While baseline score was a median of only 9 points, this still represents a modest change, even if real.

Also as expected, the revised analysis of the Physician Global Assessment continues to be statistically significant.

ANALYSES OF RESPONDERS BASED ON CDSS

Allergan states that they disagree with the proposal that 5 points change on the CDSS is the limit of reliably discerning a meaningful change in CDSS (versus the 2 points CDSS they arbitrarily selected in the analytic plan). To support their view point, they note that the analytic plan had arbitrarily selected a Global Assessment Change of +1 as clinically meaningful. In an analysis of subjects with a Global Assessment of +1, the mean CDSS change was –2.19, which rounds to 2 points.

Comment:

Allergan's comments do not address the core of the issue. In order to employ the analysis of meaningful response frequency, each subject should be classified as a responder or not based on a criterion that ensures all subjects deemed responders are recognized as having a meaningful response. CBER's analysis suggests this does not reliably occur. Subjects with a designated CDSS response are not almost all recognized as improved on the Global Assessment) until the CDSS change is 5 points or more. There are many subjects with CDSS improvements of 2 points who are not recognized as improved in the Global Assessment. Therefore, any presentation of Response Rate based on CDSS change of 2 points is flawed, and cannot be interpreted as describing only subjects with meaningful responses. Allergan's approach, rather than comparing subjects who can reliably be regarded as responders , attempts to compare frequency of all subjects who might be a responder, while mixing in many subjects who are likely not a responder. This analysis is sufficiently flawed to not be interpretable.

However, Allergan has conducted and submitted the analysis of CDSS responders with a responder defined as 5 points of improvement or more. This analysis was eventually submitted based on the correct subject set (170 Period II subjects, with imputation as noted above).

For Responder defined as a change of 5 CDSS points, there were 11% and 21.6% responders in the Placebo and Botox groups respectively, for a difference in rate of 10.6%; $p = 0.048$.

For Responder defined as a change of 2 CDSS points, there were 37.8% and 48.9% responders in the Placebo and Botox groups respectively, for a difference in rate of 11.1%; $p = 0.1$.

Comment:

These analyses in fact do not indicate different treatment associated effect sizes; approximately 10% of patients appeared to have a response due to BOTOX, irrespective of the non-conservative or conservative estimate of total responders in each group. This suggests that this estimate is reliable.

PAIN ASSESSMENT REANALYSIS

The pain assessments submitted by Allergan were initially analyzed without an intent to treat analysis. The Intensity of Pain result showed a treatment effect that was statistically significant and robust to all sensitivity analyses performed by CBER.

However, the Frequency of Pain analysis showed a much more borderline effect, and a proper analytic plan analysis suggested it may not be statistically significant. A proper analytic plan analysis was requested for submission by Allergan. This analysis (see the 170 subject analysis of the August submission) showed baseline values of 1.91 and 1.77 in the Placebo and BOTOX groups respectively, with Week 6 change from baseline of -0.01 and –0.026 respectively, for a net treatment associated difference of –0.025 (an improvement) with associated p-value of 0.048. Thus, this was of marginal statistical significance when a correct prospective analytic plan was employed. Allergan did not submit sensitivity analyses of this endpoint.

Comment:

This endpoint is again suggesting a quite small, but at least marginally statistically significant effect of benefit with BOTOX treatment. This assessment is quite consistent with the impression provided by the primary endpoints of the study. An effect on intensity of pain is more robustly demonstrated than on frequency.

FUNCTIONAL DISABILITY ASSESSMENT

Allergan provides discussion on this assessment tool, which was one of at least 7 secondary endpoints. No explicit explanation was provided to investigators on how to interpret the terminology of the assessment tool, other than the comparison to normal activities were to be the individual subject's own usual activities prior to the original onset of CD. In trying to distinguish between this and the Global Assessment, Allergan states that functional disability is focussed on function while the global assessment will include in some manner overall assessment of head position, ROM, pain, and other amorphous consideration of signs and symptoms. Allergan attempts to argue that the Functional Disability is a "static" measure, assessing absolute level of impairment, while the Global Assessment is assessing the change from the pre-treatment status, and thus not a "static" measure (not an absolute measure). No documentation or other supportive materials are supplied to uphold this discussion. A reanalysis of this endpoint is supplied based on the faulty dataset of 173 subjects. No analysis based on an appropriate dataset was submitted.

Comment:

The "definition" of normal activities is subject considerable unreliability, as it depends on the subject's recollection of their activities at some variable time in the past. The uniformity of the accuracy of the recollection is questionable. The interpretability or reliability of this endpoint remains doubtful. Any use of this endpoint in promotional materials without full explanation of the underlying uninterpretability of the endpoint would be misleading. The lack of an analysis based on a proper intention to treat analysis is not a critical absence, since the result will be uninterpretable irrespective of the numeric result. No meaningful conclusions can be made based on this endpoint.

TIME TO FAILURE ANALYSIS

Allergan's initial analysis of the Global Assessment for a time to failure was based on failure defined as worsening, while CBER believed that simple return to baseline (i.e., Global Assessment of 0) defines a practical state of failure of response. Allergan replied that the analysis criteria were selected due to the time lag to initiate the response, and that at the 2 week evaluation many subjects who subsequently went on to show a response had not yet done so, and would be deemed a failure event at Week 2. Allergan substitutes a different analysis, in which failure at the first evaluation required a score of –1 (as previously) but subsequently a score of 0 was deemed a failure (as requested by CBER). This analysis does support an impression of a difference between treatment groups, approximately a 30 day difference in median time to failure between the two groups, and the toxin group shows approximately 90% failure by day 95.

Comment:

Allergan's comments regarding not imposing a criterion of no difference from baseline at the first evaluation due to delayed onset of benefit are well founded. Their proposed analysis is well suited to address the issue. Of note, this analysis suggests that the benefits from BOTOX have largely waned by Week 14.

STUDY 140 SAFETY INFORMATION

DYSPHAGIA EVENT DETAILS

Allergan reports that they have no further details on a description of the severity of the symptoms, nor on any changes in diet that were employed. There were no medical treatments described for any of the dysphagia events.

SEVERE MUSCLE WEAKNESS

Allergan reports that Subject 410 developed neck muscle weakness graded as severe with dysphagia graded as severe after a Period I injection of 300 U of BOTOX, to 8 neck muscles including both sides of the neck. A cervical collar was provided for the weakness, no medical treatment for the dysphagia. Both of these had subsided to mild grade AE by the Week 4 evaluation.

SEVERE ORAL DRYNESS EVENTS

Allergan provides no further details on these events other than no medical treatment was administered for these events.

Comment:

Allergan has relatively little detail in the adverse event database. However, while these events were likely important to the subjects, they do not seem to have posed a serious medical risk to the subjects.

STUDY 140 ANTIBODY TESTING INFORMATION

Allergan reports that there were 214 subjects enrolled in Period I, with planned testing at the beginning and end of the study. However there were numerous planned samples that did not yield

actual test results. There were 5 samples that were inadequately labeled, but subsequently traced back and deemed to be reliably identified and were assayed. There was 1 subject with mismatched ID numbers on samples, and the assay was not included in results analyses. There were 25 samples inadequate in volume, and 71 samples which were not received by the central testing laboratory, and Allergan was unable to determine if the samples were actually obtained, or sent by the site to the central laboratory. Allergan noted that these site's recordkeeping was poor.

There were 85 subjects with only one assay obtained, and 116 with two assays, for a total of 201 subjects with at least one assay of the planned two.

ANTIBODY TESTING RESULTS

Allergan submitted a revised table of antibody testing results for Period I subjects:

Table 6: Antibody Testing Results for Subjects in Period I

Period II group	Testing point	Total N	# with test results	Ab Negative	Ab Positive	% Positive
BOTOX	Baseline	88	78	64	14	18
	Exit		68	54	14	21
Placebo	Baseline	82	72	62	10	14
	Exit		61	50	11	18
Not in Period II	Baseline	44	42	33	9	21
	Exit		10	8	2	20
Total	Baseline	214	192	159	33	17
	Exit		139	112	27	19

Comment:

This suggests the prevalence of antibody positive patients in the population who are already receiving BOTOX is approximately 17% (33 of 192 tested at baseline).

There were a total of 192 subjects with assay results at baseline for Period I, of whom 33 (17.2%) were positive. Of these, there were 13 subjects enrolled only into Period I who were positive at baseline and did not have a follow-up exit assay. Of all exit assays, there were a total of 27 of 139 assays that were positive (19.4%).

Of the subjects with two assay results, irregardless of their Period II participation:

Table 7: Subjects with Both Baseline and Exit Results Regardless of Period II Participation

	214 total enrolled 122 with 2 assays	Baseline Assay Negative	Positive
Exit Assay	Negative	102	0
	Positive	2	20

This indicates that overall, most subjects who exited with a positive assay had entered with one. However, the rate of conversion cannot be estimated from this table because there is a mixture of subjects who received only one BOTOX injection and were assayed after 3 months (did not enroll

into Period II), one BOTOX injection and assayed after 6 months (Period II placebo group) and those that received two BOTOX injections and were assayed after 6 months (BOTOX randomized group). Note also there were a large fraction of subjects who did not get the planned two assays.

Focussing on Period II subjects only, there were 116 of these subjects with two assays:

Table 8: Period II Subjects with Both Baseline and Exit Results			
170 Period II subjects 116 with 2 assays		Baseline Assay Negative	 Positive
Exit Assay	Negative Positive	94 2	0 20

Because this table does not distinguish between the placebo and Botox treated subjects, it remains difficult to interpret in terms of relationship of use of BOTOX and rate of antibody conversion.

When examined by the Period II treatment group:

Table 9: Antibody Assay Results for Subjects in Period II						
	Placebo n= 82			BOTOX n= 88		
	# with results	# Positive	% Positive	# with results	# Positive	% Positive
Baseline	72	10	14%	78	14	18%
Exit	61	11	18%	68	14	21%
Exit result for known baseline negative subjects	44	0	0%	52	2	4%

All baseline positive subjects with an exit result remained positive at exit testing.

Comment:

The important information in this table is of the 2 known conversions to positive in the entire study (and there may have been more due to the missing baseline values) both occurred in the subjects who received two injections with BOTOX. This suggests that even in subjects with a prior history of BOTOX injections for at least 6 months, and likely longer, the rate of conversion to positive antibodies with continued treatments may be approximately 4% per 6 months, or 8% on an annualized basis.

CONSEQUENCES OF ANTIBODY PRESENCE

Allergan reports that subset analyses of Period I outcomes (unblinded treatments) shows that baseline antibody positive subjects had nearly the same outcome irrespective of antibody status at baseline. However, the Period II results were less reassuring.

Table 10: Period I or II Week 6 Outcome Assessments by Baseline MPA Assay Status									
			Placebo Injection - MPA Baseline Status				Toxin Injection - MPA Baseline Status			
			Negative		Positive		Negative		Positive	
			n	Score	n	Score	n	Score	n	Score
Period I	CDSS	Baseline					159	9.5	33	12.4
		Week 6 Change					141	-4.2	29	-4
	Phys Global	% with >0					159	86.80%	33	84.80%
Period II	CDSS	Week 6 Change	62	-0.14	10	-0.9	64	-2.13	14	1.14
	Phys Global	% with >0	62	29.10%	10	80.00%	64	59.30%	14	35.80%

Comment:

It is interesting to note that the Period II baseline MPA + subjects in placebo had a substantial response (compared to the BOTOX, MPA – group) as though these subjects were already long used to having placebo responses due to real loss of efficacy from antibodies.

Nonetheless, these results strongly suggest that MPA+ status leads to a loss of response when examined in a double blind manner. This data is also very suggestive that there are substantial placebo responses being exhibited during open label treatments.

With regards to the antibody data and the interpretation, Allergan acknowledges that additional information on incidence and meaning of antibody formation are important to obtain.

Comment:

This further information will be important to obtain in formal phase 4 studies with commitment from Allergan to carry them out.

STUDY 147 RELATED ISSUES

Allergan had initially submitted analyses of the CDSS obtained in Study 147 using a method that did not apply to it's use in Study 140, by encoding in the subscores the direction of the deviation. This is not a part of the tool as defined for use in Study 140. A reanalysis of the kappa scores submitted by Allergan employing a consistent method shows that the kappa values still speak to overall correlation. The intra-rater kappa average is 0.87, and the inter-rater kappa is 0.73 for the first exam by each examiner. While these are slightly less than initially submitted by Allergan (0.94, 0.79 respectively) they do not lead to a markedly different conclusion.

However, in response to CBER request for further analyses to gauge the specific amount of agreement, Allergan submitted the requested analyses.

Table 11: Percentage CDSS Score Agreement Within Defined Range		
	Percent within Limit (n=42)	
Permitted Difference (≤± n)	Intra-Examiner	Inter-Examiner
0	17	17
1	52	38
2	79	50
3	88	69
4	90	76
5		88

Comment:

This analysis indicates that even intra-examiner the reliability of the score becomes substantial only when changes of 3 or more points are of concern. When different examiners of a single subject are employed, discounting "changes" of up to 5 points are needed to be reliable for the great majority of observations. This suggests that Study 140, where mean changes from baseline of only 2 points or less were observed was greatly hampered by the unreliability of the assessment tool. A more reliable assessment tool is needed to be sensitive to such small effect sizes. However, it does not prohibit accepting of the results of Study 140 as indicating a treatment effect, as this unreliability should not have lead to a bias between treatment groups.

STUDY 004 AND 014 SAFETY INFORMATION

Allergan reports that almost all subjects in study 004 had the designated follow-ups. There were too few violations to warrant detailed discussion in this review, and the Study can be accepted as sound on this issue.

For Study 014 further details regarding the SAEs were not available. Since this was not a prospective study, but rather a chart review study, detailed adverse event information was not available and was not a primary goal of the study. No useful additional information was available.

ADDITIONAL AREAS OF INFORMATION FROM THE CLINICAL DEVELOPMENT PROGRAM

TOXIN NAÏVE SUBJECTS

Allergan reports that they regard toxin naïve subjects to have been adequately studied in the overall clinical development program. Study OCUL 102 was entirely naïve subjects, and consisted of 51 subjects in a controlled randomized study. Study OCUL 104 was a long term open label study that had most subjects naïve for BOTOX use at entry. Allergan notes that in that study, the overall rate of dysphagia on first dose was 13%, and 7% had local weakness. Allergan believes that it is likely that many other subjects were toxin naïve at enrollment into some other studies, but that status was not recorded in those studies.

Allergan re-submitted the Final Study Report for Study OCUL 102 (originally submitted in the 1991 submission). A brief synopsis of this study is contained in the appendix of this review.

DOSE RESPONSE INFORMATION

Allergan performed post hoc dose level groupings of the Study 140 subjects and examined dose effect and dose-safety relationships. Allergan acknowledges that this may merely be confirming that subjects in this study had already had individually optimized dosing.

Comment:

> These analyses do not serve to either establish or refute any dose relationships for safety or efficacy, as noted in the original review.

GERIATRIC DATA ANALYSES

Allergan has submitted data regarding the information in geriatric subjects. In Period II of study 140 most subjects were below age 65, 18% were between 65 and 75 (31 of 170 total) and only 3 subjects of the 170 were age 75 or greater. For the limited number of subjects age 65 or greater there was no apparent notable difference in efficacy on CDSS or Global Assessment rate of success.

The adverse event profile does not seem markedly different between age groups, but such a small database of geriatric patients precludes any definitive assessment.

SUMMARY

The majority of the clinical review for this application supplement is in the review document of November 19, 1999, and should be consulted for all detailed information. This review document is limited to specific issues unresolved at the completion of the review of the response to FDA submitted in June 1999.

Uncertainties regarding the quality of study conduct for the central controlled study (Study 140) were addressed by Allergan, and none of the concerns remain as serious doubts as to the study conduct. This study's results can be regarded as reliable and informative.

There were certain anomalies in the dataset and analytic methods employed by Allergan as initially submitted. These have been reviewed and most appropriate disposition of patients has been determined, along with the analytic methods for use in the primary analyses. While the primary, prospective analytic method does not reach statistical significance for the CDSS comparison, this appears to be due to substantial sensitivity of the selected method to the missing value imputation plan in this relatively small study with relatively small treatment-associated effect. When a variety of alternative analyses are performed as sensitivity analyses, essentially all produce confidence intervals the exclude the value of no difference between treatment groups. All provide approximately same estimate of the treatment effect size as well. Thus, a reasonable conclusion is that on the CDSS endpoint Study 140 does provide evidence of efficacy, that was merely obscured by a sub-optimal selection of analytic plan and missing data imputation method. The other co-primary endpoint of "responders" on the global assessment was at issue with regard to the criterion to employ for a responder. However, analyses of alternative criteria for a responder again provide very consistent results in regards both the estimate of treatment effect size and of a finding of statistical significance. Therefore, Study 140 can be confidently regarded as having provided evidence in favor of efficacy being associated with BOTOX treatments.

Further information regarding Study 140 adverse events was generally not available. This appears to have been potentially related to the relatively limited impact of these events on the immediate status of the patients. These events do not appear to have posed any major medical risks.

Antibody formation is the presumed mechanism of development of serum neutralizing activity, and clarification of the study results on this topic was provided. There appear to be a small but notable fraction of subjects, approximately 17%, with neutralizing activity who were enrolled in this study. This study suggested that even after perhaps years of treatment with BOTOX, patients can continue to develop antibodies, and this may occur at a rate of even 4% per two treatments (approximately 6 months). An additional notable feature of this study is that it provided a strong suggestion that formation of antibodies is important to clinical response. While not a comparison between properly randomized groups, subset analysis based on baseline neutralizing antibody status suggested that patients with antibodies do not respond to BOTOX. However, this cannot be regarded as definitive conclusion due to this being a post hoc subset analysis.

Overall risk-benefit assessment can now be formed for this proposed use. In overview, the major component of the clinical evidence for efficacy derives from a single well-controlled study conducted by Allergan. The clinical evidence for safety is more broadly based. Data from the single well-controlled study is supported by data from earlier clinical studies, many of which are in the published

medical literature, as well as the spontaneous reporting of adverse events to Allergan and/or FDA from very considerable extent and duration of patient exposure occurring in off-label use of this marketed product over approximately the past 10 years.

The applicant has provided reliable data that demonstrates that there is limited amounts of efficacy with this use of BOTOX, but that there is a real treatment associated effect. The data suggest that there is a small reduction of abnormal head positioning (approximately 15%; approximately 1 point of true treatment associated effect from a baseline of 9 points), and that only approximately 20% of patients have a toxin-associated perception of improvement. Of considerable interest is that the study design of an open label run-in period followed by a blinded comparison period allow a comparison of the perceived treatment response that may be similar to perceptions in general clinical practice with that of controlled study demonstrated toxin effect. The open label perception of response (approximately 4 points on CDSS) is considerably larger than the demonstrated toxin-associated effect of approximately 1 point. This suggests that there is a considerable component of expectation bias (i.e., "placebo effect") contributing to the perceived response to BOTOX in general clinical practice.

Adverse events in the studies submitted to the PLA do not demonstrate substantial serious risks, and the safety information from other sources are consistent with this impression. Very rare reports in the medical literature do describe serious adverse events, and need to be recognized in the labeling. Thus, although there appears to be limited efficacy associated with BOTOX, the safety risks do not appear to overwhelm this demonstration. The risk benefit comparison of BOTOX for this use is in favor of the use

RECOMMENDATION

Labeling for this use of BOTOX can be adequately formulated based upon the totality of information available regarding BOTOX and treatment of cervical dystonia. Approval should be provided for this addition of a new use to the indications for BOTOX.

Concurrent with this approval, however, the applicant should be required to undertake a new study of the rate of antibody formation with the use of BOTOX. This should evaluate the rate of formation of antibodies over several years of exposure. Since there is a clear suggestion that efficacy can be lost with formation of antibodies, the rate of antibody formation can be important information to physicians and patients in deciding under what circumstances to initiate treatment with BOTOX.

APPENDIX A: SYNOPSIS OF PREVIOUSLY SUBMITTED STUDY

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 November 1999 CBER Review. Allergan has submitted the study report for Study OCUL-102 to support the assertion that sufficient information is known about use of BOTOX in toxin naïve subjects to enable labeling to be written. An summary of the study follows here.

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. Enrolled subjects were stratified into three groups based on which planes of head deviation were symptomatic, and randomized to toxin or placebo within each stratum. Only patients without prior history of use of BOTOX were eligible. Treatment dose differed for the strata, and ranged 140 to 170 U. Only Lot [redacted] toxin was used. Outcome scales include several patient subjective scales, physician subjective scales (by an unblinded examiner?), several examiner scales (performed by an unblinded examiner), and a structured dystonia rating scale (The Columbia Torticollis Rating Scale, unvalidated and not in widespread use afterwards, performed by a blinded examiner).

Subjects were examined at weeks 2, 6 and 12, although the protocol specified weeks 2, 4, 8, and 12. There were 55 patients enrolled, but only 51 retained in the analysis due to protocol deviations, with the remaining 51 randomized 25 to Botox, 26 to placebo. 5 subjects withdrew from the study during the study. No formal analytic plan was prospectively written. The study report notes 21 different endpoints which were analyzed at each of the 3 study evaluation visits. There were 5 endpoints highlighted for evaluation, but it is unclear if this may have been post hoc or not. For these 5, Investigator and Subject Global Response Assessment, Investigator and Subject Global Torticollis Severity Assessment, and Head Movement while Resting, of which two were analyzed in as both median score and percent with improvement for a total of 7 endpoints, each were compared at the 3 timepoints for a total of 21 outcome comparisons.

Table A-1: Highlighted Outcomes on Study OCUL 102									
Outcome	Week	value type	Placebo		n = 26	Oculinum		n = 25	p-value
			n	value	n missing	n	value	n missing	
Investigator	2	median	17	0	9	12	0	13	0.18
Global Resp	6	median	9	0	16	9	0	15	0.33
Assesment	12	median	10	0	14	8	0	13	0.12
Subject	2	median	26	0	0	24	0	1	0.04
Global Resp	6	median	24	0	1	24	1	0	0.001
Assesment	12	median	23	0	1	21	1	0	0.004
Investigator	2	% w/ imprvmnt	17	12		12	42		0.09
Global Resp	6	% w/ imprvmnt	9	11		9	22		0.99
Assesment	12	% w/ imprvmnt	10	0		8	25		0.18
Subject	2	% w/ imprvmnt	26	8		24	42		0.007
Global Resp	6	% w/ imprvmnt	24	8		24	58		0.001
Assesment	12	% w/ imprvmnt	23	17		21	57		0.01
Investigator	Baseline	median	17	3	9	18	2.5	7	0.8
Global Torticolis	2	median	17	3	9	12	2	12	0.17
Severity	6	median	13	2	12	11	2	13	0.9
Assesment	12	median	7	2.5	16	7	1	14	0.11
Subject	Baseline	median	26	3	0	25	3	0	0.4
Global Torticolis	2	median	26	3	0	24	3	0	0.9
Severity	6	median	23	4	4	24	3	0	0.44
Assesment	12	median	23	3	0	21	3	0	0.5
Head Movement	Baseline	mean degrees	23	66.5		20	61		0.41
Resting	2	mean degrees	19	-3.7		15	-7.7		0.015
	6	mean degrees	19	0		17	-11.8		0.006
	12	mean degrees	19	-0.5		17	-11.2		0.01

Notes: Global response assessment scores analyzed with Van Elteren stratified form of Wilcoxon test
Pecente with improvement on Global analyzed with Fisher-Irwin test
Resting head movement analyzed as change from baseline

Note there are substantial numbers of missing values at all times for the Investigator ratings.

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. Median Subject 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 median 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. Muscle strength and size did show statistically significant treatment effects.

The CBER 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.

The adverse event reporting used an idiosyncratic system, and may have been limited to only certain types of adverse effects. Additionally, the quality of AE collection is unclear given the large number of missing investigator outcome assessments. However, the reported rates in OCUL 102 of the major toxin associated AE discerned in other studies is not markedly different from those other studies.

Additionally, in OCUL 104, an open label repeat injection study, it was noted that about 13% of injection sessions have dysphagia reported as an adverse event.