

Assessment Scales for Cervical Dystonia

Several clinical investigators have developed their own evaluation procedures for CD, and published study results employing these. However, widespread use in the medical literature has been limited to two multicomponent assessment scales and to subjective "global assessment" scales.

Tsui and colleagues at U.British Columbia, Canada invented the tool now known as the Tsui Scale. This scale has 4 questions relating to the aspects of severity of the dystonia which are given point values and then the first two are multiplied together. Both the two remaining questions are then added to this product for the final total. The maximum score is 25, and this scale is reported to have a good inter-rater correlation for scores between 5 and 20 (Tsui JKC, 1986, *Lancet* ii:245-247). The Tsui scale does not incorporate a measure of pain. As pain can be a prominent feature of CD in many patients, and has been reported to be an important component of the beneficial effects of botulinum toxin treatments, the Tsui Scale alone is regarded as inadequate to fully assess CD outcome. Clinical studies employing the Tsui Scale generally also employ a simple pain severity question to supplement the scale. The Tsui Scale appears to have been the most widely used scale in the medical literature. Baseline median score in CD studies is approximately 11 to 13.

Consky, Lang and coworkers in Toronto, Canada, developed the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) in the late 1980's and early 1990's. This scale employs multiple questions in each of three subscales, rating severity of dystonia, patient perceived disability resulting from the dystonia, and pain from the dystonia (Consky ES and Lang AE, 1994, *Clinical Assessments of Patients with Cervical Dystonia*, in: Jankovic J and Hallet M, eds. *Therapy with Botulinum Toxin*. NY: Dekker, p 224-226). Each question contributes from 0 to a maximum of 2 to 5 points, which are then combined in a complex manner (some questions averaged, some question's scores are multiplied together) to give a scale that ranges from 0 (no symptoms) to 87 (maximum severity, disability and pain). The Tsui Scale and the TWSTRS-Disability Subscale have considerable overlap in content of questions. An earlier form of the assessment was reportedly evaluated for reliability and found to have fair to good interobserver agreement (Consky ES, et al., 1990, *Neurology*, 40 (Suppl 1):445) but this abstract report was never published with full details and had assessed an early form of the scale at least partly different from the form commonly in use at present. Multiple studies employing this scale have been published. This scale incorporates a pain assessment, thus not requiring a separate pain evaluation method.

In addition, many studies also use a patient or investigator global assessment scale. These evaluations are often different in detail, but generally similar in concept. The rater is asked to select a score from a range (e.g. 0 to 10, 0 to 3, or draw a mark on a 100 mm line visual analog scale) that provides an overall impression of the status of the patient at that time.

A study seeking to compare these scales has been conducted (Tarsy, D., 1997, *Movement Disorders* 12:100-102). There were 76 subjects with CD assessed with TWSTRS, Tsui, and Physician Global rating scale (a simple 0-3 scale), before and after treatment with BOTOX. Tarsy found moderate correlations of TWSTRS-Total with the Global assessment, and of TWSTRS-Severity with Tsui scales, with somewhat lesser correlations of Tsui Scale with Global Assessment, and TWSTRS-Total with Tsui. Correlation of any of the subscales of TWSTRS with another TWSTRS subscale was low, thus supporting the intent that the subscales are assessing different aspects of the disorder and its effect upon patients.

Thus, the medical field appears to have accepted both Tsui and TWSTRS Scales as valid assessment tools for CD. The TWSTRS is more comprehensive, but also a more complex composite and more difficult to interpret, especially for small changes in score. The Tsui Scale is simpler to interpret, but cannot suffice alone as pain is not assessed within the Tsui Scale. No clear basis for determining a minimal meaningful change in score has been established for either of these scales.

Allergan rejected these established evaluation scales in designing their phase 3 study in cervical dystonia. Allergan chose instead to develop a new scale, called the Cervical Dystonia Severity Scale (CDSS). This scale was to measure solely the amount of head deviation from normal position in a sensitive manner, and not incorporate any information regarding pain or other features of the disease. After extensive discussions, CBER allowed that the scale would be clinically interpretable, but had doubts either that the minimum theoretically detectable effect (1 point, equivalent to a maximum difference of 5 degrees difference in head position in one of the 3 planes of measurement) was clinically meaningful, as well as to whether or not the scale could be used in a reliable manner in the assessment of patients. Allergan acknowledged these comments, chose to continue to use the CDSS as the primary endpoint of the study, and agreed to provide evidence for the reliability of the scale.

PHASE 3 STUDY BTOX-140-8051

OVERVIEW

Study BTOX-140-8051, hereafter referred to simply as Study 140, is the sole additional source of efficacy information regarding use of Botox in treatment of cervical dystonia. This study provides the only adequate and well controlled study data for this use.

In design overview, this study enrolled patients with a known history of (off-label) use of Botox with perceived good results. The subjects then had a 1 treatment cycle run-in period to confirm apparent good responsiveness to toxin injection. Only subjects who confirmed apparent responsiveness were then randomized to an additional double blind, placebo controlled treatment session. Due to the nature of the disease and wearing off of toxin effect with time (months), this design has components of randomized withdrawal of treatment (continued wearing off of prior toxin treatment effect in the subjects randomized to placebo) as well as randomized addition of treatment (new toxin injection in patients who had substantial wash-out of the prior toxin treatment) incorporated into the interpretation of the study.

Title: A randomized multicenter, double blind, placebo controlled study of intramuscular BOTOX (Botulinum Toxin Type A) purified neurotoxin complex for the treatment of cervical dystonia.

The original version of this protocol was dated October 26, 1994, with Amendment 1 of March 7, 1995 the version that was used at the time of study initiation. Amendment 2 was dated January 9, 1997 and approved within Allergan on February 4, 1997. This was well after study operation had begun, but prior to completion. This protocol review incorporates amendment 2. There were no important changes to study conduct between Amendment 1 and 2. The analytic plan of amendment 2 was not utilized. A separate Analytic Plan document was written and finalized after completion of the study. While the analytic plan does not have a signature date, discussions with CBER occurred prior to the time Allergan reported unblinding the study results, and has a document date of November 1997. This analytic plan was subsequently discussed further between Allergan and CBER, and verbally modified by incorporation of Smirnov testing and correlation between CDSS and the physician global assessment.

CLINICAL STUDY DESIGN

Objective

To evaluate the safety and efficacy of Botox for treatment of cervical dystonia.

General Design Structure

This was a randomized, double blind, placebo controlled study at multiple centers comparing subjects randomized to placebo vs toxin injection. There were planned to be 220 subjects participating for a total of up to 26 weeks each. Each subject initially participates in an open label active treatment run-in period (Period I) with treatment at their own previously established efficacious dose (maximum of 360 U). Subjects who appear to show repeat benefit during the run-in period and have a qualifying minimal severity at week 14 to 16 post initial treatment, are eligible for randomization in the double blind period (Period II). Retained subjects then receive treatment

with blinded study agent, and have an additional follow-up period. Period I has 10 weeks of post injection follow-up, there are 2 to 6 weeks between Week 10 of Period I and Day 0 of Period II, and Period II has 10 weeks of post injection follow-up.

The study protocol warned investigators that subjects who receive bilateral injections or dose of more than 100U into SCM may be at higher risk of dysphagia.

Subject discontinuations were permitted for AE, protocol violations, lack of efficacy, and other reasons (termed administrative reasons).

Eligibility Criteria

Inclusion Criteria

- 1) Clinical diagnosis of cervical dystonia
- 2) History of treatment with BOTOX for CD for at least 2 injection sessions
Dose of toxin not more than 360 U
- 3) CD clinically stable, with stable medications at least 1 mo, and willing to maintain medications stable for study duration.
- 4) Minimum severity on CDSS of 4 at baseline for enrollment
- 4a) Minimum severity on CDSS of 4 at Period II baseline for randomization into Period II.
- 5) M/F, age 21-75 yo

Exclusion Criteria

- 1) Use of BOTOX for any other indication
- 2) Prior surgical, denervation, spinal cord Tx. For CD
- 3) Profound atrophy of the muscles planned for injection
- 4) CD of pure anterocollis, or pure shift
- 5) Other uncontrolled systemic disease interfering with ability to participate
- 6) Infection at planned injection site
- 7) Known myasthenia gravis, Eaton-Lambert Syndrome, ALS, or other known neuromuscular disease which might lead to increased risk of toxin related AE
- 8) Concurrent use of aminoglycoside antibiotics, or other neuromuscular blocking agent.
- 9) Pregnancy, child nursing, planned pregnancy during study, or inadequate contraception.

Criteria for enrollment into Period II

CDSS score of at least 4 at Period II baseline (visit 7), after an improvement from baseline following the Visit 1 Botox injection, but subject does not need to be return to baseline severity of Visit 1.

Study Treatments

Period I used open label treatment with commercially marketed vials of Botox.

At Period II, subjects were randomized to placebo or Botox. The dose volume of each blinded study agent is the same as the volume used in each subject's previously established, presumed individually optimized dose level.

The muscles eligible for injection included sternocleidomastoid (SCM), trapezius, levator scapulae, splenius capitis/cervicis, scalene muscles, or other muscles per the investigator (but must be specified).

BOTOX vials were the same as in commercial distribution; 100U toxin lyophilized with 0.5mg human albumin, 0.9mg NaCl. Placebo vials were the same without the toxin. Diluent was 0.9% saline for injection (without preservative).

Only toxin from batch []---- was used in this study.

EMG guidance of injections was per the investigator's discretion.

Randomization

Randomization was by site, with blocks of size 4.

Blinding

Study medication for Period II was drawn up by an unblinded pharmacist or nurse who did not otherwise participate in the study. Vials were not blind-labeled. Period I vials were all openly marked as to contents.

Subject Evaluations

Medical history, CD history and treatment history, neurological exam, and clinical laboratories were performed at study start, and as appropriate at the start of Period II. Adverse event recording was done at all visits. Antibody determination was also done at baseline, and end of study.

Study Period I: Open Label Run-in Period

Screening and Baseline Visit	(injections post evaluations)
Ab assessment	
CDSS, Evaluation of shift and elevation, Pain scale, ROM	
Functional Disability Scale	
SF-36 Quality of Life survey	
ADL assessment	
Week 2, 4, 6, 8, 10	
Patient Global Assessment	
Physician Global Assessment	
CDSS	

Evaluation of shift and elevation
ROM
Functional Disability Scale
ADL Scale
Pain Scale
Week 6 only: SF-36 QOL survey also

Subjects who do not have improvement on Physician Global Assessment are terminated from the study, and do not enter period II; Subjects can be terminated prior to Week 10 assessment.

Period II - Double Blind Period

Day 0 - Baseline (14-16 weeks post injections of Period I)
(study injections done post evaluations)

CDSS
Evaluation of shift and elevation
ROM
Functional Disability Scale
Pain Scale
SF-36 QOL survey

Week 2, 4, 6, 8, 10

Patient Global Assessment
Physician Global Assessment
CDSS
Evaluation of shift and elevation
ROM
Functional Disability Scale
ADL Scale
Pain Scale
Week 6 only: SF-36 QOL survey

Description of Evaluation Tools

CDSS: Cervical Dystonia Severity Scale

The CDSS is a single score (in points) which describes the sum of the amount of head deviation around each of three axes (rotation within each of three planes); rotation about a vertical axis, left-right tilting of the head around an anterior-posterior axis, and front-back tilting around the left-right axis running through both shoulders.

The subject is assessed while seated, relaxed, with eyes closed, and no assistance to alter neck position. When tremor is significant, the largest deviation including the tremor should be scored.

Rotation is measured on the horizontal plane. Laterocollis is tilt in the coronal plane. Antero or Retrocollis is measured in the sagittal plane.

Deviations in degrees are turned into point scores. There is 1 point for each 5 degree interval of deviation (1-5 degrees = 1 point; 21-25 degrees = 5 points, etc.). The CRF page offered a series of check boxes in a row, labeled by the deviation interval amount in degrees. The point score was thus automatically associated with the deviation amount and not calculated by investigators. Both Anterocollis and Retrocollis rows available; but presumed that only one feasible. There would be three scores added to give the total CDSS score.

A total of 4 points on CDSS implies at least a minimum deviation of 8 degrees; (e.g. 6; 1 ;1) but maximum of 20 degrees total deviation (e.g. 5, 5, 10). The minimum score is 0 (no deviations) and the maximum possible score is 54. However, a score of 54 is likely incompatible with life, as it requires three angles of 90 degrees of abnormality.

Global Assessment Scales

This is a subjective assessment of the relative change in the subject's severity. This evaluation tool explicitly incorporates comparison to baseline.

This was assessed on a 9 category scale of -4 to +4 (Very marked worsening to Complete Abolishment of symptoms). 0 is explicitly labeled unchanged, +1 is labeled slight improvement (about 25% improvement). Half point steps are not used.

Pain Assessments

Frequency of Pain associated with CD is assessed on a single 9 category scale of 0 to 4, with half points allowed. A score of 0 implies never for frequency, 4 is constant.

Intensity of Pain associated with CD is rated on a 9 category scale of 0 to 4 scale, with half points allowed in a similar manner. No pain is a score of 0, extremely severe pain is a score of 4.

ADL Scale

This assessment tool employed 13 specific activities in a list. An assessment on a 9 category scale, 0 to 4 scale of No difficulty to very severe difficulty, with half points are allowed is designated for each. Each of the 13 specific activities are graded and remain independent. There is no combined score cited, and the source or validation within CD of this scale is unknown.

Functional Disability

Functional Disability is scored on a global scale of 0 to 4, with half points allowed (9 category scale). No description of how patients or physicians were asked to interpret the phrase "functional disability" was provided.

Range of Motion (ROM)

ROM is the patient's active willful range of motion in each of three directions. Assessments are made of the maximum excursion possible R-L for Lateral and Rotation, forward - back for Anterior/Posterior ROM.

The ROM Scale categorizes the measured ROM in each plane by intervals (1-10; 11-20 ; 21-30 ; 31-40 ; 41-50; 51-60; 61-80; 81-100; 101-140 ; 141-180). The CRF page for ROM measurements had a row of category check boxes printed out for each measurement, so that only single check mark for each was required by investigator to indicate the ROM in degrees, with read-off in points also provided.

Endpoints and Planned Analyses

Efficacy Endpoints

Primary Endpoints: (evaluated at Week 6 of Period II)

- 1) Change from baseline in Cervical Dystonia Severity Scale
AND (both required to conclude efficacy is shown)
- 2) Percent of subjects with improvement on Physicians Global Assessment Scale

Secondary Endpoints

- 1a,b,c) Range of motion (3 assessments)
- 2a,b) Subjective evaluation of Pain (2 assessments - Frequency and Intensity)
- 3a,b) Subjective Functional Disability (2 assessments - Physician and Patient)

Tertiary Endpoints

- Time to Failure
- Quality of Life
- Activities of Daily Living
- Patient Global Assessment
- Evaluation of Shift and Shoulder Elevation

Analytic Plan

No interim analyses were planned or conducted.

All hypotheses were to be tested at the 0.05 level, two sided. Primary data analysis was stated to be an intent to treat analysis, that would be applied to all efficacy analyses.

The Primary Endpoints are evaluated at 6 weeks post injection in Period II. Statistically significant outcomes on both primary endpoints, tested at 0.05 level for each, is required to conclude a positive result for the study.

Missing values were stated to be imputed only at week 6 evaluations and only for Primary Endpoints (implying the other weeks will not be analyzed with full intent to treat). Subjects who discontinue for "lack of efficacy" will be replaced by assignment of worst value observed over all

subjects. Subjects who discontinue for other reasons will be assigned a LOCF value. Other variables and weeks will not have missing data imputation.

Comment

The wording in the analytic plan regarding imputation for missing due to lack of efficacy "will be replaced by assignment of the worst value; ... scored over all subjects". The analytic plan does not qualify this as worst within subjects of the same treatment group, nor was there any discussion between Allergan and CBER regarding use of worst score imputation just within the treatment group. However, only use of the same score for both treatment groups is consistent with the null hypothesis. This appears to be the procedure specified in the final analytic plan. This was not the procedure employed by Allergan, as discussed in the Results section.

The protocol prospectively designated a difference between groups in CDSS of 1 point as clinically meaningful, and individual meaningful response is a 2 point improvement from baseline. No basis of this designation was provided. CDSS outcomes will be analyzed as change in CDSS analyzed with ANCOVA using treatment, investigator main effects, Baseline CDSS as covariate (note that thus baseline CDSS is incorporated twice). Rates of improvement will also be analyzed by calculating rates of subjects with at least 2 points improvement over baseline.

The protocol designated a 20% difference in rates of subjects with improvement on Physician Global Assessment as a meaningful effect. No basis for this assertion was provided. Improvement on the Physician Global Assessment is indicated by any score of +1 or more. Analysis will be by ANCOVA with treatment and investigator as main effects, baseline CDSS as covariate. ANCOVA was to be used for both the analysis of percentage with any improvement, as well as a secondary analysis of the amount of improvement.

The Patient Global Assessment will be analyzed by t-test. Pain assessment and Functional Disability will be analyzed by t-test, as will each of the Activities of Daily Living. ROM is categorized into no change, intervals by 10 degrees for <60 degrees; intervals by 20 degrees for < 100 degrees, and intervals of 40 degrees up to 180 degrees. These will be analyzed as ordinal variables at outcome, not change from baseline. Analysis will be with rank-sum test.

Period I results will be summarized with descriptive statistics, but no hypothesis testing performed.

Variables with both a baseline status and follow-up evaluations will be analyzed as change from baseline.

Time to treatment was initially planned as time to exit for lack of efficacy. However, study conduct was modified to encourage investigators to continue to evaluate subjects irrespective of response. Therefore this variable was confounded as initially planned, and was not analyzed. A post-hoc analysis for this information was performed (not described in analytic plan). Time to failure was defined as the first worsening on the Physician Global Scale.

Visit tolerance windows were defined in the Analytic Plan only (i.e., post completion of study). Permissible windows generally ranged from 6 days early to 7 days later than the ideal evaluation day.

Subgroups planned for analysis were by age (21-64 vs 65-75), sex, and investigator.

Planned Sample Size

With a sample size of 182 subjects total, assuming outcome rates of improvement of 40% and 20% in the two groups, at alpha 0.05, there is 80% power to detect the outcome.

With 182 subjects total for the CDSS, there is 85% power to detect a mean 1 point difference between groups at alpha 0.05, and s.d. of 2.25.

Sample size was increased to 220 subjects enrolled into Period I to allow for dropouts before completion of Period II. No specific plan for percentage of Period I exclusion from Period II was stated.

Protocol Modifications

There were no additional protocol modifications other than those described above. The analytic plan was completed just immediately prior to unblinding. Deviations from the analytic plan nonetheless occurred, and are described in the appropriate parts the report of results.

STUDY PERFORMANCE AND SUBJECT DISPOSITION

Enrollment and Subject Disposition

This study was conducted between May 1995 and October 1997 at 21 US and 1 Canadian site. A total of 214 different subjects were evaluated in Period I. There were 170 subjects who completed all evaluations in Period I. There were 44 discontinuations; 18 for lack of efficacy, none for AE, and 26 for other reasons.

Due to errors in study conduct there were re-enrollments of some subjects into Period I, who were given new Period I subject numbers. Therefore, there are 220 Period I subjects, but comprised of only 214 actual unique subjects. 5 subjects who were enrolled and then determined to have failed the study entry criteria for Period I (subjects 906, 907, 605, 654, 006) were discontinued from Period I. They subsequently did qualify for period I and were re-enrolled (as subjects 910, 909, 607, 668, 010). Allergan has retained only the second enrollment data in the analyses. See Protocol Deviations regarding the sixth repeat subject, # 159-160.

Of the 170 subjects eligible for consideration for Period II, all continued participation and 135 subjects completed all Period II evaluations. Of the 35 who discontinued during Period II, none were for AE, 27 for lack of efficacy (8 toxin, 19 placebo) and 8 for other reasons. Of the discontinuations for lack of efficacy (LoE) there were 4 in the Botox and 3 in the placebo group by the time of Week 6, the primary endpoint visit.

Characteristic	Number of Patients			
	Period I	Period II		
	Total	Total	Placebo	BOTOX
Enrolled	214	170	82	88
Completed	170	135	58	77
Discontinued Due to:				
AE	0	0	0	0
Lack of Efficacy	18	27	19	8
Protocol Violation	6	0	0	0
Missed Visits	5	3	2	1
Unable to Continue	3	3	2	1
Other	12	2	1	1

Comment:

Of the 220 subjects enrolled in Period I, 191 showed an improvement on the Physician Global Assessment at Week 6 of Period I. Approximately 10% of these subjects were later disqualified for other reasons prohibiting enrollment into Period II. Thus, in this open label run-in period, 87% of subjects tested appeared to show an improvement with treatment.

Protocol Deviations**Procedural Violations**

Subject 159 enrolled in Period I but when continuing into Period II received study drug intended for Period I subject 160 by error rather than an assigned Period II study drug. Allergan has not stated if randomization assignment did occur, what the randomization assignment was, or what was done with the assigned randomization slot. Similar events for subject 607 who received Period I study drug intended for subject 608 rather than correct Period II drug, and Subject 007 who was re-injected at Period II start with the remaining Period I study drug (not stated if drug was for Subject 007 or some other subject). For all these subjects data was not included for Period II, and retained for Period I analyses. Subject 159 was treated as a re-enrollment into Period I as subject 160, and continued thereafter. Subject 607 had two enrollments in Period I, and the inadvertent Period I drug injection for Period II, and then withdrawn.

Analytic Plan deviations did occur, and are described in the section on results for each specific endpoint.

Visit Windows were not defined in the protocol, but they were in the Analytic Plan. No analysis of visits per the analytic plan was performed, contrary to the analytic plan.

When the data were to be examined for site-related effects, pooling of sites to achieve at least 10 subjects per site was required, so that only 5 "pooled sites" were left. This was not prospectively planned in the Analytic plan. This model was not investigated intensively.

Eligibility Violations

There were 46 Period I subjects that did not have history of 2 consecutive successful BOTOX injections prior to enrollment into Period I, which occurred with Allergan consent for 35 subjects until September 1995 when investigators were informed that such would no longer be permissible. These 35 were allowed to continue participation, and 29 went on to participate in Period II. There were 11 subjects enrolled into Period I in violation of this criterion after Allergan notified sites this was not permitted, and these subjects were withdrawn from the study.

There were additional violations for 5 subjects: Subject 413 was 76 yo on enrollment; Subject 001 had been previously treated with BOTOX for blepharospasm, and went on to participate in Period II. Three subjects (229, 452 who had surgical or chemical denervation for CD; 407 who became pregnant) were withdrawn from the study by the end of period I.

Other Violations

- 1 subject used outdated BOTOX for Period I
- 1 subject received the volume equivalent of 380 U in Period II, but was on placebo arm
- 2 subjects enrolled in Period II although they did not meet the criterion of showing CD not worse than enrollment into period I (# 367, 118)
- 1 subject failed to meet minimum CDSS criterion at Period II baseline (# 413)
- 5 subjects missed consecutive visits in Period I, 3 in Period II (457, 552, 553) and were withdrawn from the study (this rule was applied for some unstated period of time, although never written into the protocol)
- 1 subject missed Period II baseline exam and minimum CDSS of 4 is unconfirmed (653)
- Several events of missassignment of randomization numbers:
 - Subjects 454, 455, 456, 457 (site 2035)
 - 106, 107, 109, 110, 118, 119 (site 2065)
- 1 period II number never assigned at site 2352 - J04
- 3 subjects were injected with Period I drug instead of Period II drug, as described above.
- 1 subject who received Period II enrollment too soon (week 12 after Period I, rather than 14-16 weeks)
- 1 erroneous use of commercial BOTOX for a subject in Period II (subject 552 randomized to placebo, given 40U of commercial BOTOX by mistake, and then given 220 U of blinded study medication.) included in Placebo group for analysis
- 1 site where some CDSS evaluations done by study coordinator rather than investigator (subjects 221, 223, 225, 226 at visit 9; 230 at visits 3, 5, 11) at site 1738

No subjects used prohibited medications

Study Sites and Study Enrollment

There were 22 total sites participating in this study, 21 US and 1 Canadian. There was good balance in the numbers of patients allocated to each treatment group within the sites due to blocking. Site contribution to Period II ranged from 0 to 19, with 7 sites of 10 or more subjects in Period II, and 5 with 1 to 3 subjects.

Site Number	Number of Patients Enrolled			
	Period I		Period II	
	Total	Total	Placebo	BOTOX
1991	23	19	10	9
2352	19	15	7	8
2035	15	13	6	7
2303	5	3	2	1
1739	3	3	1	2
2302	4	4	2	2
2342	9	8	4	4
2368	11	7	4	3
2325	15	13	6	7
2340	10	6	2	4
2309	8	7	3	4
2345	7	6	3	3
2065	19	18	10	8
2326	8	5	2	3
2335	5	3	2	1
2305	10	7	3	4
2662	9	7	3	4
2301	2	1	0	1
2332	2	0	0	0
1749	20	13	6	7
1738	12	10	5	5
2310	4	2	1	1

Treatment Administered

All toxin in this study was from [] bulk toxin, lot numbers 10439, 10735 or 11027.

The mean dose of toxin was 241 U in Period I and 236 U in Period II. No subject received more than 360 U in either period. EMG was used in 64% of Period I treatments, 64.8% of Period II BOTOX subjects, and 63.4% of Period II placebo subjects.

Muscle	Period I		Period II		
	n	dose (U)	Placebo		BOTOX
			n	n	
Any muscle	214	241	82	88	236
SCM	184	60	72	77	55
Trapezius	118	70	42	49	70
Lev. Scapu.	123	53	46	52	49
Splenius mm.	207	92	80	83	87
Scalene	36	39	15	15	42
Others	72	69	31	34	70

Comparison to dosing in Period I for subjects who went on to Period II shows that the dosing in Period I was much like that of Period II, and there was highly similar dosing between the two Period II groups during their Period I participation.

Muscle	Placebo		BOTOX	
	n	dose (U)	n	dose (U)
Any muscle	82	236	88	235
SCM	71	62	77	56
Trapezius	44	66	50	67
Lev. Scapu.	45	47	52	52
Splenius mm.	81	89	86	90
Scalene	15	38	12	40
Others	31	70	33	65

Bioresearch Monitoring Inspections

These were still pending at the time of writing this review document.

Study Population Characteristics

The study population characteristics in age and sex distribution are similar to that expected from the medical literature. Essentially all subjects were Caucasian, as has been seen in other studies. The baseline severity, while difficult to judge when based on this new CDSS scale without prior experience to reference, appears to be of low to moderate severity.