered pivotal. His concerns are that it was conducted at a single site, that the investigators at that site had a substantial financial interest in the outcome (0.2% of net sales), and that there were no reported protocol deviations. As noted earlier, the Applicant did not search for protocol deviations in the available data. I share Dr. Brodsky's concerns.

Table 3: Clinical Success, Overall and By Joint Type (Source: Table 5, Clinical Study Report)

	AA4500 N=23	Placebo N=12
All Primary Joints		
First injection		
N	23	12
Number (%) clinical success	16 (69.6%)	0.0
p-value ^b	<0.001	-
Last injection		
N	23	12
Number (%) clinical success	21 (91.3%)	0.0
p-value ^b	<0.001	-
Average number of injections for success	1.4 (0.7)	-
Mean (SD)	1, 3	-
Min, Max		
Primary MP Joints		
First injection		
N	14	7
Number (%) clinical success	10 (71.4%)	0.0
p-value ^c	0.004	-
Last injection		
N	14	7
Number (%) clinical success	12 (85.7)	0.0
p-value ^c	<0.001	-
Average number of injections for success	1.3 (0.6)	-
Mean (SD)	1, 3	-
Min, Max		
Primary PIP Joints		
First injection		
N	9	5
Number (%) clinical success	6 (66.7)	0.0
p-value ^c	0.031	-
Last injection		
N	9	5
Number (%) clinical success	9 (100.0)	0.0
p-value ^c	<0.001	-
Average number of injections for success	1.6 (0.9)	-
Mean (SD)	1, 3	-
Min, Max		

Data source: Section 14.2; Tables 10, 10.1, and 10.2

MP=metacarpophalangeal; PIP=proximal interphalangeal

^a Clinical success: a reduction in contracture (flexion deformity) to $\leq 5^\circ$ of normal as measured by finger goniometry 30 days after an injection.

^b p-value based on Cochran-Mantel-Haenszel test comparing treatment groups, stratified by joint type.

^c p-value based on the Fisher's exact test comparing treatment groups.

AUX-CC-857

Study Design and Endpoints

AUX-CC-857 was a double-blind, placebo-controlled study which enrolled 308 subjects in 16 centers in the United States. Of the enrolled subjects, 204 were randomly assigned to the CCH arm and 104 were assigned to the placebo arm.

The design was similar to that for DUPY-303. The treatment schedule was slightly different, however: repeat injections were given every 30 days, rather than every 4 to 6 weeks. Also, the protocol was somewhat more precise on how joints should be selected and prioritized, stating that the goal was to “provid[e] the subject with complete functionality of the treated hand.”

As with DUPY-303, the primary endpoint was clinical success after the last injection to the primary joint. Clinical improvement, defined as a reduction in contracture from baseline of at least 50% at day 30, was a secondary endpoint. Other secondary endpoints included percent reduction in contracture from baseline at day 30, change from baseline in ROM at day 30, and time to first achieve and maintain clinical success (which must have been maintained through day 30). The ITT set was defined as all randomized subjects who received at least one injection. The primary analysis population, however, was the modified ITT population. According to the statistical analysis plan, subjects were to be excluded from the modified ITT population either if all of their pre-injection contracture measurements were five degrees or less, or if there were no post-first-injection contracture measurements. This is not an ideal analysis population, but only two subjects were actually excluded.

Randomization was stratified by joint type and baseline contracture severity, using permuted blocks. In this study randomization was by subject; all joints treated during the double-blind period were given the same treatment. There was no separate randomization for each joint as in DUPY-303. The double-blind period lasted for 90 days, and injections were given on days 0, 30, and 60.

Patient Disposition, Demographic and Baseline Characteristics

Table 4, which was provided by the Applicant, shows the disposition of subjects. I was able to reproduce these findings from the analysis datasets. Of the 308 subjects enrolled in the study, all were in the ITT population and 306 were included in the modified ITT population. Table 5 shows the demographics of the subjects in the ITT set.

Table 4: Subject Disposition, ITT Set (Source: Table 6, Clinical Study Report)

	AA4500 N=204	Placebo N=104	Total N=308
Intent-to-treat (ITT)	204 (100.0)	104 (100.0)	308 (100.0)
Modified intent-to-treat ^a	203 (99.5)	103 (99.0)	306 (99.4)
Per protocol ^b	182 (89.2)	91 (87.5)	273 (88.6)
Completed double-blind phase, N (%)	191 (93.6)	100 (96.2)	291 (94.5)
Discontinued double-blind phase, N (%):			
Withdraw consent	4 (2.0)	3 (2.9)	7 (2.3)
Lost to follow-up	4 (2.0)	1 (1.0)	5 (1.6)
Adverse events	3 (1.5)	0	3 (1.0)
Other	2 (1.0)	0	2 (0.6)
Number of injections during double-blind, N (%):			
1	61 (29.9)	4 (3.8)	65 (21.1)
2	46 (22.5)	7 (6.7)	53 (17.2)
3	97 (47.5)	93 (89.4)	190 (61.7)
Number of joints treated during double-blind, N (%):			
Primary	138 (67.6)	102 (98.1)	240 (77.9)
Primary and secondary	49 (24.0)	2 (1.9)	51 (16.6)
Primary, secondary, and tertiary	17 (8.3)	0	17 (5.5)
Total number of joints treated	287	106	393
Days in Study			
N	204	104	308
Mean (SD)	92.2 (18.0)	92.0 (17.9)	92.2 (18.0)
Median	92.0	92.0	92.0
Min, Max	2, 161	2, 149	2, 161

Data source: Table 14.1.1

^a Intent-to-treat subjects were excluded from this population if they did not have fixed-flexion measurements after the first injection or had both screening and Treatment 1, Day 0 fixed-flexion measurements between 0 and 5 degrees.

^b Modified intent-to-treat subjects were excluded from this population if their primary joint: 1) had a baseline contracture less than 20° or greater than 100° for MP (80° for PIP); 2) received incorrect study medication; 3) received reduced number < 3 injections and did not reach clinical success but still had a palpable cord, and did not stop treatment due to an adverse event; and/or 4) did not receive the Day 30 evaluation after the last injection.

Note: AA4500 = CCH.

Table 5: Demographics of Subjects, ITT Set (Source: Reviewer)

	AA4500 N=204	Placebo N=104	Total N=308
Age			
Mean (SD)	62 (10)	63 (9)	6 (9)
Min, Max	33, 89	42, 83	33, 89
Gender, N(%)			
Male	171 (84%)	74 (71%)	245 (80%)
Female	33 (16%)	30 (29%)	63 (20%)
Race, N (%)			
White	203 (99.5%)	104 (100%)	307 (99.7%)
Hispanic	1 (0.5%)	0	1 (0.3%)

Protocol Deviations

Thirty five subjects had significant protocol deviations related to the primary joint. These included 22 subjects who did not receive the full regimen of injections that they were eligible for (having failed to respond to previous injections). Since there is virtually no evidence of a clinical response from placebo injections, inclusion of these subjects can only serve to underestimate the efficacy of CCH. There were also five subjects who received the wrong treatment at least once and eight subjects who did not have a 30 day measurement after their last injection. Inclusion of these subjects should favor the null hypothesis of no treatment effect. Finally, there were two subjects who did not have a fixed-flexion contracture $\geq 20^\circ$ at baseline.

The Applicant judged which protocol deviations were significant. Some common examples of protocol deviations deemed non-significant include: out-of-window visit, labs not done, vital signs not done, grip strength missing, and contracture measurements not reported at screening. There were four subjects with missing contracture measurements on the primary joint at screening. The four subjects were evenly balanced across the treatment arms, however, and each arm had one success and one failure.

Statistical Methods

The primary efficacy analysis was a CMH test on clinical success, stratified by joint type and baseline contracture severity. This analysis was also used for clinical improvement. Reduction in contracture and change in ROM were analyzed using an ANOVA model with treatment, baseline severity, and joint type as factors. A full factorial model was used, i.e., every possible interaction between the factors was included in the model. The main effect was tested using type III sum of squares, which gives each combination of severity and joint equal weight. Time to clinical success was analyzed using a log-rank test, stratified by baseline severity and joint type. Multiplicity was controlled by using a fixed sequence of testing, as shown in Table 7.

The primary missing data method for clinical success was last-observation-carried forward. As a planned sensitivity analysis for this endpoint, subjects who did not have a day 30 evaluation after their last injection or who were not in the modified ITT set were assigned an outcome of no success.

Results and Conclusions

Table 6, which was provided by the Applicant, shows the results for the primary endpoint of clinical success on the primary joint. I confirmed the reported results from the tabulation and analysis datasets. Table 7 shows the results for the secondary endpoints, following the planned order of testing. It was also provided by the Applicant, but I was able to reproduce the results from the analysis data set. The results for the change in contracture and change in ROM endpoints were not changed when type II sum of squares was used instead of type III, giving equal weight to each patient.

The results of the planned sensitivity analysis for the primary endpoint were quite similar to those for the primary analysis. The success rate was 63% (128/204) for the active arm and 7% (7/104) for the placebo arm, again a highly significant difference. Note that this analysis used the ITT set.

An examination of the change in ROM data submitted by the Applicant yielded two concerns. First of all, it was apparent that the imputation described in the statistical analysis plan was not carried out. A second concern was that the change-in-ROM values for some subjects were set as missing in the analysis file and hence excluded from the statistical analysis. This violated the principle that all the subjects in the planned analysis set must actually be included in the analysis. The original imputation (which was not reported) also allowed for values to be left missing after imputation. We therefore requested two more groups of analyses: one group using the original imputation, and another that assigned a value of zero (no improvement) for subjects who would otherwise be excluded from the analysis. (I refer to *groups* of analyses because there were six difference endpoints related to change-in-range of motion.) All of these analyses yielded results consistent with Table 7.

Table 6: Clinical Success, Modified ITT set
(Source: Table 10, Clinical Study Report)

	AA4500 N=203	Placebo N=103
All Primary Joints		
First injection		
N	203	103
Number (%) clinical success	79 (38.9)	1 (1.0)
p-value ^b	<0.001	-
Last injection		
N	203	103
Number (%) clinical success	130 (64.0)	7 (6.8) ^c
p-value ^b	<0.001	-
Average number of injections administered		
N	203	103
Mean (SD)	1.7 (0.8)	2.9 (0.4)
Min, Max	1, 3	1, 3
Average number of injections for success		
N	130	7
Mean (SD)	1.5 (0.7)	2.6 (0.8)
Min, Max	1, 3	1, 3

Data source: Table 14.2.2.1

^a Clinical success: reduction of contracture to 5 degrees or less within 30 days of an injection.

^b p-value based on Cochran-Mantel-Haenszel test comparing treatment groups, stratified by baseline severity group and joint type.

^c Two placebo subjects (1154-2715 and 1182-4309) had a reduction in contracture to within 0-5° after receiving AA4500 in error at their second injection (Appendix 16.2; Listing 16.2.6.1).

Table 7: Hierarchy of Testing Endpoints, with p-values
(Source: Table 9, Clinical Study Report)

Order/Parameter	Injection Number	Joint Type	Observed p-value	Hierarchy p-value
1/Clinical success	Last	All primary joints	<0.001	<0.001
2/Clinical improvement	Last	All primary joints	<0.001	<0.001
3/% change in contracture	Last	All primary joints	<0.001	<0.001
4/Time to clinical success	Last	All primary joints	<0.001	<0.001
5/Change from baseline in ROM	Last	All primary joints	<0.001	<0.001
6/Clinical success	Last	Primary MP	<0.001	<0.001
7/Clinical improvement	Last	Primary MP	<0.001	<0.001
8/% change in contracture	Last	Primary MP	<0.001	<0.001
9/Time to clinical success	Last	Primary MP	<0.001	<0.001
10/Change from baseline in ROM	Last	Primary MP	<0.001	<0.001
11/Clinical success	Last	Primary PIP	<0.001	<0.001
12/Clinical improvement	Last	Primary PIP	<0.001	<0.001
13/% change in contracture	Last	Primary PIP	<0.001	<0.001
14/Time to clinical success	Last	Primary PIP	<0.001	<0.001
15/Change from baseline in ROM	Last	Primary PIP	<0.001	<0.001
16/Clinical success	First	All primary joints	<0.001	<0.001
17/Clinical improvement	First	All primary joints	<0.001	<0.001
18/% change in contracture	First	All primary joints	<0.001	<0.001
19/Change from baseline in ROM	First	All primary joints	<0.001	<0.001
20/Clinical success	First	Primary MP	<0.001	<0.001
21/Clinical improvement	First	Primary MP	<0.001	<0.001
22/% change in contracture	First	Primary MP	<0.001	<0.001
23/Change from baseline in ROM	First	Primary MP	<0.001	<0.001
24/Clinical success	First	Primary PIP	0.002	0.002
25/Clinical improvement	First	Primary PIP	<0.001	<0.001
26/% change in contracture	First	Primary PIP	<0.001	<0.001
27/Change from baseline in ROM	First	Primary PIP	<0.001	<0.001

Table 8 shows the results on the primary endpoint for patients on the active treatment by joint, for the three most common primary joints: MP on little finger, PIP on little finger, and MP on ring finger. One of these joints was selected as primary 89% of the time (among patients later randomized to active treatment). As the table suggests, either of the MP joints was more likely to be successfully treated than the PIP joint on the little finger (exact $p < .01$). Also, the MP joint on the ring finger had a higher success rate than the same joint on the little finger (exact $p = .02$). A separate analysis of the two hands shows similar success rates for each joint.

Table 8: Clinical Success from CCH Treatment by Finger and Joint (Source: Reviewer)

Finger/Joint	Prop. Success, Last Inj.	N	Lower*	Upper*
Little/MP	0.68	69	0.56	0.79
Little/PIP	0.39	54	0.26	0.53
Ring/MP	0.86	57	0.74	0.94

*95% Clopper-Pearson confidence interval

In summary, this study showed significant treatment effects for the primary and secondary variables in the testing hierarchy. The study provides substantial evidence that CCH is effective for both MP and PIP joints with contracture, but that it is more effective for MP joints.

AUX-CC-859

Study Design and Endpoints

AUX-CC-859 was a double-blind, placebo-controlled study which enrolled 66 subjects in five sites in Australia. The design was similar to that of AUX-CC-857. Of the enrolled subjects, 45 were randomly assigned to CCH and 21 to placebo.

The primary and other major efficacy endpoints were the same as in study AUX-CC-857. Unlike that study, however, the primary analysis set was intent-to-treat, defined as all treated patients.

Patient Disposition, Demographic and Baseline Characteristics

Table 9 displays the disposition of subjects. It was provided by the Applicant, but I was able reproduce the content. Table 10 shows the subject demographics.

Table 9: Subject Disposition, ITT Set (Source: Table 7, Clinical Study Report)

	AA4500 0.58 mg (N=45)	Placebo (N=21)	Total (N=66)
Intent-to-treat	45 (100.0)	21 (100.0)	66 (100.0)
Per protocol ^a	43 (95.6)	21 (100.0)	64 (97.0)
Completed double-blind phase, N (%)	45 (100.0)	19 (90.5)	64 (97.0)
Discontinued double-blind phase, N (%):	0	2 (9.5)	2 (3.0)
Withdraw consent	0	2 (9.5)	2 (3.0)
Number of injections during double-blind, n (%):			
1	11 (24.4)	1 (4.8)	12 (18.2)
2	7 (15.6)	1 (4.8)	8 (12.1)
3	27 (60.0)	19 (90.5)	46 (69.7)
Number of joints treated during double-blind, n (%):			
Primary	23 (51.1)	20 (95.2)	43 (65.2)
Primary and secondary	17 (37.8)	1 (4.8)	18 (27.3)
Primary, secondary, and tertiary	5 (11.1)	0	5 (7.6)
Total number of joints treated	72	22	94
Days in study			
N	45	21	66
Mean (SD)	90.6 (8.6)	80.1 (17.6)	87.3 (13.0)
Median	86.0	85.0	85.0
Min, Max	81, 121	28, 94	28, 121

Data source: Table 14.1.1a

^a Intent-to-treat subjects were excluded from this population if their primary joint: 1) had a baseline contracture less than 20° or greater than 100° for MP (80° for PIP); 2) was mistreated due to incorrect randomization; 3) received too much or too little study drug; and/or 4) did not receive the Day 30 evaluation.

Table 10: Demographics of Subjects, ITT Set (Source: Reviewer)

	AA4500 N=45	Placebo N=21	Total N=66
Age			
Mean (SD)	63 (8)	66 (11)	64 (9)
Min, Max	45, 88	41, 86	41, 88
Gender, N(%)			
Male	39 (87%)	17 (81%)	56 (85%)
Female	6 (13%)	4 (19%)	10 (15%)
Race, N (%)			
White	45 (100%)	21 (100%)	66 (100%)

Protocol Deviations

The Applicant reports that 40 subjects had protocol deviations during the double-blind phase of the study, but deemed all but two of the deviations “non-significant”. The exceptions were a subject who received placebo for the second injection instead of the assigned CCH treatment (6002-1504) and a subject who missed the Day 30 assessment after the second injection of CCH (6006-1803).

In addition, there were also nine subjects who did not receive the full course of injections despite their failure to respond to earlier injections. However, the inclusion of these subjects should bias the results toward the null hypothesis of no treatment effect.

Statistical Methods

Except for the choice of analysis population, the statistical methods were substantially the same as those used in study 857.

Results and Conclusions

Table 11 includes the primary endpoint and related results. It was produced by the Applicant, but I confirmed the contents. The p-value for success on the first injection is listed as NA because that endpoint was not reached in the testing sequence. Table 12 displays the results for the secondary endpoints in order of testing. I was able to confirm these results from the analysis data. Using type II sum of squares instead of type III did not alter the statistical significance of the change in contracture and change in ROM endpoints. The results of this study strongly support a finding of efficacy.

Table 11: Clinical Success, ITT Set (Source: Table 14, Clinical Study Report)

	AA4500 0.58 mg (N=45)	Placebo (N=21)
All Primary Joints		
First injection		
N	45	21
Number (%) reduction in contracture to 5° or less	12 (26.7)	1 (4.8)
p-value ^a	NA	-
Last injection		
N	45	21
Number (%) reduction in contracture to 5° or less	20 (44.4)	1 (4.8)
p-value ^a	<0.001	-
Average number of injections administered		
N	45	21
Mean (SD)	1.7 (0.8)	2.8 (0.6)
Min, Max	1, 3	1, 3
Average number of injections for reduction in contracture to 5° or less		
N	20	1
Mean (SD)	1.5 (0.7)	1.0
Min, Max	1, 3	1, 1

Data source: Table 14.2.2.1

NA=not applicable

^a p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group and joint type.

Table 12: Hierarchy of Testing Endpoints, with p-values
(Source: Table 13, Clinical Study Report)

Order/Parameter	Injection Number	Joint Type	Observed p-value	Hierarchy p-value
1/Reduction in contracture to 5° or less	Last	All primary joints	<0.001	<0.001
2/Clinical improvement	Last	All primary joints	<0.001	<0.001
3/% change in contracture	Last	All primary joints	<0.001	<0.001
4/Time to reduction in contracture to 5° or less	Last	All primary joints	<0.001	<0.001
5/Change from baseline in ROM	Last	All primary joints	<0.001	<0.001
6/Reduction in contracture to 5° or less	Last	Primary MP	0.003	0.003
7/Clinical improvement	Last	Primary MP	<0.001	<0.001
8/% change in contracture	Last	Primary MP	<0.001	<0.001
9/Time to reduction in contracture to 5° or less	Last	Primary MP	0.003	0.003
10/Change from baseline in ROM	Last	Primary MP	<0.001	<0.001
11/Reduction in contracture to 5° or less	Last	Primary PIP	0.069	NS
12/Clinical improvement	Last	Primary PIP	0.005	NA
13/% change in contracture	Last	Primary PIP	0.003	NA
14/Time to reduction in contracture to 5° or less	Last	Primary PIP	0.030	NA
15/Change from baseline in ROM	Last	Primary PIP	0.032	NA
16/Reduction in contracture to 5° or less	First	All primary joints	0.014	NA
17/Clinical improvement	First	All primary joints	<0.001	NA
18/% change in contracture	First	All primary joints	<0.001	NA
19/Change from baseline in ROM	First	All primary joints	<0.001	NA
20/Reduction in contracture to 5° or less	First	Primary MP	0.029	NA
21/Clinical improvement	First	Primary MP	<0.001	NA
22/% change in contracture	First	Primary MP	<0.001	NA
23/Change from baseline in ROM	First	Primary MP	<0.001	NA
24/Reduction in contracture to 5° or less	First	Primary PIP	0.245	NA
25/Clinical improvement	First	Primary PIP	0.020	NA
26/% change in contracture	First	Primary PIP	<0.001	NA
27/Change from baseline in ROM	First	Primary PIP	0.004	NA

Data source: Table 14.2.1

MP=metacarpophalangeal; NA=not applicable; NS=not significant; PIP=proximal interphalangeal; ROM=range of motion

3.2 Evaluation of Safety

The safety profile of CCH was reviewed by Eric Brodsky, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 13 shows the primary endpoint by gender and treatment group. The results are pooled from all Phase 3 studies, which all had the same 2:1 randomization ratio. No subset analysis could be done for race, as all but one of 407 subjects in the Phase 3 studies were classified as white/Caucasian. This high proportion of white subjects is reflective of the general population of Dupuytren's contracture patients. Table 14 shows the results by age.

Table 13: Clinical Success by Gender, All Studies (Source: Reviewer)

Gender	Arm	N Obs	Success (%)
Female	CCH	41	29 (71%)
	Placebo	38	4 (11%)
Male	CCH	230	142 (62%)
	Placebo	98	4 (4%)*

*Includes two subjects who erroneously received an injection of CCH.

Table 14: Clinical Success by Age, All Studies (Source: Reviewer)

Age	Arm	N Obs	Success (%)
< 55	CCH	47	29 (62%)
	Placebo	25	4 (16%)*
55-64	CCH	114	76 (67%)
	Placebo	46	2 (4%)*
65+	CCH	110	66 (60%)
	Placebo	65	2 (3%)

*Includes one subject who erroneously received an injection of CCH.

4.2 Other Special/Subgroup Populations

Due to the difficulty in properly injecting CCH into the Dupuytren's cord, the clinical staff in DAARP is concerned that the effectiveness of treatment may depend on the skill level and training of the provider. An advisory committee meeting has been scheduled to address this concern, but has not occurred at the time of writing.

The type of investigator training varied between studies. For Study 859 (AUX-CC-859), rheumatologists performed the injections at one site and hand surgeons performed the injections at the other sites. (Two of the hand surgeons were board-certified, and the third was an orthopedic surgeon with experience in hand surgery.) In Study 857, all injections were performed by either hand surgeons or orthopedic surgeons. In Study 303 (DUPY-303), all injections were done by a hand surgeon.

Table 15 shows the primary endpoint by site for Study 859. The estimated success rate with active treatment was virtually identical at the site with a rheumatologist (45%) vs. the sites with

hand surgeons (44%). It should be noted, however, that these percentages have standard errors of 15% and 9%, respectively. In Study 857, the injections were done by surgeons and the subjects achieved a 64% success rate. In Study 303, the single site had a hand surgeon as the investigator and also had a strikingly high success rate of 91% with active treatment.

In summary, of the 272 subjects injected with CCH in the Phase 3 trials, all but 11 were treated by hand or orthopedic surgeons. Due to this homogeneity of experience, it is not possible to make any reliable conclusions about the effect of investigator training.

Table 15: Clinical Success by Site, Study 859 (Source: Reviewer)

Site	Specialty	Arm	N Obs	Success (%)
6002	Rheumatology	CCH	11	5 (45%)
		Placebo	5	0 (0%)
6003	Hand Surgery	CCH	8	3 (38%)
		Placebo	4	1 (25%)
6005	Hand Surgery	CCH	10	6 (60%)
		Placebo	5	0 (0%)
6006	Hand Surgery	CCH	9	3 (33%)
		Placebo	3	0 (0%)
6007	Hand Surgery	CCH	7	3 (43%)
		Placebo	4	0 (0%)
All sites with hand Surgeons	Hand Surgery	CCH	34	15 (44%)
		Placebo	16	1 (6%)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The three Phase 3 studies provide overwhelming evidence for an effect of treatment with CCH on the primary endpoint. In these studies the success rate of treatment ranged from 44% to 91%; in comparison, the placebo response rate was no more than 5% in any study (excluding patients who were erroneously given active treatment.) Findings from the secondary endpoints were supportive.

The efficacy of CCH was notably dependent on the primary joint. Although CCH was effective for both MP and PIP joints in two studies, the largest study showed a significantly higher response rate for MP joints. Admittedly, the fact that MP joints were given priority complicates interpretation of this effect. Comparing the two most common MP joints, the ring finger had a higher response rate than the little finger.

A particular question in regard to this product is whether successful use is related to the specialized training of the physician performing the injections. Unfortunately, the three Phase 3 studies do not provide adequate comparative data to make any conclusions about the effect of

training. Of the 272 subjects injected with CCH in the Phase 3 trials, all but 11 were treated by hand or general orthopedic surgeons.

Dr. Brodsky raised concerns about the conduct of Study 303. He noted that the study was conducted at a single site by investigators who had a substantial financial interest in the outcome. Also, there were no reported protocol deviations. In response to an information request, the Applicant stated, “No comprehensive review of the database for DUPY-303 was planned nor carried out for determination of protocol deviations...” I share Dr. Brodsky’s concerns, and do not consider DUPY-303 to be pivotal.

5.2 Conclusions and Recommendations

The results of studies 857 and 859 strongly support a finding that CCH is efficacious for treatment of Dupuytren’s disease. Study 303 also had positive findings for efficacy, but I recommend that this study not be included in the labeling.

5.3 Review of the Proposed Label

Selections from the Applicant’s proposed label language are shown in *italics*, and my comments are shown in regular type. The references to figures use different numbering than the rest of the report.

(b) (4)

SIGNATURE LIST

Jonathan Norton, Primary Statistical Reviewer:



Date: 9/4/2009

Dionne Price, Statistical Team Leader:



Thomas Permutt, Biometrics Division Director:

