EXPLORATORY ANALYSES OF STUDY RESULTS

Exploratory analyses were conducted by CBER as well as Allergan to examine for differential relationships of treatment with efficacy in subject subsets based on several criteria. Only Study 140 is suitable for inclusion in these analyses, thus there are only a limited number of subjects available. Only Week 6 outcomes of Period II were examined.

Efficacy Relationship to Baseline Disease Severity

An exploratory analysis was carried out to examine the estimated treatment effect in subsets of narrowed Baseline severity range. The subjects were divided into 4 subsets of more homogeneous severity, and few subjects with most severe disease that were sparsely distributed at severity 19 to 27 by baseline CDSS were not included. The following table shows thee results within these subsets, as analyzed in the form of absolute change in CDSS points as well as fraction of baseline, for several different methods of addressing missing values.

Table 28: Treatment Effect in Narrowed Ranges of Baseline Severity

		Baseline 3-5			Baseline 6-7			Baseline 8-10			Baseline 11-18		
		Placebo	Botox	Tx Effect	Placebo	Botox	Tx Effect	Placebo	Botox	Tx Effect	Placebo	Botox	Tx Effect
No. Enrolled		12	21		19	22		25	18		22	21	
No. Without Missing Value		11	20		16	21		21	16		21	18	
Change	A	1.91	-1.00	-2.91	-0.06	-0.81	-0.75	-1.14	-3.06	-1.92	-1.62	-3.44	-1.83
in CDSS	B	1.75	-1.10	-2.85	0.11	-0.73	-0.83	-1.16	-2.94	-1.78	-1.59	-3.14	-1.55
	C	1.75	-1.10	-2.85	0.58	-0.73	-1.31	-0.84	-1.94	-1.10	-1.59	-2.57	-0.98
Percent	B	40.4	-22.6	-63.0	0.6	-11.3	-11.9	-13.3	-32.3	-19.0	-12.2	-22.0	-9.8
Change	C	40.4	-22.6	-63.0	8.5	-11.3	-19.8	-9.7	-21.2	-11.5	-12.2	-17.6	-5.4

As previously employed in the CBER exploratory analyses, the A method indicates subjects with missing values were dropped, B is LOCF for all missing values, and C is a per-Analytic Plan analysis, when the analytic plan is properly applied. These analyses indicate that there is evidence that the beneficial treatment effect occurs across all baseline severity ranges examined in the study. There is suggestion that the absolute magnitude of the effect size, in angle of head deviation corrected (degrees) is little different across the severities; so that the fraction of deviation corrected declines considerably as disease severity increases.

Efficacy Relationship to Subsets by Sex

Allergan reports that their analyses suggest that females treated with Botox had greater efficacy response than males, and that this trend was consistent across head position (CDSS) global assessments, and both frequency and intensity of pain.

Comment:

Exploratory analyses conducted by CBER concur with this apparent difference in amount of effect. Both men and women had benefit associated with Botox injection. In general this was not due to striking differences in the change in symptoms within the placebo group, but much greater response within the Botox group.

Table 29: CDSS Treatment Effect in Subsets by Sex						
	Male			Female		
	Placebo	Botox	Tx Effect	Placebo	Botox	Tx Effect
No. Enrolled	16	26		66	62	
No. Without Missing Value	13	23		59	56	
Change in CDSS A	-0.62	-0.87	-0.25	-1.03	-2.77	-1.73
Change in CDSS B	-0.63	-1.08	-0.45	-0.95	-2.66	-1.71
Change in CDSS C	0.25	-0.46	-0.71	-0.70	-1.89	-1.19
Percent Change B	-1.0	-8.9	-7.9	-3.4	-27.3	-23.9
Percent Change C	3.6	-5.8	-9.4	0.2	-21.2	-21.3

Sensitivity analyses for missing data imputation employed no imputation (drop subjects, method A), LOCF for all missing (method B) or LoE imputed with worst observed, LOCF for all others (method C)

Table 29: Physician Global Assessment Treatment Effect in Subsets by Sex						
% with	Male			Female		
Amt of Improvement	Placebo	Botox	Tx Effect	Placebo	Botox	Tx Effect
(No. Enrolled)	16	26		66	62	
Any (score > 0)	31.3	46.2	14.9	37.9	61.3	23.4
At least Moderate	18.8	30.8	12.0	21.2	40.3	19.1

However, this male/female disparity in the size of response was not observed in the Period II subjects during their period I experience. During Period I, the week 6 mean change from baseline in CDSS was -4.7 points for men, -4.1 points for women. Thus, in general medical practice, a sex related disparity in apparent response may not be observed. While these Period I and II treatment effects might seem to initially suggest sex related differences in placebo effect (amount of inflation of true treatment effect occurring in open label treatment), interpretation of these results is difficult, as the placebo group Week 6 outcomes in CDSS on Period II were not substantially different between men and women.

Efficacy Relationship to Dose Received

Allergan reports that there was no important relationship between amount of efficacy associated with toxin injection and the amount of toxin injected.

Comment:

However, Allergan's observation has limited interpretability. Only Study 140 affords any real opportunity to examine actual efficacy, as this study illustrated the substantial degree of placebo affect that can occur in open label studies. When the Study 140 data are examined by sequential dose-amount groupings, there is no dose-response effect discernable. However, dose in Study 140 was not randomly assigned. Dose for each subject was the dose that had been previously determined, through the process of normal practice of medicine, to be that which appeared to provide optimal response with acceptable adverse effects for each subject. Thus, no true dose-response comparisons can be made from these data, and none are available elsewhere in the Allergan studies.

Thus, there is little basis upon which to provide dosing or dose adjustment guidance. Only rare subjects were given a dose less than 100U, and while Study 140 allowed doses up to 360 U, later Allergan studies limited dose to 300U. This suggests that physicians perceive 300U to be the limit of worthwhile dosing.

Efficacy within Subsets by Age

There was no notable trend for a differential amount of efficacy associated with toxin treatment in subjects less than age 65 vs those equal to or greater than age 65. There were only 3 subjects of age 75 or greater, so that no conclusions may be drawn regarding subjects of age 75 or more.

Efficacy Relationship to Subsets by Race

There were very few subjects enrolled in any of these studies of race subset other than Caucasian. No analyses for differential efficacy or safety were possible.

Efficacy Related to Variations in Subject Weight

When examined by body weight, there was no clear differential efficacy by body weight apparent.

Efficacy Effects of Antibody Formation

These analyses were described within the review of Study 140. These analyses suggested that subjects with pre-existing neutralizing antibodies to Botox do not respond to additional toxin injections when they are compared in a blinded, randomized manner. However, these subjects did appear to subjectively experience responses when injected in open label treatment session.

SUMMARY

CLINICAL DEVELOPMENT PROGRAM

Overview

This application was initially submitted based upon 5 controlled studies and 3 uncontrolled studies conducted prior to 1990. The initial review of this marketing application determined that these studies were seriously flawed in their design, conduct and documentation so that no definitive conclusions could be drawn from them.

In order to address this deficiency, Allergan conducted a single additional controlled Phase 3 study, Study BTOX-140-8051. Due to the fact that this study employed a newly devised evaluation tool as the primary endpoint, an additional study, BTOX-147-0000 was conducted to assess the reliability of this evaluation.

Allergan then changed the bulk toxin lot used for manufacture of finished Botox, from Lot [redacted] to Lot [redacted]. Study 191622-004 was conducted as a safety evaluation of the new toxin lot. Study 191622-014 was a retrospective chart review study designed to further assess the meaningfulness of any differences in clinical performance between Botox from each of the two bulk toxin lots.

Phase 3 Controlled Study

Study 140 was a placebo controlled randomized study that had extensive screening component for subjects perceived responsive to Botox during open label treatment. Only apparently responsive subjects were entered into the randomized portion of the study. The dose tested in the study was highly individualized based upon each subject's prior treatment characteristics in off-label use within practice of medicine clinical care. The actual mean dose to subjects was approximately 240 U. Subjects received a single blinded treatment session, and were followed for up to 10 weeks thereafter. Co-Primary endpoints consisted of the newly devised Cervical Dystonia Severity Scale (CDSS) and a Physician Global Assessment, both at the Week 6 time-point. Multiple other evaluations were performed, included as both secondary and tertiary endpoints.

A total of 170 subjects were enrolled into the controlled portion of the study. There were numerous errors in study conduct in the run-in phase of the study, and some errors in the intended entry of subjects into the controlled portion. Not all these errors have yet been fully detailed by the applicant.

There were deviations from the prospective analytic plan regarding imputation of missing data. These deviations appear to make an important difference in the p-value associated with the study result. Additionally, missing value imputation, and thus a true Intent-to-Treat analysis, was performed only for the primary endpoint calculations. All secondary endpoints and calculations of results for weeks other than week 6 were conducted with dropping of subjects with missing data.

The study population was well balanced between study groups in demographic and baseline disease status characteristics. The study population appears to be representative of the disease population

in general with regards to these characteristics as best as can be determined by comparison with the medical literature.

Evaluation Tool Supportive Study

Study 147 was a non-treatment study intended to assess the reliability of the CDSS evaluation tool. Subjects were evaluated with the CDSS 4 times, two times by each of two evaluators. The evaluations by both evaluators were interleaved, and each evaluators two assessments were completed within 90 minutes of each other. Analysis of the results was to be by calculation of kappa values for inter-rater and intra-rater comparisons.

There were 42 subjects enrolled in the study across 4 study sites, involving a total of 8 evaluators. The study subjects had a distribution of CDSS similar in general to those subjects enrolled in Study 140. Evaluations by the two evaluators were performed one shortly after the other (minutes apart). Many of the intra-rater paired evaluations were as little as 30 minutes apart. There is likely to be substantial memory-carry-over for the intra-rater evaluations.

There was a serious analytic deviation in this study. CDSS was not analyzed in the manner employed in Study 140. The CDSS components were assigned positive or negative values depending on the direction of the head position deviation, a feature which was not performed in Study 140. This resulted in very different CDSS value ranges than when the positive/negative value method is not used.

Open Label Safety Study

Study 191622-004 was an open label safety study designed to assess the adverse events associated with use of Botox manufactured from Lot [----------. Subjects who had been receiving [---- Botox in medical care were enrolled and received a single open label injection of Botox and was followed for recording of adverse events.

There were 70 subjects enrolled, who received a mean dose of 240 U of Botox. Study treatment was generally similar in characteristics to that administered to subjects in Study 140.

Retrospective Chart Review Study

Study 191622-014 was a retrospective chart review study designed to assess relative rates of adverse events and changes in treatment characteristics between the last two treatments with [---- Botox and the first two treatments with [--------- Botox. Only subjects who had charts with all 4 of the required treatment sessions were included. Minimal amounts of data were to be extracted from the review of patient care charts.

There were numerous errors and violations of planned procedures in the selection of sites and charts. However none of these errors are likely to have had any impact upon the results of this study. Some of the violations were related to the difficulty of finding sites with enough patients to

offer for potential inclusion, and some of the errors in procedures were rendered inconsequential by the low fraction of patients whose charts were reviewed and who actually qualified for inclusion in the study. The study enrolled 191 subject charts, slightly fewer than initially intended.

EFFICACY

Study 140 is the only source of efficacy information from an adequate and well-controlled study available in this PLA. This study had co-primary endpoints, where both were prospectively stated as required to be statistically significant to conclude the study showed efficacy. The Global Assessment evaluation did show a statistically significant effect in favor of the Botox treatment in the percentage of patients who appeared to have improvement. This outcome was robust to various exploratory and sensitivity analyses.

However, the other co-primary endpoint of change from baseline in CDSS was not a robust outcome. The analysis submitted by Allergan was performed in violation of the prospective analytic plan and should not be further considered. A reanalysis of the submitted data performed by CBER according to the analytic plan properly implemented indicated that statistical significance was not achieved. Other sensitivity analyses yield p-values that do achieve statistical significance. These sensitivity analyses include both parametric testing using different methods for addressing missing data, non-parametric testing using both the prospective missing value imputation plan and other methods, and both parametric and non-parametric methods on change in CDSS examined as percentage of each individual subject's baseline CDSS rather than absolute change in CDSS points. Additionally, the estimated size of the treatment effect is largely similar with the different methods of missing value imputation. Thus, it appears that the failure to achieve statistical significance on the primary endpoint is related to both the method of imputation of missing values (imputation of the most extreme values observed for all subjects with the cause of missing value of lack of efficacy, and use of a parametric testing procedure which is sensitive to the non-normal distribution that is created by the imputation scheme.

There was only approximately a 5% rate of missing for lack of efficacy in this study. However, post hoc review of the data suggests that the results are made highly sensitive to this problem because of the very minor size of the response that is actually observed. Depending on the method of missing value imputation, the size of the treatment effect has point estimates of 1.0 to 1.3 CDSS points. This only an improvement in head position of 5 to 10degrees, divided amongst three planes of deviation, and only approximately 15% of the total head deviation.

These impressions of the effect on head position based on CDSS remain somewhat tentative, as no valid analysis of the reliability of CDSS has yet been submitted. An invalid analysis suggested reasonable reliability in this assessment, and if borne out by the proper analyses when submitted will be firmer. Nonetheless, the CDSS appears to be an assessment tool of limited value, as it detects changes that are of questionable value. Correlation with Global Assessment suggests that only substantial changes in CDSS will reliably be detected as a meaningful, worthwhile change.

When the amount of efficacy is examined via the other co-primary endpoint, the Physician Global Assessment, the impression provided is again of limited amounts of benefit. When examined by percentage of subjects perceived as having any benefit, only 20% are attributable to use of Botox. The mean change in Global Assessment Score is less than 1 point.

Pain is an important component of this disease, and Pain Assessments were included as secondary endpoints, although the impression of pain effect is likely to have also been incorporated into the Global Assessment. Allergan did not submit proper ITT analyzed results for these assessments. CBER analyses of these endpoints suggest that there was a statistically significant but very modest amount of benefit on the aspects of pain that were assessed. Again the results seem to be robust to a variety of analytic methods, and consistently indicating a modest size of effect across all methods.

Overall, this study suggests that an improvement does occur with Botox treatment, but that it is a rather modest amount of improvement. Substantially more of the disease symptoms are left unrelieved by Botox treatment than are relieved. The tertiary endpoint of the Activities of Daily Living items further underscores the clinical value of the observed effects. No significant effects were observed in the ADL questions.

A notable feature of the submitted data is ability to compare open label and blinded controlled treatment responses in the same subjects. This comparison indicates that there is a substantial component of the routinely observed response in general medical practice that may be attributable to "placebo effect". Amount of response and percentage of subjects who do respond are substantially smaller when the comparison is performed with blinded study injections, even when the dose is the same. Thus, open label treatments are an inappropriate basis for characterizing the response to Botox injections.

SAFETY

Safety assessments were obtained in three studies, Study 140, Study 004, and Study 014, for three different purposes. Study 140 provides the only well controlled comparison of adverse events associated with the use of Botox. Study 004 provides the only prospective collection of adverse events associated with the use of [redacted] Botox, but was an open label, uncontrolled study. Study 014 provides the only same-study basis for comparison of adverse event rates with [redacted] Botox and [redacted] Botox, but was a retrospective study.

All studies did not raise any issues related to occurrence of fatal or other serious adverse events associated with Botox use. This is consistent with the general impression of the medical community derived from their off-label use of Botox for this indication.

The most notable adverse event associated with Botox use in these studies was the same as previously recognized from the off-label use, dysphagia. Most dysphagia events were graded as mild, but there were an important fraction graded as moderate, and a minority graded as severe. Full details on the consequences of these events to the subjects was not supplied, and should be requested from Allergan prior to forming a definitive conclusion on this therapy. However, these events appear not to have led to dropout from studies, or to have caused the event to rise to the level of being a serious AE. Unlike the reports of amount of efficacy, reports of dysphagia were consistent between the open label and blinded periods in Study 140. This suggests that safety reporting of this AE can be relied upon from open label studies.

Other adverse events that were associated with Botox treatments that appear to be causally related are neck weakness (an expectable event given the site of application of the toxin) and dry mouth.

These appear not to have been important enough to cause subjects to drop out of studies or to decline further injections in most cases.

In study 004 the same adverse events were highlighted. No new adverse events were discerned to be associated with toxin use. However, the incidence of dsyphagia was increased over that seen in Study 140. While the severity was not remarkably different, the incidence was approximately twice as high. This finding, coupled with apparently small benefits of Botox use seen in Study 140 raised concern that the risk-benefit comparison could not confidently formed from attempting to compare modest benefits seen in one study with modest risks seen in another study. In order to provide some additional information regarding the comparison between toxin lots, Study 014 was designed and carried out as an attempt to provide adequate information without proceeding immediately to a new blinded, controlled study of [redacted] Botox in CD.

Study 014 collected observations from charts of patients who had received regular treatments with Botox for CD, and received at least three doses of [redacted] Botox since the introduction of the new toxin into the commercial supplies in November 1997. For these subjects, the relative increase in incidence of dsyphagia was documented. However, the increase in dysphagia did not result in any apparent change in dosing practice, as might be expected if the adverse event was of clinical import. Therefore the conclusion of this study is that while an increased incidence of dysphagia was established, it is not clinically important to the management of patients. An objection to this conclusion might be raised that subjects for whom it was of major importance might have dropped out of treatment prior to completing three treatment sessions with [redacted] Botox, and thus have never been eligible for the chart review. However this is not likely. If there were substantial numbers for whom the increased AE rate or severity was highly problematic, there should also have been some for whom the increase was notable, and led to recorded attempts to adjust dosing, but persisted with adjustments for at least three attempts prior to discontinuing toxin treatment completely. These were not seen. Thus, Study 014 is reassuring that the risk-benefit comparison in general clinical use with [redacted] toxin is not markedly different from that which was the case with [redacted] Botox.

OTHER ISSUES

Change in Bulk Toxin Lot

A change in the Bulk Toxin Lot from [redacted] to [redacted] occurred during the clinical development period. Most studies were conducted with [redacted] toxin, while only [redacted] toxin is available for marketing. There were not issues of loss of efficacy, but there was evidence of an increase in adverse event rates, which raised concern about a change in the risk-benefit comparison. These were addressed as discussed under the Safety Summary section. While dysphagia appears to be increased, the overall risk-benefit appears to be largely unchanged.

Antibody Formation

Antibody formation has long been thought to be an important issue in the utility of botulinum toxin, but has been poorly understood as to how to interpret results. Study 140 raised concern that the rate of antibody formation, even in patients with a long history of Botox exposure may be substantial

over time. Preliminary analyses of these data suggest that while the effects of antibodies on effect may not be discernable when used in an open label manner, but may be clear within a study suitable for a careful comparison.

No serious adverse events associated with antibodies were discerned, but loss of efficacy was suggested by CBER analyses. If this is borne out by additional analyses requested of Allergan, then if approved for this use, further phase 4 studies to better assess the rate of antibody formation and the consequences are warranted.

Additional Issues

No evidence to indicate important disparities between subject subsets based on any demographic or baseline status parameters was discerned. Subsets by race, of the very elderly or very young were not contained within the dataset, and cannot be evaluated.

No useful data was available to permit analyses of response with variations in dose was available. All dosing in these studies was highly individualized based on up to years of experience within each subject.

Another important issue with regards to potential labeling is that all of these studies have enrolled only subjects with established use histories of Botox for CD. There is no information offered in the recent submissions that can advise on what dose level to begin at for toxin-naïve patients or what to expect interms of risks or amount of benefit at that dose level.

OVERALL RISK-BENEFIT ASSESSMENT

The overall risk-benefit assessment cannot be definitively formed at present due to the several questions for additional information that must be submitted by the sponsor. However, if the additional information does not shift the present understanding of the benefits and risks, then comments can be formulated at present.

There appears to be a benefit associated with toxin use, albeit a small one. There are certainly adverse events associated with toxin use, both of those that occur with reasonable frequency and can be assessed in studies of the size employed here, and those that have not been observed, but are quite plausibly suggested by the medical literature reports of use of botulinum toxin. Study 014 appears to indicate that the comparison is judged a favorable one even with the modest increase in dysphagia that has occurred with [redacted] Botox.

RECOMMENDATION

The applicant has provided limited amounts of credible information regarding the use of Botox in treatment of cervical dystonia. Some questions remain as to important details of the information. However, pending review of responses to requests for follow-up information, what has been submitted in well designed studies indicates that the risk-benefit comparison is quite marginal, but enough benefit appears to be offered to out weigh the apparent risks. On these grounds, eventual approval can be recommended.

However, there remain several questions regarding the data submitted that will need to be evaluated before that assessment can be made definitive. The answers to these questions may be very important to the details of the labeling and should be examined prior to writing any labeling or providing any approval.

Additionally, the applicant should be required to formulate and initiate a study (potentially to be conducted mostly as a Phase 4 study if approval does occur) that will better assess the incidence and consequences of antibody formation. This may be an important factor to physicians and patients when deciding if, and at what dose to undertake Botox treatments. Evidence that antibody formation does or does not occur in a substantial number of people, has or has not an effect to lessen efficacy, and incidence is or is not related to dose level or numbers of repetitive doses over time can influence these choices.

APPENDIX A: SYNOPSES OF PREVIOUSLY SUBMITTED STUDIES

The original submission of PLA 91-0184 contained 5 controlled studies and 3 uncontrolled studies. These had been designed and conducted by Occulinum, Inc., prior to Allergan Inc.'s acquisition of the Botox product. These submitted studies were deemed inadequate to proceed with marketing approval for the cervical dystonia indication, as described in the Introduction. Brief summaries of the controlled studies are provided here. For more complete information, the original reviews should be consulted (see Introduction).

Study OCUL-102

Title: A parallel double blind study of Botulinum toxin in the treatment of torticollis

This study was conducted at a single center, Columbia U., by S. Fahn et.al., from June 1987 to August 1988. Subjects were enrolled and stratified into three groups based on which planes of head deviation were symptomatic. Subjects were randomized to toxin or placebo within each stratum. Treatment dose differed for the strata, and ranged 140 to 170 U. Outcome scales include several patient subjective scales, physician subjective scales, several examiner scales (performed by an unblinded examiner), and a structured dystonia rating scale.

Subjects were examined at weeks 2, 6 and 12, although the protocol specified weeks 2, 4, 8, and 12. There were 51 patients enrolled, randomized 25 to Botox, 26 to placebo. 5 subjects withdrew from the study. There were 4 subjects disqualified from analyses, leaving 47 of 51 subjects for analysis. No formal analytic plan was prospectively written. The study report notes 21 different endpoints which were analyzed at each of the 3 study evaluations.

The subject global assessment of response showed treatment associated differences favoring the toxin of approximately 40% more subjects showing improvement with toxin, and with p-values of 0.001 to 0.011 at the three timepoints. Mean Global scores also showed improvements with toxin, p-values ranging 0.04 to 0.001.

The Physician global assessment showed no significant effects in percent of subjects with improvement or in mean global score, although there were weak trends to improvement, with p-values ranging 0.09 to 0.3. Unblinded examiner assessment of magnitude of head movement showed treatment effects with p-values of 0.006 to 0.015.

Most other endpoints did not show stastically significant differences. The previous three endpoints seem to have been selected retrospectively. Muscle strength and size did show statistically significant treatment effects.

The review conclusion was that while this study was suggestive on the Patient Global assessment, the multiplicity of endpoints, along with other design and analysis flaws prohibited this study from being regarded as definitive.

Study OCUL-105

Title: A double masked, vehicle controlled crossover trial of Oculinium for cervical dystonia.

This single center study was conducted by W. Koller from May 1988 to September 1988. This study employed a two period crossover design with injections of 150 U of toxin. No detailed protocol was provided to fully assess the study design, but multiple endpoints focussing upon the unstructured global assessments predominated. Timing of evaluations was variable, as well as the timing of the crossover injection. Of the 29 subjects enrolled, 27 were deemed evaluable. Some data was discarded from other subjects as well.

There appeared to be considerable carry-over effect between study periods, so that additional analyses were performed with the period 1 data only. Retrospectively, several of the global endpoints were named as most prominent, and these showed p-values of 0.02 in many of the analyses. The multiplicity of the endpoints again discredited many of the observations, with considerable missing data further confounding interpretation.

Study OCUL-101

Title : A double masked, vehicle controlled dose response crossover trial of Oculinum for cervical dystonia.

This single center study was conducted by P.Aminoff between February 1987 and June 1989. This was a 4 period cross over design of placebo and 3 dose levels of botox. Dose was not well defined, but mean dose within period ranged from 65 U (low dose) to 252 U. There were 41 subjects enrolled. Follow-up evaluations occurred 6 weeks after treatment. Subjects progressed from one period to the next whenever subjective assessment appeared to indicate no benefit. There were 11 outcome measures evaluated, of which 5 were post hoc selected as important. Some endpoints had p-values of < 0.05.

Study OCUL-103

Title: A double masked, vehicle controlled crossover trial of Oculinum for cervical dystonia.

This single center study was conducted by Perlmutter et.al. from July 1987 to June 1988. There were 21 subjects enrolled into this crossover study of placebo or 100 U of Botox. Similar to the other early studies, this study also evaluated multiple endpoints and did not have a good analytic plan. Many outcomes had p-values on the order of 0.01, but without an analytic plan this is difficult to interpret.

Study OCUL-106

Title: A double masked, vehicle controlled crossover study of oculinum for cervical dystonia.

This single center study was conduced by J.Tsui, from July 1995 to February 1986. This was a crossover design, where subjects received 100 U Botox or placebo. Follow-up was at 10 days and 6 weeks, with the second injection given 12 weeks after the first. ;There were 21 subjects enrolled, but only 16 used in the full crossover analysis, which also employed multiple assessments and no prospective analytic plan. This study failed to demonstrate efficacy of the toxin.