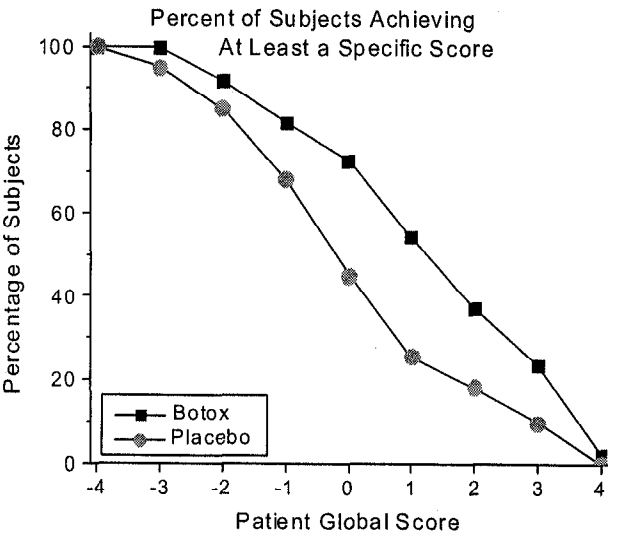
Figure 8



Activities of Daily Living Assessments

Table 18: Period II Activities of Daily Living Change from Baseline at Week 6 - Study 140				
Evaluation		Placebo n=82	BOTOX n=88	p-value
Number Evaluated	n	57	75	
Reading	mn	0.19	-0.11	0.61
Writing	mn	0.19	-0.09	0.57
Eating	mn	0.11	0.08	0.98
Housework	mn	0.28	-0.07	0.14
Hygiene	mn	0.19	0.19	1
Speaking	mn	0.1	0.11	1
Sleeping	mn	0.04	0.04	1
Desk Work	mn	0.06	-0.01	0.98
Walking	mn	0.18	0.07	0.44
Shopping	mn	0.11	0.08	0.4
Watching Television	mn	0.13	0.14	1
Driving a Car	mn	0.19	0.09	0.63
Leisure Activities	mn	0	0.09	0.99

Although the ADL scales are unvalidiated in this setting, they do provide simple assessments readily interpreted. No significant effects were shown on these questions.

SAFETY RESULTS

Deaths, Serious Adverse Events, and Withdrawal due to AE

There was one death reported during this study. One subject was disqualified from period I after toxin injection due to eligibility criteria violation. The subject suffered sudden death 91 days after the toxin injection, and presumed due to acute MI. No autopsy was performed, and the death was considered unrelated to study treatment.

There were 6 subjects with serious adverse events reported during the entire study, including the death. Two subjects were hospitalized during Period I. One subject had pelvic masses in the setting of a history of endometriosis, had exploratory surgery which led to oophorectomy and bowel resection due to adhesions. A second subject was hospitalized and treated for cholelithiasis 2 months after toxin injection in period I. An additional period I SAE was a 52 yo woman who was hospitalized briefly with chest pain and had MI ruled out 70 days after toxin injection. Source of the chest pain and paresthesias were not identified. This subject did continue to Period II, and participated without recurrence.

One subject in Period II was hospitalized for revision of a pre-existing hip prothsesis, The sixth SAE was a 46 yo male who received placebo in Period II, withdrew from the study approximately 2 weeks later due to lack of efficacy and immediately received a treatment with 200 U of open label toxin. This subject then reported neck pain and dysphagia, which lead to hospitalization on an unstated day, with an additional injection of toxin.

Frequent Adverse Events

Table 19: Percent Incidence of Most Frequent Adverse Events in Study 140

Adverse Event	Period I % n= 214	Period II % BOTOX n = 88	Placebo n = 82
Neck Pain	9	8	7
Back Pain	4	7	4
Headache	9	6	7
Flu Syndrome	5	3	7
Pain	6	3	8
Dysphagia	8	7	4
Dyspepsia	2	3	0
Oral Dryness	1	2	0
Hypertonia	3	6	0
Respiratory Infection	8	12	7
Rhinitis	4	7	0
Sinus Infection	1	1	7
Muscle Weakness	8	1	0

The most notable AEs with increased incidence associated with toxin use was dysphagia. The AEs categorized under dyspepsia, oral dryness, hypertonia and rhinitis were also increased, but to a more mild degree.

Dysphagia

There was one serious dysphagia event during this study, in subject 372 at week 2 of Period II, after having received a placebo injection at week 0. The duration of this event was only 4 days, occurred after a placebo injection, and is not likely to be related to the Botox injection of Period I.

In Period I there were 18 dysphagia events, only 1 severe, with 5 moderate and 12 mild. Treatment was unstated.

In Period II there were 6 dysphagia events in the Botox group, none severe, 3 moderate and 3 mild.

Dysphagia appeared to be consistent in incidence between Period I and Period II, at 7-8 %.

Other Adverse events

Hypertonia, while imbalanced, was largely reports of leg cramps or other localized muscle spasms (e.g., low back), and does not appear a significant concern for use of Botox. However, the AE of muscle weakness was often neck weakness following a toxin injection. In Period I there were 18 of these events, with 1 graded as severe and 6 moderate.

In Period I there were 2 reports of oral dryness, both graded as severe.

OTHER EXPLORATORY ANALYSES

Antibody Formation Testing

Serum samples were assayed for antibodies at baseline of Period I and at end of Period II. However, there was considerable missing data for the antibody testing. Of the 191 valid antibody tests at baseline, 32 were positive, for a 17% prevalence. Allergan reports that there were 114 subjects who had more than 1 valid antibody assay, of which 97 were negative at baseline, and 17 positive (15%). Of the 97 negative at baseline who participated in Period II and had follow-up testing, there were 2 who became positive by the end of the study (2% rate of conversion over a 6 month period).

Comment:

Although too small a number of antibody conversions to draw firm conclusions from, both of these conversion to positive were amongst the 50 Period-I-Negative who received Botox in Period II. None in the 40 Period I negative and received placebo in Period II subjects converted to antibody positive. This suggests the possibility that the conversions were related to dosing with Botox-Botox, rather than Botox-Placebo (Period I – Period II), and that the conversion rate with repetitive dosing may be higher than the 2% per half year

overall rate. Note also that Medical Officer review only finds 107 subjects with Period I tests and Period II tests both reported valid.

The consequences of antibody formation has often been unclear in the medical literature. An exploratory analysis was conducted to examine the outcome of treatment in subjects with subsets by baseline antibody status. During Period I, there was no substantial difference in open label response between antibody positive and negative subjects. The mean change in CDSS from baseline to Period I Week 6 was –4.2 for subjects without antibodies (n= 142) and –4.1 for those with antibodies (n=29. However, the more rigorous Period II evaluation, there did appear to be a difference in net treatment effect between the subjects without antibodies and those with antibodies at baseline. As shown in Table XX, while the majority of subjects without antibodies against Botox produced the response seen in the overall group, there was no trend of beneficial effect associated with Botox in subjects with antibodies at baseline.

Table 20: Period II Responses in Subset by Baseline Antibody Status

			Placebo	Botox	Tx Effect
		Total Randomized	82	88	
Baseline	N in subset		60	64	
Antibody	Change in CDSS	Mean, points	-0.3	-1.8	-1.5
Negative	Change in CDSS	mn, % of Baseline	6.0	-22.5	-28.5
	Examiner Global Assessment	% with improvement	30	59	29
Baseline	N in subset		10	13	
Antibody	Change in CDSS	Mean, points	-0.9	1.3	2.2
Positive	Change in CDSS	mn, % of Baseline	-18.8	13.3	32.1
	Examiner Global Assessment	% with improvement	80	31	-49

This analysis suggests that antibody formation is an important factor, and can lead to complete loss of response. However, comparison of responses in Period I (described above) with Period II (table XX) again suggests that this disease is subject to a significant placebo effect in the response.

Correlation of CDSS with Physician Global Assessment

Responding to CBER requests, Allergan conducted analyses to assess the correlation of the CDSS evaluation with the Global Assessment. Examining just the Week 6 change in CDSS with the Physician Global Assessment, in Period I there was an r= -0.32 (n=193) and in Period II there was an r = -0.55 (n=149). Correlations with log Change in CDSS were slightly better, –0.48 and –0.64, respectively.

There was no substantial difference in Period II results when examined by treatment group; r= -0.48 for the Botox group, and –0.59 for the Placebo group.

Comment:

Allergan appears to have performed Pearson correlations on these variables, which is appropriate for continuous variables. Neither CDSS nor Global Assessment are continuous variables. Spearman Rank Order correlations are more appropriate in this case. These provide correlations of –0.38 for change in CDSS with Examiner Global Assessment and –0.23 with Patient Global Assessment (n= 196) for Period I assessments.

For period II, the Spearman r values are –0.61 for Examiner Global and –0.47 for Patient Global Assessment with Change in CDSS (n=151, 150). These figures are quite similar to those Allergan calculated for the inappropriate correlation. These values appear imply moderate agreement between the two scales. However, examination of scatterplots provides additional information, as shown for the Period II correlation of CDSS change with Examiner Global, in Figure XX.

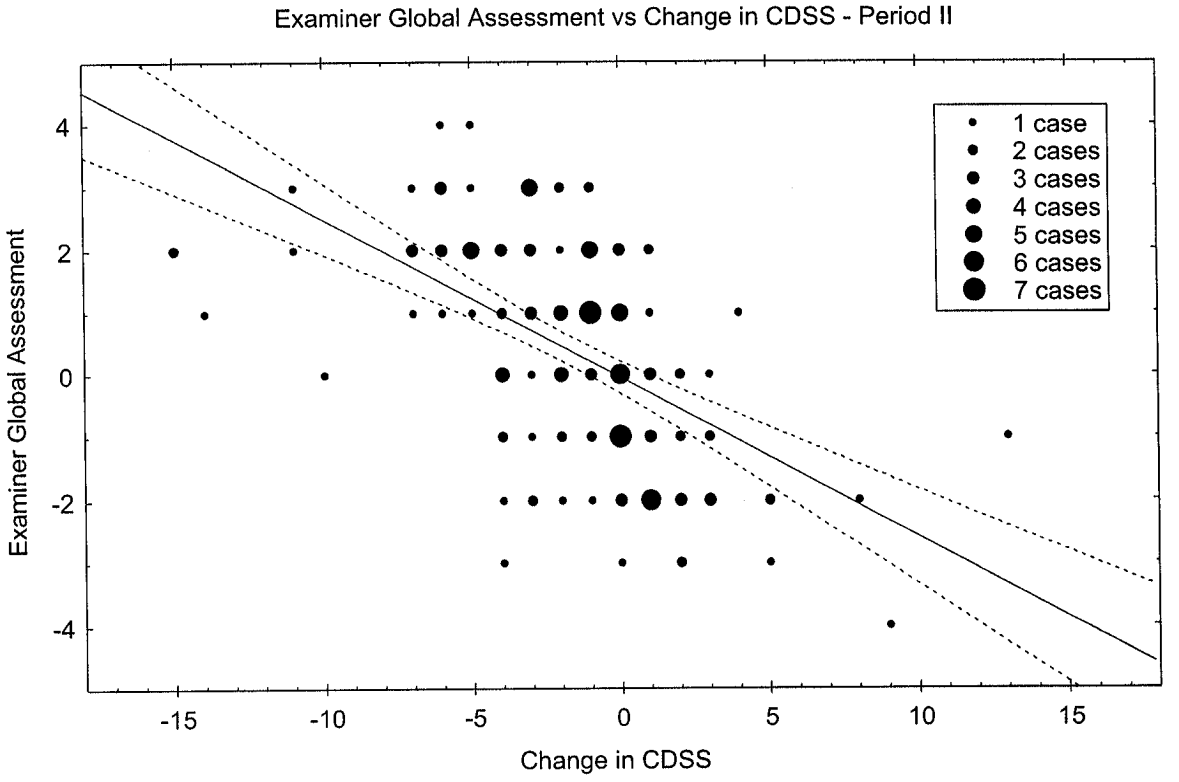


Figure XX shows that while there is a general trend of same direction agreement (worsening on Global Assessment with worsening on CDSS) there is little agreement on small changes. For subjects who improve on CDSS, an improvement (decrease in score) of 5 points is necessary before it is reliably perceived as an improvement on the Global Assessment. Thus, the Allergan proposed criterion of 2 points on CDSS as an improvement is not supported as meaningful.

The Patient Global Assessment is even less supportive of the CDSS interpretability in Period II. On that scatterplot, there is no indication of a CDSS change that is reliably perceived as an improvement by the patient. In the Period I scatterplots, the almost all subjects were perceived by the examiner and the patient as having improved at Week 6 (study visit 4), but almost all were given a change in CDSS of improvement as well. Thus in Period I, where open label treatments were performed, the ability to discern a threshold CDSS change reliably detected as an improvement is not feasible.

If the relationship is examined as a percent of baseline CDSS change vs. Global Assessment, a scatterplot suggests that a change in CDSS by approximately 50% of the baseline CDSS is necessary to be reliably perceived as an improvement, by either the Physician or the Patient Global Assessment.

If the value of CDSS improvement by 5 points is used to indicate a subject who meaningfully improved, then the Period II outcome rates of improvement are 22% for the Botox group (19/88) and 11% for the placebo group (9/82). This suggests a true rate of Botox related meaningful improvement of 11%, which while supportive of efficacy with Botox, suggests even lesser numbers of patients benefit from the treatment than the prior analyses have suggested. However, this remains a post hoc analysis which cannot provide a definitive conclusion. It does serve to further undermine the arbitrary and unsupported criteria for meaning of the outcome scales selected by Allergan.

Time to Treatment Failure

Allergan has provided an analysis of time to treatment failure based on an analysis of the Physician Global Assessment score. Time from Period II study treatment to a Global Assessment of –1 or worse was analyzed. This analysis suggested a median time to failure in the Botox group of 12 or more weeks (follow-up was not carried out past 10 weeks, so that this is extrapolation of fitted curves to earlier timepoints).

Comment:

[----------

STUDY BTOX-147-0000

OVERVIEW

This study, hereafter referred to as Study 147, was a non-treatment observational study designed to assess the reliability of the Allergan devised CDSS. It was undertaken by Allergan due to CBER's statements to Allergan that the reliability of the assessment tool was a key element to being able to interpret the outcome of Study 140. The conceptual goals of this study were the subject of repeated discussions between Allergan and CBER, and draft versions of other studies intended to address this question but never actually conducted (but which may have used the same designation of Study 147) were reviewed and commented upon by CBER. However, this design of this study was never submitted to CBER prior to the study being conducted, completed, and analyzed.

Title: Cervical Dystonia Severity Scale (CDSS) Reliability Study

The final protocol carries a date of February 12, 1997.

CLINICAL STUDY DESIGN

Objective

To evaluate the reliability of the Cervical dystonia severity scale (CDSS) in patients with cervical dystonia.

General Design Structure

This is a multicenter observational study (no treatment intervention) to assess the inter-rater reproducibility and intra-rater reproducibility of CDSS. Subjects are examined twice by two raters in a single clinic visit. Raters will receive training in CDSS prior to study initiation. The protocol planned that 40 subjects with cervical dystonia will participate. Each rater will evaluate the subject twice, each rater's two exams will be approximately 30 to 90 minutes apart in time. Each subject's participation in the study will last just several hours on a single clinic visit.

Eligibility Criteria

Inclusion Criteria

Clinical diagnosis of cervical dystonia
M/F, 21 – 75 yo

Exclusion Criteria

Pure head shift as the sole component of CD
Participation previously in Study 140
Participation in any clinical study within past 30 days.

Treatment

There was no investigational treatment in this study. Subjects were to maintain their normal medications for the day of the study.

Subject Evaluations

In addition to minimal demographic information on the subjects, each subject had 4 CDSS evaluations performed; 2 by each of two raters. CDSS is assessed as was done for Study 140.

Endpoints and Analysis

Endpoints

Intra-rater correlation of CDSS
Inter-rater correlation of CDSS

Analytic Plan

The Analytic Plan incorporates no instructions as to any unusual manner of calculation of CDSS. Reliability will be assessed with kappa statistics, with 95% CI. Intra-rater reliability will be assessed as a pooled estimate of all raters, inter-rater reliability will be assessed using the first evaluation performed by each rater on each subject.

The protocol states that excluding a kappa value of 0.4 in CI will indicate at least fair agreement between evaluations.

The sample size estimation stated that 40 is sufficient because the one sided 95% CI on correlation coefficient with r= 0.7 with n= 40 has lower CI limit of kappa = 0.535. This was deemed sufficient because it exceeds 0.4, the prospectively stated fair agreement level.

STUDY PERFORMANCE AND SUBJECT DISPOSITION

Enrollment and Subject Disposition

This study was conducted at 4 sites in March and April 1997. These sites were also involved with Study 140 so that the CDSS training for this study was confirmation of proper evaluation for Study 140. Each site enrolled 9 to 12 subjects, with a total of 42 subjects.

All subjects completed all evaluations. There were no drop-out subjects or missing data. There was one eligibility violation; enrollment of 1 subject who was 79 yo at enrollment.

The study report states an Allergan representative was at the study site on the day of conduct of the study. Each site completed all of their enrolled subjects on a single day.

The study protocol did not state the order of raters performing their evaluation upon patients. In practice, raters followed each other closely in time (within just a few minutes) for the first rating, waited at least 30 minutes, and then performed the second evaluation. The second rating had reverse order for the evaluations. Thus for each subject, the rater evaluation order was A –B –B – A or B-A-A-B (subjects were divided between which rater was first).

A Weighted Kappa was used for calculation of results, although use of weighting had not been explicitly specified in the analytic plan.

Comment:

There was a significant deviation of the analytic method of CDSS in Study 147 from the Study 140 method. For analysis in this study, the direction of rotation and laterocollis (left or right) was incorporated into the CDSS by making leftward deviations have a negative score for that component, and rightward retained the normal positive score. Components were then summed after this change in sign. Thus for many subjects, the total CDSS was the sum of both positive and negative values. In Study 140 this process was not used (left-right direction was ignored), and CDSS was the sum of only positive numbers.

The study report notes that one subject, # 410, had a rating for both retrocollis and anterocollis. Since these are mutually exclusive, Allergan chose to proceed with analysis by ignoring the lesser of these scores, and retention of the worst score. No explanation was provided of how a score for both retro- and antero-collis was recorded for the subject, nor the possible implications for investigator understanding of how to perform the evaluation.

Subject Demographics and Baseline Characteristics

Mean age 52.5 yrs
Race: 39/42 Caucasian
Sex: 57% female, 43% male
Prior Treatment history:

40 of 42 had a history of treatment with Botox prior to enrollment into Study 147. Some subjects were scheduled to receive clinical care including an injection session that day; however procedures were not preformed on subjects either just prior or during the evaluations of Study 147.

Weight/height mean: 77.6 kg, 170 cm

"Baseline" CDSS: The median CDSS of the first exam of each subject was 8.5 (mean 9.0). This is approximately 1 CDSS point lower than that of Study 140.

Table 21: Mean CDSS Scores in Study 147

Site #	Examiner	Mean CDSS Score	
		First Eval.	Second Eval.
1991	[----------	9.5	11.2
	[----- --- - - -	11.3	10.2
2065	[------	11.2	12.8
	[-------- ----	8.4	8.9
2303	[------	8.9	8.0
	[-------	5.7	5.1
2345	[- - --	9.5	10.0
	[-------	10.2	11.3

RELIABILITY RESULTS

Overall the intra-rater kappa reported by Allergan was 0.94, with lower limit C.I. of 0.90. For the individual examiners, 7 of the 8 examiners had kappa values ranging 0.87 to 0.98. One examiner had an intra-rater kappa of 0.38.

Table 22: Intra-Examiner Kappa in Study 147 by Invesitgator			
Site #	n	Investigator	Kappa
1991	12	[- ---------	0.88
	12	[--------- - - -	0.92
2065	9	[--- ----	0.94
	9	[------- ----	0.98
2303	11	[------	0.38
	11	[-----	0.9
2345	10	[- - --	0.87
	10	[-------	0.93
		All; first for each	
All 4	42	Subject	0.94
		95% CI :	(0.09, 0.97)

The inter-rater kappa reported by Allergan was 0.79 for the comparison of the first exam by each rater. The comparison between the second two exams of each rater provides a kappa of 0.86. For the first exam kappa, three of the four sites had kappa's of 0.72 or 0.9. One site had a markedly low kappa of 0.11.

Table 23 : Inter-Examiner Kappa in Study 147			
Site #	n	Exams 1:2	Exams 3:4
1991	12	0.72	0.9
2065	9	0.91	0.87
2303	11	0.11	0.54
2345	10	0.9	0.86
All 4	42	0.79	0.86
	95%CI	(0.67, 0.92)	(0.79, 0.92)

Comment:

The intra-examiner kappa may not be fully informative of true intra-rater variability for this assessment tool, since the examinations were relatively close in time. For approximately half of each examiner's evaluation pairs, the exams were approximately 30 minutes apart, and not more than 90 minutes for the remainder. The intra-rater reliability of exams spaced out over weeks apart in time was not assessed. There is likely to have been substantial memory bias in these evaluations. However, there was planned to be no communication between examiners during this process, either direct or indirect (e.g., through the subject). Thus, the inter-rater reliability may be more soundly assessed by this study, and is likely to form a credible lower limit of reliability for the intra-rater comparison as well.

Comment:

However, the method of CDSS calculation used for Allergan's analyses is not the method used for analysis of CDSS in any of the treatment investigation studies, and thus cannot be applied to those studies. CBER performed some of these analyses with properly calculated CDSS values. The intra-rater assessment was not significantly different, with a kappa point

estimate of 0.87 for the rater designated as A within each center, and 0.91 for that designated as B. The more informative inter-rater kappa was 0.71 between first rating by each rater of each subject. This is slightly lower than that reported by Allergan with their inappropriate method, a kappa of 0.79. The kappa obtained with appropriate analysis of the study is not importantly different than that submitted by Allergan.

Comment:

However, Kappa scores provide a sense of the broad reliability of the assessment across the entire scale. Kappa values do not describe the degree of reliability of assessment in comparison to any specific treatment effect size, an issue also appropriate to consider. An alternative manner of analyzing this data to examine the paired exams by the percentage that were within specified degrees of closeness of agreement. This is shown in Table XX:

Table 24: Percentage of CDSS Scores with Designated Closeness of Agreement

Degree of Agreement	Inter-Rater n= 42	Intra-Rater n= 84 (2 raters/subject)
Exact	14	17
Within 1	36	50
Within 2	50	75
Within 3	69	88
Within 4	76	92

This table indicates that repeat examination of the same subject has very little exact agreement. The agreement within 2 points is substantial, but not complete. For this artificial circumstance, the intra-rater agreement is near complete when ignoring disagreement of 3-4 points or less. This is not the case for the inter-rater agreement which has only 76% agreement of pairs when even a 4 point difference is ignored. Compared to the actual observed treatment effect size seen in Period II of Study 147 (median of 2-3 points difference from baseline) this is relatively low reliability. This study may represent a best-case circumstance. Extrapolation suggests that some amount less than 50% of between evaluation differences of 2 points in size can be confidently believed to be real differences, and somewhat less 75% (but likely at least 50%) of differences of size 3 can be regarded as real differences. However, while this is a poor degree of reliability for treatment effects of the size observed in Study 147, there is no expectation that this would occur in manner biased by treatment group. Thus, this unreliability will serve to decrease the power of a study, but not necessarily to bias it (i.e., not to increase the Type I error rate).

STUDY 191622-004

OVERVIEW

In the later portion of this decade, Allergan reorganized it's internal designations for clinical and product programs, and the designation for Botox internally changed from [----- (e.g. study BTOX-[----------) to [-------- at the time that production lot changed from [----- to [---------. Thus this study will be referred to hereafter as Study 004, even though it was conducted after Studies 140 and 147.

This study was initiated after discussions between Allergan and CBER regarding the change in manufacturing lot of Botox from [---- to [----------, and that additional clinical data regarding the use of [--------- Botox would be necessary. This study was intended purely as a safety study, to provide an indication that there was not a markedly different safety profile with [--------- toxin from that of [---- toxin. The overall design consisted of enrolling subjects on stable and apparently beneficial treatment with [---- Botox during use in clinical practice. A single open label treatment session with [--------- for all subjects is given to all subjects, and then follow-up evaluations for up to 3 months. The primary focus was on adverse events, although CDSS evaluations were also obtained.

Title: An open label, multicenter clinical evaluation of the safety of intramuscular BOTOX (Botulinum toxin type A) purified neurotoxin complex manufactured from neurotoxin complex batch [--------- in the management of cervical dystonia.

This protocol was finalized in August 1997. No amendments were made to this protocol.

CLINICAL STUDY DESIGN

Objective

The stated objective was to evaluate the safety of [--------- Botox when used in cervical dystonia [patients] at doses of up to 300 U.

General Design Structure

This was an open label multicenter study of intramuscular Botox in patients who were previously treated with Botox from batch [---- according to usua l clinical practice for cervical dystonia. The study was planned to enroll 65 subjects, each for 12 weeks of participation.

Eligibility Criteria

Inclusion Criteria

1) Clinical diagnosis of cervical dystonia
2) Patient and physician expect the current medical management regimen to remain stable during the study period.

3) History of responsiveness of CD symptoms to treatment with commercial Botox from batch [redacted]---- for at least two treatment sessions.
4) Most recent Botox injection at least 8 week prior, and currently clinically appropriate for re-injection based on recurrence of symptoms.
5) Male or female, age 21 to 75 yo.

Exclusion Criteria

1) Prior use of Botox for any reason other than CD
2) Prior use of botulinum toxin type B
3) Prior history of surgery or other permanent treatment for CD
4) Profound atrophy of the muscle to be injected, pure retro or antero-collis.
5) Any important uncontrolled system disease
6) History of aspiration pneumonia.
7) Diagnosis of any neuromuscular disease that would interfere with the study, or use of potentially neuromuscular blocking drugs (aminoglycosides, curare, etc.)
8) Pregnancy, nursing, or planned pregnancy during study, inadequate contraception.

Study Treatment

Vials of Botox from batch [redacted]---------, openly marked as such, and otherwise the same as commercially available vials were used. Treatment was to be the same as prior treatment sessions with Botox from [redacted]----, with any modifications as would be indicated by standard clinical care practice.

Subject Evaluations

Baseline
Medical history, CD history, CDSS, Pain Scales for frequency, intensity
Week 2
Clinic visit for elicitation of adverse events only
Weeks 4, 6, 12
Adverse events
CDSS and Pain Scales for frequency and intensity

Endpoints and Planned Analyses

Primary Analyses
Adverse events seen up to Week 6
Additional Analyses
Adverse events seen through the entire study
CDSS
Pain Scales

Analytic Plan

The analysis of this open label, non-randomized study were stated to be primarily descriptive and not hypothesis testing. Essentially all data would be analyzed for descriptive statistics.

The sample size was picked on the ability to provide what Allergan regarded as an appropriate confidence interval on incidence rates for the adverse events likely to be seen in the study. For example, and AE observed at a 6% rate would have a CI for the true rate of 0% to 16%; one with an observed rate of 16% would have a CI of 4-28%. No explanation of why these intervals were deemed appropriate was provided.

For the efficacy variables (CDSS and Pain Scales), missing values would be estimated using regression techniques in a secondary analysis. The primary analytic method would be with ignoring of missing data, resulting in dropping of subjects for some analyses.

STUDY PERFORMANCE AND SUBJECT DISPOSITION

Enrollment and Subject Disposition

There were a total of 70 subjects enrolled in 10 sites in the U.S. Sites enrolled between 3 to 13 subjects each. The study was conducted between October 1997 and February 1998. One subject discontinued for "personal" reasons, one for a serious AE.

There were 3 eligibility protocol violations. Two subjects with less than 8 weeks between the prior two Ⅎ---- Botox injections were enrolled, and 1 subject had previously received botulinum toxin Type B treatment.

The numbers of subjects with safety follow-ups at weeks 2, 4, or 6 was not summarized. There were 68/70 subjects available for CDSS measurements at week 4, and 66/70 at week 6. Of these follow-up evaluations at week 6, the day of follow-up ranged from 36 to 50 (mean 42).

Subject Characteristics and Treatment Administered

The mean age of subjects was 52.7 years, 93% of subjects were Caucasian, 54% female. The mean weight of subjects was 74.6 kg, the mean height 170 cm. The mean duration of CD was 10.6 years. The mean baseline CDSS was 12; Pain Frequency score 2.2, and Pain intensity score 2.2.

The mean prior dose of Ⅎ---- Botox was 234 U. The mean dose of Ⅎ---------- Botox administered in this study was 240 U. The sternocleidomastoid muscle was injected in 84% of subjects with a mean dose of 57 U; the trapezious muscle in 59% with 64 U; the Levator scapulae in 57% with 47 U, the Splenius muscles in 97% of subjects with mean dose 98 U, the Scaline muscles in 29% with 43 U, and other muscles in 29% of subjects with mean dose 74 U.

Comment:

Although this study limited the maximum dose to 300 U of Botox, less than the maximum dose permitted in Study 140, in fact there was little important difference in the study group's dosing from that of Study 140. The mean total dose was similar here to that of Study 140,