

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125360

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type BLA
Application Number 125360 / 1
Priority or Standard Standard

Submit Date July 1, 2009
Received Date July 2, 2009
PDUFA Goal Date May 2, 2010
3 Month Extension August 1, 2010
Division / Office DNP / ODE I / OND / CDER
Reviewer Kenneth Bergmann, MD
Team Leader Gerald D. Podskalny, DO
Review Completion Date June 1, 2010
Revised June 16, 2010
Final July 14, 2010
Established Name IncobotulinumtoxinA
Trade Name Xeomin®
Therapeutic Class Botulinum Neurotoxin Type A
Applicant Merz Pharmaceuticals GmbH

Formulation Injectable (Lyophilized powder for dilution)
Dosing Regimen Up to (b)(4) units, IM injection
Indication Blepharospasm
Intended Population Adults

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	10
2.1	Product Information	10
2.2	Tables of Currently Available Treatments for Proposed Indications	11
2.3	Availability of Proposed Active Ingredient in the United States	11
2.4	Important Safety Issues With Consideration to Related Drugs	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	12
2.5.1	Pre-IND / End of Phase II Meeting – September 14, 2004	13
2.5.2	Release from Clinical Hold - June 29, 2006	14
2.5.2	Type C Meeting - June 11, 2007	16
2.5.3	Pre-BLA Meeting – December 12, 2008	18
		(b) (4)
2.5.5	Request for Waiver of Pediatric Studies	18
2.6	Other Relevant Background Information	19
3	ETHICS AND GOOD CLINICAL PRACTICES	19
3.1	Submission Quality and Integrity	19
3.2	Compliance with Good Clinical Practices	20
3.3	Financial Disclosures	20
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	20
4.1	Chemistry Manufacturing and Controls	20
4.2	Clinical Microbiology	21
4.3	Nonclinical Pharmacology/Toxicology	21
4.4	Clinical Pharmacology	21
4.4.1	Mechanism of Action	22
4.4.2	Pharmacodynamics	23
4.4.3	Pharmacokinetics	28
5	SOURCES OF CLINICAL DATA	28
5.1	Tables of Studies/Clinical Trials	29
5.2	Review Strategy	30
5.3	Discussion of Individual Studies/Clinical Trials	31
5.3.1	Confirmatory trial of NT 201 for the treatment of blepharospasm (MRZ 60201-0433/1)	31
5.3.2	Open label repeated injection trial for the treatment of blepharospasm (MRZ 60201-0433/2)	68

5.3.3 Supportive trial of NT 201 compared to BOTOX® in blepharospasm (MRZ 60201-0003)	81
6 REVIEW OF EFFICACY	101
Efficacy Summary	101
6.1 Indication	102
6.1.1 Methods	102
6.1.2 Demographics	104
6.1.3 Subject Disposition	104
6.1.4 Analysis of Primary Endpoint(s)	104
6.1.5 Analysis of Secondary Endpoints(s)	105
6.1.6 Other Endpoints	106
6.1.7 Subpopulations	107
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations	107
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects	109
6.1.10 Additional Efficacy Issues/Analyses	109
7 REVIEW OF SAFETY	109
Safety Summary	109
7.3.5 Submission Specific Primary Safety Concerns	110
7.4.6 Immunogenicity	111
8 POSTMARKET EXPERIENCE	113
9 APPENDICES	115
9.1 Literature Review/References	115
9.2 Labeling Recommendations	115
9.3 Advisory Committee Meeting	117
9.4 Dataset Requests to Sponsor	117

Table of Tables

Table 1: FDA approved botulinum toxin preparations	11
Table 2: Phase I studies (source: Sponsor)	22
Table 3: Maximal area of anhydrosis (mm ²) at 6 weeks in PPS (source: Sponsor).....	26
Table 4: Phase III trials supportive of NT 201 in blepharospasm (source: Sponsor)....	29
Table 5: Trial 0433/1 Visit checklist (source: Sponsor).....	36
Table 6: Trial 0433/1 Assignment by analysis population (source: Sponsor)	42
Table 7: Trial 0433/1 Baseline JRS ratings in ITT cohort (source: Sponsor).....	43
Table 8 Trial 0433/1 Summary of doses administered by injection area (source: Sponsor)	46
Table 9: Trial 0433/1 Summary of injection volume and number by site (source: Sponsor)	46
Table 10: Trial 0433/1 Major protocol violations (source: Sponsor)	47
Table 11 Trial 0433/1 Logistic Regression Analysis of Response Rate in ITT-LOCF Population (source: Sponsor)	48
Table 12: Jankovic Rating Scale, Severity Subscale (JRS-S).....	49
Table 13: Trial 0433/1 Change in JRS-S (Visit 4 – Visit 2).....	51
Table 14: Jankovic Rating Scale, Frequency Subscale (JRS-F)	52
Table 15: Trial 0433/1 Baseline JRS-F subscore at baseline (Visit 2).....	53
Table 16: Trial 0433/1 Change in JRS-F from baseline to week 6	53
Table 17: Trial 0433/1 JRS Severity Subscale Patient Diary.....	54
Table 18: Trial 0433/1 Baseline BSDI scores.....	56
Table 19: Trial 0433/1 BSDI change from baseline to week 6.....	56
Table 20: Trial 0433/1 PEGR contingency table	59
Table 21: Trial 0433/1 GAE contingency table	60
Table 22: Trial 0433/1 Agreement between PEGR and GAE.....	61
Table 23: Trial 0433/1 Patient reported onset and waning of treatment effect	61
Table 24: Trial 0433/1 Days after randomization to loss of effect (quartiles).....	64
Table 25: Trial 0433/2 Visit checklist (source: Sponsor).....	71
Table 26 Trial 0433/1 and /2: NT 201 exposure by injection (source: Sponsor).....	74
Table 27 Trial 0433/1 and /2: NT 201 by dose group and length of exposure (source: Sponsor)	74
Table 28 Trial 0433/1 and /2: NT 201 length of exposure by number of injections (source: Sponsor)	74
Table 29: Trial 0433/2 Injected dose of NT 201 by treatment session	75
Table 30: Trial 0433/2 JRS-S by number of treatments received.....	76
Table 31: Trial 0433/2 BSDI by number of treatments received.....	77
Table 32: Trial 0433/2 PEGR by number of treatments received	78
Table 33: Trial 0433/2 PEGR from blinded and open label trials compared.....	79
Table 34: Trial 0433/2 Interval between treatments by number received.....	79
Table 35: Trial 0433/2 Total NT 201 dose by number of treatments received.....	80
Table 36: Trial 0003: Visit checklist (source: Sponsor).....	84
Table 37: Trial 0003 Baseline total JRS score	88
Table 38: Trial 0003 Dose of trial medications administered (source: Sponsor)	89
Table 39: Trial 0003 Dose comparison (ITT cohort, total units for both eyes).....	90

Table 40: Trial 0003 JRS change from baseline analysis of covariance	90
Table 41: Trial 0003 JRS-S change from baseline analysis of covariance.....	92
Table 42: Trial 0433/1 JRS-S change from baseline at 3 weeks.....	93
Table 43: Trial 0003 vs. Trial 0433/1 JRS-S change from baseline at 3 weeks	93
Table 44: Trial 0003 vs. Trial 0433/1 JRS-S at baseline	94
Table 45: Trial 0003 PEGR at 3 week outcome evaluation.....	95
Table 46: Trial 0003 PEGR at trial final visit.....	95
Table 47: Trial 0003 vs. Trial 0433/1 PEGR at final visits compared for NT 201 arms..	95
Table 48: Trial 0003 vs. Trial 0433/1 PEGR scored “moderately improved” or better compared for NT 201 arms	96
Table 49: Trial 0003 vs. Trial 0433/1 Interval from treatment session to final visit for NT 201 treated arms.....	96
Table 50: Trial 0003 vs. Trial 0433/1 Duration of treatment effect for NT 201 treated arms.....	97
Table 51: Trial 0003 vs. Trial 0433/1 Interval to next injection quantiles in days for all treatment arms.....	98
Table 52: Trial 0003 Patient reported waning of treatment effect (weeks)	99
Table 53: Trial 0433/1 Range of doses administered (source: Sponsor).....	103
Table 54: Trial 0433/1 JRS-S change from baseline to outcome visit (week 6)	104
Table 55 Trial 0433/1 JRS-S patient diary change from baseline to outcome visit.....	105
Table 56: Trial 0433/1 BSDI change from baseline to outcome visit.....	105
Table 57: Trial 0433/1 PEGR at end of trial.....	106
Table 58: Trial 0433/1 GAE at end of trial	106
Table 59 NT 201 Cumulative dose exposure at 24 and 48 weeks	108
Table 60: Trial 0433/1 Subjects reporting AE of special interest.....	110
Table 61: Trial 0433/2 Subjects reporting AE of special interest.....	111

Table of Figures

Figure 1: BoNT Mechanism of Action.....	23
Figure 2: Percent of EDB CMAP decrement following BoNT injection	24
Figure 3: Primary efficacy parameter: decrement in CMAP at 4 weeks	25
Figure 4: Duration of paretic effect; weeks to return to 80% of baseline	25
Figure 5: Area of anhydrosis by subject over time after NT 201 (source: Sponsor)	27
Figure 6: Design of Trial 0433/1 (source: Sponsor).....	32
Figure 7: Case Report Form Injection site identification (source: Sponsor).....	37
Figure 8: Trial 0433/1 enrollment by clinical site	41
Figure 9: Trial 0433/1 Subject disposition (source: Sponsor)	42
Figure 10: Injection point schema (source: Sponsor).....	45
Figure 11: Trial 0433/1 JRS-S scores at baseline (Visit 2) by arm	50
Figure 12: Trial 0433/1 JRS-S scores at 6 weeks (Visit 4) by arm	50
Figure 13: Trial 0433/1 JRS-S change from baseline (Visit 4 minus Visit 2) by arm	51
Figure 14: Trial 0433/1 Regression plot of NT 201 arm (F Ratio 6.0954, $p < 0.0159$)... ..	52
Figure 15: Trial 0433/1 JRS-F change from baseline to week 6 (Visit 4 - Visit 2).....	53
Figure 16: Trial 0433/1 JRS-S Patient Diary Change from baseline to week 6	55
Figure 17: Trial 0433/1 JRS-S Patient Diary Residuals Leverage Plot.....	55
Figure 18: Trial 0433/1 Change in BSDI from baseline to week 6.....	57
Figure 19: Trial 0433/1 BSDI Residuals Leverage Plot.....	57
Figure 20: Trial 0433/1 Patient Evaluation of Global Response (PEGR) at final visit (source: Sponsor)	58
Figure 21: Trial 0433/1 Investigator's Global Assessment of Efficacy at final visit (source: Sponsor)	60
Figure 22: Trial 0433/1 Days from injection session to retreatment	62
Figure 23: Trial 0433/1 Elapsed time from Week 4 to termination visit (top: NT 201; bottom: Placebo).....	63
Figure 24: Trial 0433/1 Elapsed time to failure after treatment (survival model)	64
Figure 25: Trial 0433/1 Elapsed time to failure: lack of covariate effect in regression model by leverage plot (top: total dose NT 201; bottom: baseline JRS-S score)	65
Figure 26: Trial 0433/1 Relationship of PEGR to Duration of Effectiveness.....	66
Figure 27: Trial 0433/1 Relationship of PEGR to JRS-S change from baseline	67
Figure 28: Trial 0433/2 Subject disposition	72
Figure 29: Trial 0433/2 Number of subjects by number of treatment sessions in open label extension trial	73
Figure 30: Trial 0433/2 Distribution of total NT 201 doses (units, both eyes) administered at first (left) and fifth (right) treatment sessions	76
Figure 31 Trial 0433/2 PEGR Box plot by number of treatments received.....	78
Figure 32: Trial 0003 Subject disposition (source: Sponsor)	86
Figure 33: Trial 0003 Injection point schema (source: Sponsor)	89
Figure 34: Trial 0003 JRS change from baseline box plot.....	91
Figure 35: Trial 0003 JRS-S change from baseline box plot.....	92
Figure 36: Trial 0003 vs. Trial 0433/1 JRS-S change at 3 weeks box plot.....	94
Figure 37: Trial 0003 vs. Trial 0433/1 Interval from treatment to final visit box plot.....	97

Figure 38: Trial 0003 vs. Trial 0433/1 Interval to next injection survival plot 98

1 Recommendations/Risk Benefit Assessment

Following assessment of the clinical data, it is the opinion of this reviewer that incobotulinumtoxinA (NT 201, Xeomin®) is effective for the treatment of Benign Essential Blepharospasm (BEB) when the solubilized powder is used for periorbital intramuscular injection. It has a side effect profile consistent with its class (botulinum neurotoxins or BoNT) and its overall risk to benefit ratio is therapeutically acceptable.

1.1 Recommendation on Regulatory Action

My review of the clinical data finds sufficient evidence to support incobotulinumtoxinA's use in the treatment of Benign Essential Blepharospasm in patients previously successfully treated with onabotulinumtoxinA (BOTOX®). In this submission, the basis of approval is a single double blind, placebo controlled efficacy trial of 20 weeks duration in BEB using a well-accepted design. The dose given was that previously used in the patient's last two BOTOX® treatment sessions, up to 50 units per eye. The primary endpoint was the change from baseline of the severity subscale of the Jankovic Rating Scale for blepharospasm (JRS-S) at six weeks following a single treatment session. While this is the first time that this metric is used to support efficacy in blepharospasm, consistent support come from key secondary measures and a long-term open label extension trial with repeated treatment sessions.

At 6 weeks following treatment in the blinded placebo controlled trial, this review finds that NT 201 was superior to placebo injection in the periorbital muscles ($p < 0.0004$). The JRS-S score improved (moved negatively) by -0.84 points (95%CI -1.09, -0.58), for the active treatment arm compared to placebo which worsened (moved positively) by 0.21 points (95%CI -0.17, 0.58). In this trial, waning of the therapeutic effect as determined by the need for retreatment occurred after a median of 70 days (95% CI 49, 77). To put this change into clinical perspective, the level of functional disability as measured by a patient reported outcome, the Blepharospasm Disability Index (BSDI) also improved significantly in the active treatment arm ($p < 0.0023$). The BSDI improved (moved negatively) by -0.48 points (95%CI -0.65, -0.30), compared to the placebo arm which worsened (moved positively) by 0.15 points (95%CI -0.23, 0.26). Secondary measures which included clinical global impressions by the patient and blinded investigator all moved consistently in the direction favoring the active treatment group.

To fulfill entry criteria, the subjects in this trial had had previous successful treatment with BOTOX®. As a result, it is unknown what the magnitude of drug effect might be in a treatment naïve population with blepharospasm. There is no clinical *a priori* evidence to suggest that the response in these two populations would differ greatly. However, potentially poor responders would have been excluded from this trial and drug naïve patients may respond in more vigorous fashion to treatment initiation.

Because the clinical phenomenon of blepharospasm is often found accompanied by other movement disorder phenomena (one third of the subjects in this confirmatory trial had other craniofacial dystonia), it is recommended that an indication be granted for the treatment of blepharospasm as a symptom in addition to, or in place of, the syndrome of BEB.

A double blinded, active control non-inferiority trial compared incobotulinumtoxinA to onabotulinumtoxinA (BOTOX®), (b) (4)

This is due to methodological shortcomings including inadequate justification for the non-inferiority margin and lack of assay sensitivity in the trial.

1.2 Risk Benefit Assessment

After discussion with the DNP safety reviewer, it appears that no new or unexpected adverse events were discovered in the course of the development program for this BoNT. The benefit resulting from treatment combined with a low occurrence rate of severe adverse events or treatment emergent events of a serious nature suggests that incobotulinumtoxinA will be a useful addition to the class of BoNT agents. However, review of the safety data suggests that there is the same possibility of spread of toxin effect, i.e.: unintended paralytic effects in both contiguous and remote parts of the body, even with the lower doses used in the treatment of blepharospasm.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Because of the risk for unintended treatment effects outside of the targeted muscle, it is proposed that the REMS assigned to other members of the class of botulinum toxins (all serotypes) should also apply to incobotulinumtoxinA. Following discussion with the safety reviewer, no additional REMS requirements appear indicated at this time and may follow closely the evaluation plans and risk mitigation strategies currently in effect for the three marketed BoNT products in the US. This includes a Medication Guide and a Communication Plan (Dear Healthcare Provider letter).

1.4 Recommendations for Postmarket Requirements and Commitments

It is proposed that the sponsor will provide evidence of effectiveness of the REMS Communication Plan and change the plan as necessary to ensure the communication of potential risks to patients and healthcare providers. Although the Sponsor proposes the first assessment at (b) (4) a timetable currently in use with other BoNT suggests assessments at 18 month, 3 years and 7 years following launch. In particular this will include reports of treatment emergent adverse events and errors in use.

Because the syndrome of blepharospasm is found exclusively in adults, no Pediatric Research Equity Act (PREA) -based requirement is proposed. After review, a full

waiver was granted by the PREA Subcommittee of the Pediatric Review Committee (PeRC) on February 24, 2010.

2 Introduction and Regulatory Background

Blepharospasm is a focal dystonia characterized by involuntary contraction of the periorbital orbicularis oculi muscles, causing involuntary forced eye closure.

The pathophysiology of this disorder (and the dystonias in general) is not well understood. While this family of movement disorders is generally thought to have their origin in dysfunctional basal ganglia circuits, this has not been proven. Functional MRI and PET studies of the brain reveal numerous cortical and subcortical regions of dysfunction (Hallett et al, *Neurology* 71: 1275-1282, 2008). A meta-analysis of 83 published series of over 5000 dystonia patients shows the mean age of onset of blepharospasm was 56 years of age. It does not appear to exist in the pediatric population. Family studies suggest that there is likely a genetic relationship among all the focal dystonias (O'Riordan, et al *Neurology* 63, 1423-1426, 2004).

Prior to the medical use of botulinum neurotoxin, there was no effective medical or surgical treatment of this disorder. In 1989, BOTOX® (then named Oculinum) received FDA approval for blepharospasm, including benign essential blepharospasm and / or VII cranial nerve disorders in patients 12 years or older. (The pediatric safety data came from the strabismus population studied.)

2.1 Product Information

NT 201, the Sponsor's designation of this biological during its development, is a botulinum type A neurotoxin. Its USAN and trade names are incobotulinumtoxinA and Xeomin®, respectively.

NT 201 is a single chain polypeptide of 1296 amino acids, weighing approximately 150 kDa. It is synthesized from a (b) (4) strain of *Clostridium Botulinum*, its bacterial source in nature. The native toxin is part of protein complex with a molecular weight of approximately 900kDa. (b) (4)

The drug product is supplied as a lyophilized powder for reconstitution with commercially available 0.9% physiological saline. Each vial of powder contains 50 or 100 units with strength equal to the LD₅₀ in a mouse assay. Sucrose and human serum albumin are excipients.

Its intended use in this BLA is in adults who suffer with benign essential blepharospasm. The Sponsor proposed labeling indicating intramuscular injection of no more than (b) (4) units per eye per treatment session into the periorbital muscles. Interval between treatment sessions was not specified. (b) (4)

(b) (4)

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

In the US, three injectable botulinum neurotoxin (BoNT) products are available. Even though only one is approved for use in blepharospasm, all BoNTs are listed due to the extensive off label use these products enjoy.

Table 1: FDA approved botulinum toxin preparations

Botulinum Neurotoxins	Trade name	Indication
onabotulinumtoxin A	BOTOX® (also Botox Cosmetic®)	Cervical dystonia Blepharospasm Strabismus Glabellar frown lines Primary axillary hyperhidrosis
rimabotulinumtoxin B	Myobloc®	Cervical dystonia
abobotulinumtoxin A	Dysport®	Cervical dystonia Glabellar frown lines

2.3 Availability of Proposed Active Ingredient in the United States

This version of botulinum toxin A is not currently marketed in the United States but is marketed elsewhere. Merz Pharmaceuticals GmbH is the license holder for NT 201, marketed under the trade name Xeomin®. It was first approved in Germany in May 31, 2005 and the EU in October 2007. It is now approved in 13 EU countries as well as Argentina, Canada, Korea, Mexico, Russia and Uruguay.

It is approved for the treatment of blepharospasm, cervical dystonia (spasmodic torticollis), post stroke spasticity of the upper limb, and glabellar frown lines. For this last indication, it is marketed under the trade name Bocouture®.

The sixth PSUR covering the period up to July 1, 2009 has been submitted. The post marketing experience with Xeomin® is reviewed further in **Section 8**.

2.4 Important Safety Issues With Consideration to Related Drugs

Because of the potential for serious toxicity, the class of botulinum toxin agents is subject to special scrutiny. Two specific issues are of concern:

The first is the potential for the spread of toxicity to both contiguous and distant tissues, with a potentially fatal outcome.

The second is that biological proteins inevitably arouse some immunological response in the host. In humans, this response produces blocking antibodies which may be associated with the development of treatment resistant symptoms in some patients.

These are considered further in **Section 7.3.5 Submission Specific Safety Concerns**.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A variety of regulatory interactions between the division and the Sponsor leading to this submission have taken place over the years.

- IND 12,821 for the treatment of cervical dystonia was submitted on December 1, 2005 and was released from clinical hold on June 29, 2006.
- BB-IND 100,163 was submitted May 3, 2006 for the indication of blepharospasm and was also allowed to proceed on June 29, 2006.

[REDACTED] (b) (4)

Specific regulatory opinions related to areas other than the indication of blepharospasm are not covered here and the reader is referred to the primary reviews in these other disciplines.

2.5.1 Pre-IND / End of Phase II Meeting – September 14, 2004

A Type B meeting was held to discuss the pre Phase III state of the Xeomin® development program, which had performed outside the US. The Sponsor submitted a pre-meeting package of progress to date and 14 questions on the topics of preclinical, clinical, and drug quality. The aim of the meeting was to obtain agreement on the acceptability of the clinical development plan. An FDA memorandum dated October 12, 2004 documents the Division's responses. The Division indicated that the proposed nonclinical program was adequate to support the Phase III trial and the BLA submission, subject to review.

The Sponsor had conducted a Phase 3 trial for blepharospasm in Europe in support of the BLA. The FDA noted that the Sponsor would need to establish "substantial evidence" of effectiveness in order to support a marketing application in the U.S., which can be interpreted to mean more than one adequate and well-controlled investigation that provides "independent substantiation" of experimental results. The Division pointed out the requirements for, and shortcomings of, non-inferiority trials. Because a reliable effect size can not be established due to robust and unpredictable placebo response, and the lack of adequate historical data concerning the active comparator, this type of trial is not considered confirmatory. The Sponsor acknowledged their understanding of this problem.

The Division also indicated that "dose ranging information is valuable for writing an adequate label to guide initial dosing of toxin-naive patients [with blepharospasm]. If a dose-ranging design without a placebo group is being contemplated, then the Sponsor should bear in mind that it is important to evaluate a broad enough range of doses such that differences can be demonstrated across the range of doses examined. That is, the lowest dose evaluated should have low efficacy compared to the higher doses, to permit statistical comparisons to succeed."

The Division also indicated that clinical issues (some of these above) which may have been discussed in the context of cervical dystonia, apply equally to blepharospasm. The supporting clinical studies and proposed pivotal protocols were relying primarily on subjects that had responded to BOTOX® therapy. "Reliance on a select responder population generally does not adequately support a claim of safety and efficacy in a more heterogeneous clinical population of patients with [blepharospasm]." The Agency noted the Sponsor's concern regarding limiting the placebo period in order to minimize subject dropouts and allow for early re-injection of patients. The Agency concurred that an extensive placebo period may be problematic for patients. "However, it is highly desirable to develop adequate placebo- controlled safety data for NT-201 (which is not available from the previous clinical investigations) and to measure the NT-201 duration of effect in [blepharospasm], if possible. For these reasons, the Agency strongly recommends extending the placebo period (b) (4) in the second study synopsis, preferably on the order of 6-8 weeks. FDA explained that the sponsor would need to establish evidence of effectiveness in blepharospasm

specifically and that studying a BOTOX®-naive population (to the extent possible), would be important.”



The Agency recommends that you discuss your assay method with our Office of Biological Products to determine if there is a more efficient two-step assay (e.g., ELISA + Mouse Hemi diaphragm study) that will allow you to evaluate all clinical samples for immunogenic responses to NT-201. Having a more complete immunologic profile will be important for writing an adequate label for your product.”

Specific ECG cardiac and pulmonary evaluations were not considered to be required unless particular concerns arose. However it was emphasized that there should be specific and frequent evaluation for adverse events related to collateral spread of NT201 in these and other areas of adjacent muscles: dyspnea, respiratory infections, dysphagia, speech problems, facial weakness, general body weakness, and so forth. Adverse events were to be followed until they stabilize or resolve. They were to be elicited for up to 4 weeks following the last injection.

Given that blepharospasm is a chronic condition, the Agency wished to see evidence of retreatment efficacy sustained over time, approaching the requirements listed in ICH recommendations.

Further comments were made about the Statistical Analysis Plan, and the need for strict definition of analysis groups, methods, and assumptions. Use of an independent DSMB was strongly recommended.

2.5.2 Release from Clinical Hold - June 29, 2006

The IND for study of blepharospasm (as well as cervical dystonia) had been put on clinical hold because of a lack of non-clinical information needed to support the human clinical trials. This information was submitted and discussed with the Division and the clinical hold ended on June 29, 2006.

The following non-hold comments were directed to the Sponsor at that time with a request for comments (verbatim):

1. Your protocol does not specify a standardized method for eliciting adverse event reports. In the absence of a standardized approach, ascertainment of adverse events is likely to be substantially incomplete and may vary substantially among centers, confounding the interpretation of the study results. We recommend that you revise the protocol to specify a standardized method of eliciting adverse event reports. This standardized method should include the following:

- an open-ended question to elicit reports of unanticipated adverse events
- a set of questions directed at adverse events of predetermined concern (including common adverse events such as ptosis, diplopia, and xerophthalmia)
- directed questioning for gastrointestinal adverse events

2. Your protocol does not provide details of the methods for administering and scoring the Jankovic Rating Scale (JRS) severity subscore, the primary outcome variable. The absence of appropriate, detailed, standardized testing procedures may increase the risk of high variability among centers and biased results, confounding the interpretation of the study results. Also, in the absence of specified testing procedures, we are not able to assess the appropriateness of your procedures for administering and scoring the JRS. Therefore, we recommend that you develop detailed procedures for administering the JRS and submit those procedures for review.

3. Your protocol specifies a “recommended order” for assessment of the Blepharospasm Disability Index (BSDI) and JRS during clinic visits. Investigators may interpret a “recommended order” as implying substantial latitude, resulting in high variability in the order of the assessments. Such variability may confound the study results. To decrease the risk of such variability, we recommend that you revise the protocol to specify a standard order that you expect all investigators to follow for all outcome assessments.

4. Some of your patient-reported outcome measures include terms that may be unfamiliar to patients. For example, the JRS contains terms such as ‘stimuli’ and ‘spasm’ that should not generally be used in a patient interview (see comment #2 above, regarding the need for detailed, standardized testing procedures) and the BSDI contains terms such as ‘involuntary.’ Patients may misinterpret these terms, increasing the variability of the study results, and confounding the interpretation of the study results. To decrease the risk of such variability, we recommend that you review the patient-reported outcome indices to ensure that they are at a reading level appropriate for patients, as discussed in the FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (<http://www.fda.gov/Cder/guidance/5460dft.pdf>).

5. Your protocol does not include a “responder analysis” for the primary efficacy endpoint. A “responder analysis” can be helpful to assess the clinical importance of a

study result. We recommend that you revise the protocol to include a “responder analysis” as a sensitivity analysis of the primary efficacy endpoint.

2.5.2 Type C Meeting - June 11, 2007

A Type C meeting was held on June 11, 2007. The clinical substance of that meeting related to this indication is taken from the minutes with the questions posed by the Sponsor, followed by the Agency’s response and any discussion that took place (edited for brevity but not content):

[Redacted text block]

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)
[REDACTED] (b) (4)f

Meeting Discussion covering Questions 1-4

a) [The Sponsor] agreed to follow the Agency's advice to conduct a study on 75 treatment-naïve blepharospasm patients, in addition to the study of pretreated blepharospasm patients. The treatment-naïve study will consist of a placebo arm and two fixed dose arms. The Division agreed that the treatment-naïve study could be for supportive purposes, and that it need not be powered to show statistical superiority of active drug.

The Division agreed that the two studies in blepharospasm (study of treatment naïve patients and study of pretreated patients) together with a second pivotal study in another indication (cervical dystonia or glabellar lines) appeared capable of fulfilling the requirement for two adequate and well controlled trials necessary for a BLA for blepharospasm.

b) The Sponsor explained the difficulty of recruiting treatment-naïve blepharospasm subjects. Many patients with blepharospasm have been previously treated with botulinum toxin for other indications, such as glabellar lines. The sponsor further noted that it was not unusual for blepharospasm patients to have a history of previous undertreatment with botulinum toxin. The sponsor estimated that in the U.S. only 1,000- to 2,000 patients were diagnosed with blepharospasm each year. The Division agreed that "treatment naïve" patients could be defined as patients that had not been treated with botulinum toxin type A for the indication of blepharospasm for one year. Patients treated for indications other than blepharospasm within one year would still be considered "treatment naïve" in terms of blepharospasm.

The Division expressed concern that the treatment-naïve study population should reflect the type of treatment-naïve patients that would be encountered in clinical practice, including patients with no previous exposure to botulinum toxin. The sponsor estimated that 20% to 30% of those enrolled in the treatment-naïve blepharospasm study would have been treated with botulinum toxin at some time in the past. The sponsor agreed to submit to FDA an explanation of their efforts to enroll treatment-naïve blepharospasm subjects, and their rationale for enrolling patients with some previous exposure to botulinum toxin.

2.5.3 Pre-BLA Meeting – December 12, 2008

A Type B meeting for INDs 12,821 (cervical dystonia) and 100,163 (blepharospasm) was held to discuss administrative, quality, non-clinical and clinical questions for the preparation of a BLA submission. Questions were also directed toward the indication of spasticity, though it should be noted that this indication was not studied under an IND in the US. The questions posed were only indirectly related to the blepharospasm indication. Agreement was reached concerning the content and presentation of summary reports in the eCTD. The requirements for long term exposure were outlined, and the requirements suggested for spasticity and cervical dystonia were also adequate for the blepharospasm indication. Agreement was reached concerning the pooling of adverse events datasets for individual indications as well as the entire trial-exposed population.

FDA comment: “The pooling of datasets for the [Adverse Events of Special Interest] analyses should be for each indication and across all indications. In addition to the analysis based on the list of AESI in the briefing book, please perform another analysis based on the following terms: Botulism, muscular weakness, muscle paresis, paralysis, paralysis flaccid, areflexia, hyporeflexia, hypotonia, peripheral nerve palsy, peripheral paralysis, cranial nerve palsies multiple, paresis cranial nerve, cranial nerve paralysis, bulbar palsy, facial paresis, facial palsy, accommodation disorder, diplopia, eyelid function disorder, eyelid ptosis, pupillary reflex impaired, vision blurred, vocal cord paralysis, vocal cord paresis, speech disorder, dysphonia, dysarthria, dysphagia, aspiration, pneumonia aspiration, dyspnea, respiratory depression, respiratory failure, respiratory arrest, diaphragmatic paralysis, bradycardia, dry mouth, constipation, ileus paralytic, pelvic floor muscle weakness, and urinary retention.”

During the meeting discussion, the Sponsor agreed with the above request. The Division agreed to review the Sponsor’s alternate proposal regarding those of the above terms that do not match MedDRA terms. On 1/14/09 the sponsor sent via email a list of all MedDRA preferred terms to cover ‘muscle paresis’ which does not exist as a MedDRA preferred term. These preferred terms were acceptable.

(b) (4)

2.5.5 Request for Waiver of Pediatric Studies

The Sponsor applied for a waiver from the pediatric clinical requirement under the Pediatric Research Equity Act. This was presented to the Pediatric Review Committee

(PeRC) and because blepharospasm does not occur in the pediatric age group, a full waiver was granted on February 24, 2010.

2.6 Other Relevant Background Information

This BLA is being evaluated in parallel to a related submission for the treatment of cervical dystonia designated BLA 125360 / 0. A separate safety review encompassing the clinical experience for all indications is being performed by the Division of Neurology Products. This is part of an ongoing assessment of safety related to all botulinum neurotoxin products.

There have been reports of systemic adverse drug reactions remote from the injection site including respiratory compromise and death following the use of botulinum toxins A and B for both FDA-approved and unapproved uses. The most serious reactions occurred mostly in children treated for cerebral palsy-associated limb spasticity. Following review of post-marketing data and case reports, class labeling was changed to reflect the seriousness of these events.

In 2009, Risk Evaluation and Mitigation Strategies (REMS) were approved for onabotulinumtoxinA (BOTOX®/Botox Cosmetic, BLA 103000/5189), rimabotulinumtoxinB (Myobloc®, BLA 103846/5120) and abobotulinumtoxinA (Dysport®, BLA 125274/0 and /1). The REMS created a communication plan and revised prescribing information including a Boxed Warning and a Medication Guide highlighting the risk, signs and symptoms of drug effect remote from the site of injection. In addition, established USAN names were revised for each botulinum toxin product to reinforce the understanding that each product has an individual potency and is not interchangeable with any other BoNT product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Clinical review of BLA 125360 revealed that the submission was well organized within the eCTD, though the Sponsor did not comply with all requests made to create linked bookmarks within PDF files. The data submission files, while complete with regard to the presence of data within the dataset, were deficient in their organization to such an extent that they were not in a format that could be analyzed. They were CDISC non-compliant, in general, and an extensive request for reorganization of the datasets was made to the Sponsor (see **Appendix 9.4 Dataset Requests to Sponsor**).

The reviewer concludes that the data appears to be of good quality, gathered according to GCP and there are no other questions related to the integrity of the data of this BLA.

3.2 Compliance with Good Clinical Practices

The Sponsor affirms that all studies in the clinical development program of NT 201 in blepharospasm were performed using standards consistent with Good Clinical Practice (GCP), in compliance with CFR 21 Parts 312.50 and 312.56. Trials were approved by ethics committees or institutional review boards, in line with Good Clinical Practice guidelines, the Sponsor's and CRO's Standard Operating Procedures (SOPs) and according to the Declaration of Helsinki, version 1996. Written informed consent was obtained from all patients prior to any study related procedure. The Sponsor certifies that it did not use any investigators or services debarred under Section 306 of the Food, Drug, and Cosmetics Act.

Data quality was assured by monitoring according to SOPs by the CRO on a fixed schedule. Surveillance of CRF completion, protocol compliance and comparison to source documents were performed. Timeliness of the reporting of all adverse events was checked. Both study monitors and investigators underwent appropriate training for their respective tasks. Internal audits were performed by the Sponsor of the CRO, contract laboratory, and the supplier for packaging and logistics.

Two clinical sites from the confirmatory trial were audited by the Office of Compliance, Division of Scientific Investigations and were found to be in compliance with GCP.

3.3 Financial Disclosures

The Sponsor provided required information regarding financial disclosure for the confirmatory blepharospasm trial MRZ 6020 -0433. Financial disclosures were complete. Form FDA 3455 was reviewed for the investigators from 33 sites (31 of which enrolled patients). Three investigators received payments above the threshold for reporting at sites (b) (4) for duties related to the execution of the trial (administrative and training). These sites enrolled (b) (4) patient(s) respectively. Site (b) (4) was also chosen for inspection by the Office of Compliance, Division of Scientific Investigations and was found to be in compliance with GCP. The Sponsor cites measures taken to avoid the potential for bias at the affected clinical sites. The numbers of subjects at these sites are insufficient to alter the outcome of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The actual drug substance (designated (b) (4) by the sponsor) is synthesized by *clostridium botulinum* in a fermentation process. Each batch is the product of a (b) (4). It is run on a scale of (b) (4) which produces (b) (4).

of purified drug substance, in a dedicated facility. The sponsor anticipates that (b) (4) will create adequate drug supply.

(b) (4) is manufactured into NT 201 by a (b) (4) process of formulation with sucrose, (b) (4) and human serum albumin before packing into vials for lyophilization.

At the time of completion of this review there are still unresolved issues with regard to CMC process, including cleaning of the production equipment and adequate sealing of drug product filled vials. The reader is referred to the CMC review for specific analysis of the issues related to the manufacture of the drug product and creation of NT 201 in final form.

4.2 Clinical Microbiology

A master cell bank of the clostridia colony is maintained for the creation of working cell banks. A single WCB is used to generate each batch of (b) (4). Microbacterial criteria for purity and testing of the product and its packaging have been established by the sponsor but await verification.

The reader is referred to the Microbiology review for specific analysis of the problems related to the manufacture of the drug product and creation of NT 201 in final form.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical studies reveal no obvious issues specific to NT 201 that are not related to BoNTs as a class. As expected from a pure cholinergic blocker, *in vitro* hERG channel testing revealed no effect of NT201 at a concentration of 10,000 LDU/mL and no effect on ECG in monkeys.

Most BoNTs, whether free or in protein complexes, do not diffuse from the injection site in any great quantity. While local anatomy and tissue type determines the diffusion capability, a small amount of toxin diffuses into local tissue and then into the blood stream. It has been demonstrated that diffusion could be considerable, e.g.: 5 cm in a rabbit (Borodic, et al: Head and Neck 12: 392-398, 1990). Single fiber EMG has detected electrophysiological changes in the extensor digitalis brevis (EDB) muscle in the foot of subjects who received BoNT injection in the head/neck region (Garner, et al: Mov Dis 8(1) 33-37, 1993).

4.4 Clinical Pharmacology

The nature of botulinum toxins and their inherent toxicity limits the possibilities for studying their pharmacokinetic and pharmacodynamic profiles in humans.

The Sponsor did perform three Phase I trials in healthy volunteers to compare the action of Xeomin® to onabotulinumtoxinA (BOTOX®), a currently marketed biologic in the US.

Table 2: Phase I studies (source: Sponsor)

Trial Countries (Study report location)	Phase, Population and Design	Study Treatment	Primary Endpoint
9901 (HV) Germany (Section 5.3.4.1)	Phase I 14 healthy male volunteers Open-label, within-treatment comparison	4 U NT 201 or Botox intramuscular	Change in maximal amplitude of CMAP
0113 (HV) Germany (Section 5.3.4.1)	Phase Ib 32 healthy male volunteers Double-blind, within-treatment comparison examining dose response profile, systemic diffusion and duration of effect	2, 4, 16, or 32 U of NT 201 or Botox intramuscular	Reduction in CMAP M-wave at Week 4. Follow up for 52 weeks
0709 (HV) Germany (Section 5.3.4.1)	Phase I 29 healthy female volunteers Double-blind, randomized, single-dose, single-center study	5 U NT 201 or 5 U Vistabel or 12.5 U Dysport intramuscular	Maximal area of anhidrosis

CMAP: Compound muscle action potential; HV: healthy volunteer (subject); U: Units

The relevant contribution of each trial (from the reviewer's perspective) is described in this section.

4.4.1 Mechanism of Action

Botulinum neurotoxins all act by targeting the same cellular vesicle fusion machinery. The single polypeptide chain is activated endogenously by proteases which cleave the protein into a 100kDa heavy (H) chain and 50 kDa light (L) chain linked by a disulfide bridge. This is the biologically active form of the agent.

The toxicity of BoNT is a result of a multistep mechanism. The neurotoxin binds to the pre-synaptic nerve terminals of cholinergic neurons and enters by receptor-mediated endocytosis. The carboxyl terminal of the H chain binds to the target, while the amino terminal interacts with the L chain, a zinc dependent metalloprotease, and translocates internally into the neuron (Lacy, et al. *Nat Struct Biol* 5 (10) 898-902, 1998). This zinc-dependent catalytic domain is common to all BoNT serotypes and specifically attacks the vesicle machinery in the neuron necessary to release packets of neurotransmitter into the synaptic cleft. It does this by cleaving one of three different SNARE proteins essential for synaptic vesicle fusion: synaptobrevin, syntaxin, or SNAP-25. This cleavage results in inhibition of acetylcholine secretion, ultimately leading to paralysis. Serotype A has the longest paralyzing effect of the seven immunologically distinct serotypes (Davletov, et al, *TINS* 28 (8) 446-452, 2005). The cartoon below from the TINS article illustrates these steps from (i) where it hijacks the cellular machinery to enter the cell to (iii) where it blocks fusion of the vesicle for release of neurotransmitter.

Figure 1: BoNT Mechanism of Action
Copyright Material

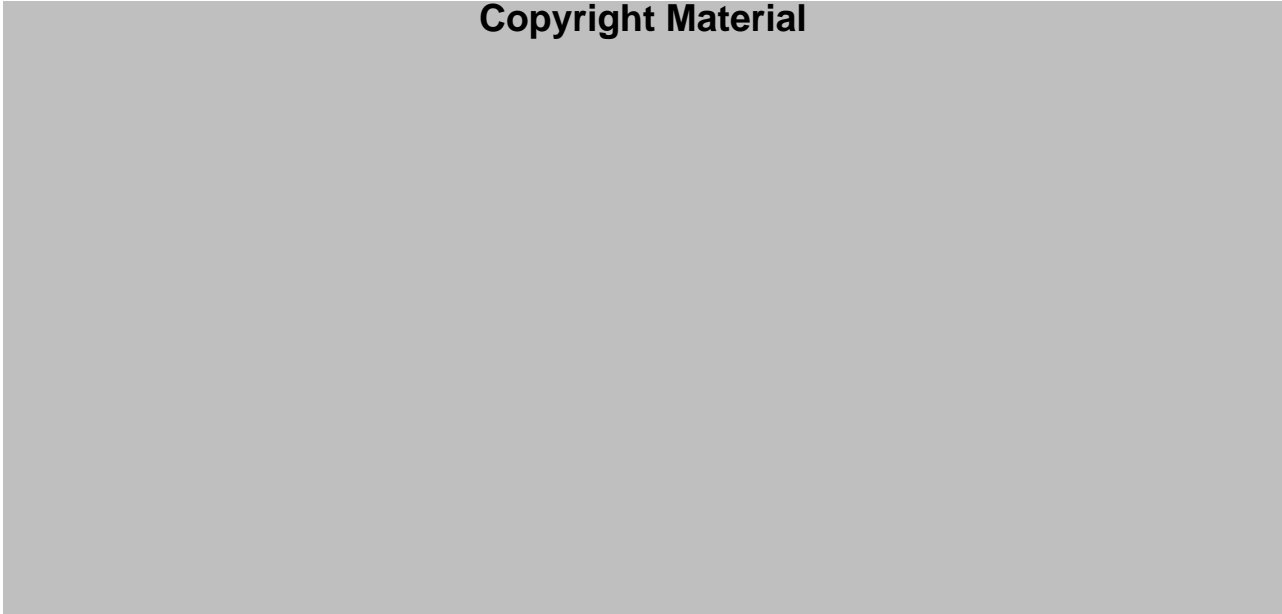
This ability to paralyze muscular contraction makes BoNTs useful for the treatment of disorders where small amounts of localized muscular paralysis may aid function. These disorders include the focal dystonias and spasticity, both neurological syndromes in which alterations of posture and tone result from abnormal contraction resulting from muscular dyscontrol by different central nervous system circuits.

4.4.2 Pharmacodynamics

Two Phase I trials compared the action of NT 201 to BOTOX® in healthy volunteers. The first trial (BTC 60201-9901) compared a single intramuscular injection of 4 units of NT 201 and BOTOX® into contralateral extensor digitorum brevis (EDB) muscles on the lateral aspect of the foot in 14 normal men. The outcome parameter was the compound muscle action potential (CMAP) of surface electromyography (EMG). It was measured for time to onset of paralytic effect (CMAP $\leq$ 70% of baseline) and the duration of the effect. 50% of subjects responded in a day to either treatment and over the course of observation time the response to either BoNT was not statistically different. The time course for duration of effect was also not distinguishable. This study (and the figure below) has been published: Jost, et al., J Neural Transmission 112: 905-913, 2005.

Figure 2: Percent of EDB CMAP decrement following BoNT injection

Copyright Material



The second trial used a similar methodology for a single injection ascending dose trial in 32 healthy men. A single dose of 2, 4, 16 or 32 units of NT 201 and ®® were injected intramuscularly into contralateral EDBs. The patients were then observed at intervals over 52 weeks. The effect of paralysis on CMAP at 4 weeks after injection was the outcome parameter, as well as muscle power of the toes. Twelve subjects were randomization failures (6 found before and 6 after unblinding). The nature of these failures is unclear from the sponsors report but analysis was performed on data from 26 subjects.

At Week 4, all dose groups of both BoNT products had significant paralytic effect by the CMAP measure. This difference was larger for the 32 unit vs. 2 unit dose groups for both products, but no other differences were seen. The duration of effect was also not statistically significantly different. This trial has also been published: Wohlfarth, et al., Clin Neuropharmacol 30: 86-94, 2007. This paper is the source of the next two figures. The first illustrates the primary efficacy parameter: decrement in CMAP at 4 weeks and the plot shows median, minimum, maximum and 25% and 75% quartiles. The second figure shows the duration of paretic effect by time (weeks) to return to 80% of baseline EDB CMAP.

Figure 3: Primary efficacy parameter: decrement in CMAP at 4 weeks

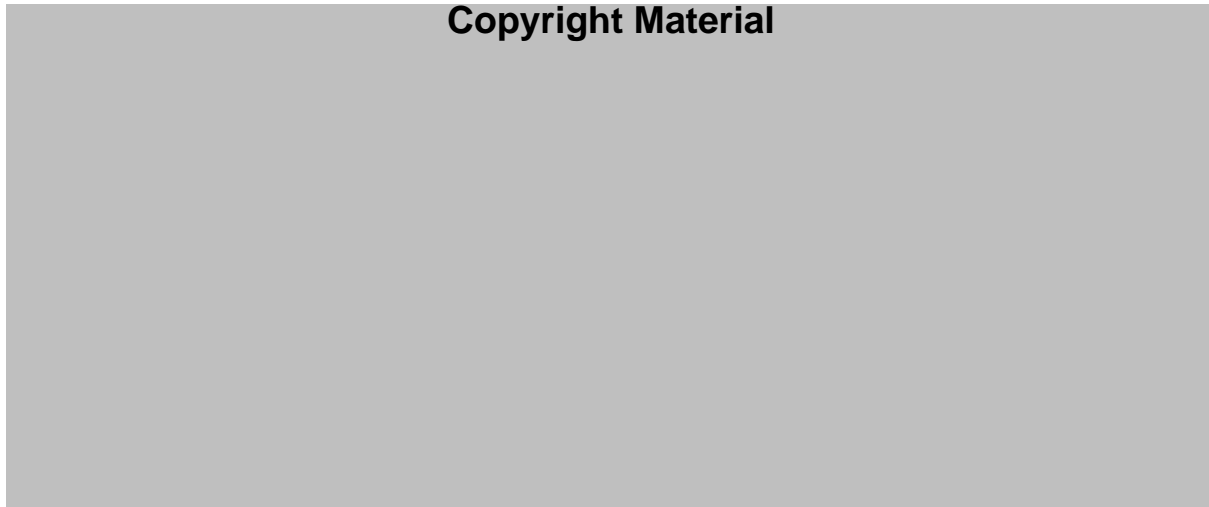
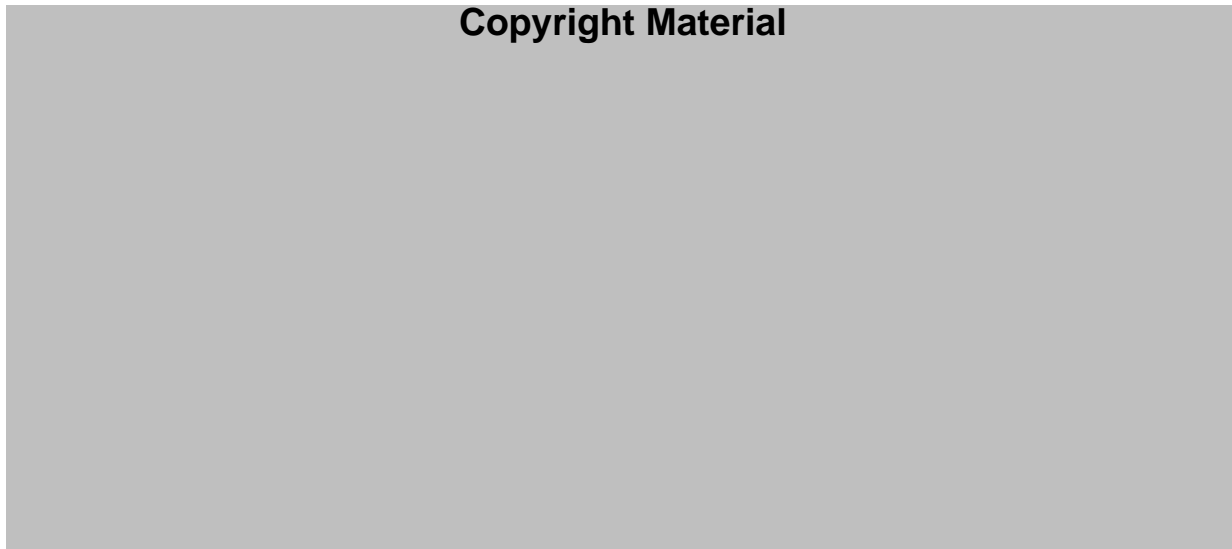


Figure 4: Duration of paretic effect; weeks to return to 80% of baseline



An important element of pharmacodynamic understanding of potential toxicity of Xeomin® has to do with the ability of a botulinum toxin product to have an effect at a distance from the injection site. While objective safety data will come from the adequate and well controlled trials, the Sponsor looked at this potential in a Phase I trial:

Trial MRZ 60201-0709/1, Double-blind, randomized, single-dose, single-center study with healthy female subjects to evaluate the migration potential of Xeomin® as compared to two other botulinum toxin type A products Vistabel® and Dysport®

This trial was conducted at a single center in Germany in 2007 – 2008 and enrolled 29 women. They were randomized to receive two separate injections from a panel of three different BoNT A products, randomized 1: 1: 1, so that the final tally consisted of equal numbers of injections of each product. The botulinum toxin A products, NT 201, Vistabel (EU trade name for BOTOX®, onabotulinumtoxinA) and Dysport® (abobotulinumtoxinA) were injected intramuscularly into the forehead and the resulting area of anhydrosis was recorded photographically over time. Each individual was treated with two different medications (one to each side of the forehead), dosed as 5 units each of NT 201 and Vistabel and 12.5 units of Dysport® in equal volumes.

The rationale for the trial was that the botulinum toxin injected intramuscularly spreads into surrounding tissue such as skin. Cholinergic-innervated skin structures i.e.: sweat glands are affected by the toxin. This model makes use of the effect of botulinum toxin on sweat glands in the skin of the forehead by measuring the area of anhydrosis around the injection site. Outcome measurement were made frequently over a 6 month period but the outcome the plan specified was a photographic result of the Minor's starch / iodine sweat test blindly read by a dermatologist and image analysis recorded at 6 weeks and 6 months post injection. 29 subjects were enrolled, 1 subject was discontinued for having missed both evaluation days, and 23 completed the protocol and were evaluable.

It is of interest that the Sponsor reports: "In 6 subjects there were incomplete or implausible (area of anhydrosis was too diffuse so that no clear border could be defined) results in the Minor test on right or left side of the forehead [between days 15 and 29]... As these incomplete or implausible data fell into the time of expected maximum of area of anhydrosis they were regarded as major protocol deviations," and excluded from the Per Protocol Set (PPS) analysis. It is not known whether these were relatively larger or smaller areas.

Maximal area of anhydrosis (mm²) at 6 weeks post injection (Per Protocol Set)

Table 3: Maximal area of anhydrosis (mm²) at 6 weeks in PPS (source: Sponsor)

Treatment	N	Mean	SD	CV	Minimum	Q1	Median	Q3	Maximum
NT201	13	364.3	138.13	37.9	220	270	298	430	630
Vistabel	16	343.1	110.72	32.3	199	228	345	426	540
Dysport	17	459.1	151.81	33.1	260	330	436	534	731

The Sponsor used the PPS population and a 90% confidence interval (two sided) for change from the NT201 measurement and found "highly significant" results indicating

that NT 201 and Vistabel were comparable, while the anhydrotic area was significantly larger for Dysport®.

Looking the size of the anhydrotic area for Xeomin® by subject over the timeframe of the entire trial shows that early after injection there is a larger area in general that decreases with time. This is true of the other preparations as well.

Figure 5: Area of anhidrosis by subject over time after NT 201 (source: Sponsor)

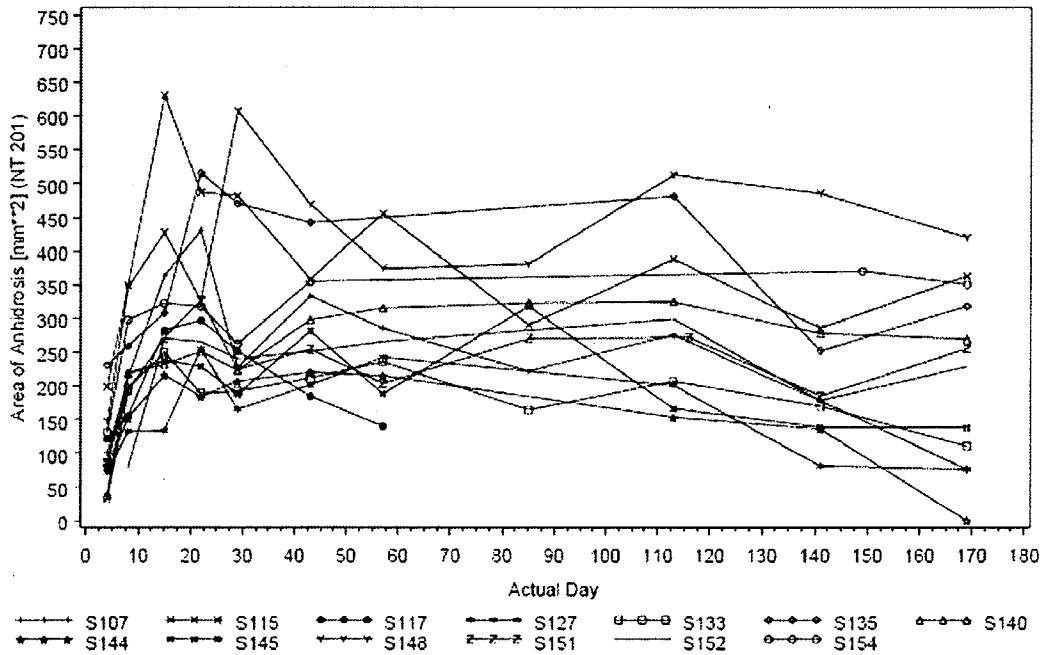


**Figure 4 Area of Anhidrosis [mm²] by Subject, Day, and Treatment. Analysis Population: Per-Protocol Set
Figure of Xeomin®**

A major flaw of the trial is that there is no way of knowing true dose equivalency for these biologics: the data does not exist. There has been some modeling of dose equivalency based on non-clinical data and presumably the chosen doses are based on similar work (Aoki, et al. Eur J Neurol 13 (Suppl 4):10-19, 2006). The reviewer wonders if the excluded subjects were anomalous as the Sponsor thought, or at one end of the diffusion spectrum. It is not possible to draw any firm conclusions about diffusion of BoNT from this trial.

4.4.3 Pharmacokinetics

Kinetic studies of Xeomin® have not been performed. If there is systemic absorption of NT 201 (and BoNT products in general), it is too small to be detected with available assay methods.

5 Sources of Clinical Data

All documents and datasets reviewed for this BLA submission are in electronic form. This information is accessible via Global Submit Review (Version 4.2) and may be found in the CBER Electronic Document Room via the path:

\\cbsap58\M\CTD_Submissions\STN125360\125360.enx

Clinical studies may be categorized into two groups: Phase I studies supportive of the NT 201 application in general which are described in **Section 4.4 Clinical Pharmacology**, and Phase III trials supportive of specific indications in spasticity, cervical dystonia, and blepharospasm. Only the Phase III trials supportive of blepharospasm are described in this review.

The Sponsor's tables found in Module 5.1 of the eCTD list the clinical trials contributing efficacy data for the indication of blepharospasm. The contributions of each trial to the program are defined further in **Section 5.2 Review Strategies**, and individual reviews of the studies in subsequent sections.

In addition to the listings below, the confirmatory trial in blepharospasm MRZ 60201-0433/1, has a long term open label follow-up trial still in progress, designated MRZ 60201-0433/2. Trials related to the indications of cervical dystonia and spasticity (three trials each) are also not included in the list.

5.1 Tables of Studies/Clinical Trials

Table 4: Phase III trials supportive of NT 201 in blepharospasm (source: Sponsor)

Phase 3	MRZ 60201-0433/1	5.3.5.1 (BEB)	Safety and Efficacy of NT 201 compared with placebo in pre-treated subjects with Blepharospasm	Randomized, double-blind, placebo-controlled, multicenter study	Up to 50 U NT 201 per eye vs. placebo in a 2:1 ratio	n=109 ITT	Pre-treated patients with Blepharospasm Previous successful treatment with Botox in two consecutive sessions before trial entry	Up to 20 weeks	Finalized ICH
Phase 3	MRZ 60201-0003	5.3.5.1 (BEB)	Non-inferiority of NT 201 compared to Botox in terms of efficacy and safety in patients with Blepharospasm	Randomized double-blind active-controlled parallel group multicenter trial to test non-inferiority	≤35 U per eye NT 201 ≤35 U per eye BOTOX* intramuscular injection at baseline	n=300 ITT n=256 TPP n=303 EFS	Patients with Blepharospasm Previous successful treatment with Botox in two consecutive sessions before trial entry	Up to 16 weeks	Finalized ICH

5.2 Review Strategy

The review strategy focuses upon the following areas and their supporting trials:

- Does NT 201 act like a botulinum toxin is expected to act in human muscle?
 - Phase I trials reviewed in **Section 4.4 Clinical Pharmacology**, above
- Is NT 201 effective in reversing the symptoms and disability of blepharospasm?
 - Trial MRZ 60201 – 0433/1 Randomized, double blind, placebo controlled confirmatory trial in blepharospasm.
- How durable is the clinical effect of NT 201 upon blepharospasm?
 - Trial MRZ 60201 – 0433/2 One year open label treatment extension to the double blind placebo controlled trial.
- How does NT 201 compare to another botulinum toxin A product which approved for the treatment of blepharospasm?
 - Trial MRZ 60201 – 0003 Randomized, double blinded, active control, non-inferiority trial (NT201 vs. BOTOX®)

Reviewer's Note: It should be noted, as will become evident as the trial populations are discussed, no BoNT treatment naïve subjects with blepharospasm were enrolled in this development program.

Because of safety concerns specific to botulinum toxins, and because human experience with NT 201 was derived from three different disease entities with a wide range of dosing regimens (blepharospasm, cervical dystonia and spasticity), this BLA submission is the subject of separate comprehensive safety analysis created within DNP. The reader is referred to that document in lieu of Section 7 in this document.

However, this reviewer does comment on two particular safety issues also related to clinical efficacy, i.e.: evidence for the spread of toxin effect from the injection site past the target muscles and immunogenicity. For this reason, **Section 7.3.5 Submission Specific Primary Safety Concerns** and **Section 7.4.6 Immunogenicity** are retained.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Confirmatory trial of NT 201 for the treatment of blepharospasm (MRZ 60201-0433/1)

Trial

Prospective, double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of blepharospasm (MRZ 60201-0433/1)

Phase III

Purpose

The objective of this trial was to determine the efficacy, safety and tolerability of a single injection of NT 201 compared to placebo when injected intramuscularly in patients with benign essential blepharospasm (BEB). All subjects had had a satisfactory therapeutic response to BOTOX® injection on at least two previous occasions.

This multicenter trial randomly assigned subjects to NT 201 or placebo in a 2:1 ratio. A single injection session was administered. Subjects received up to 50 U of NT 201 per eye, the total administered dose being equivalent to the total dose of BOTOX® given at the last two treatments prior to enrollment. The evaluation period lasted at least 6 weeks but no more than 21 weeks.

A long term, open label extension trial covering further treatment with a maximum of 5 injection sessions for up to 48 weeks, with 20 weeks of observation following the final injection, allowed further safety observations. This is described separately in **Section 5.3.2 Open label repeated injection trial for the treatment of blepharospasm.**

Both trial periods were monitored by a Data Safety Monitoring Board (DSMB).

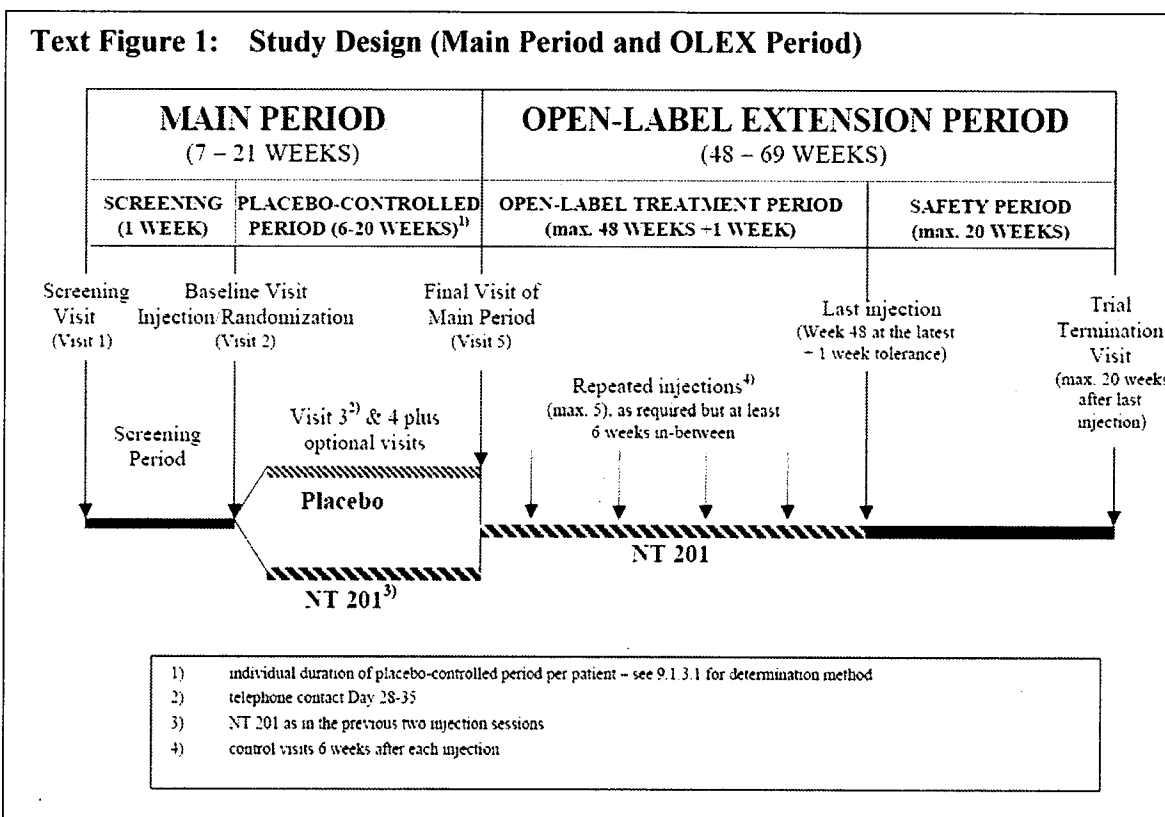
The primary objective of the study was to measure the relief of blepharospasm after a single session of peri-orbital injections of NT 201 using a maximum dose up to 50 U per eye.

The primary outcome measure used to evaluate this is the change from base line of the Jankovic Rating Scale blepharospasm severity subscore (JRS-S), as assessed by a blinded rater, six weeks following NT 201 administration. Secondary measures include the same JRS-S rating by patient diary, change in Blepharospasm Disability Index (BSDI) six weeks after administration, and the Patient Evaluation of Global Response (PEGR) at the final visit, up to 20 weeks following drug administration.

Trial design

The trial, using a prospective, double-blind, placebo-controlled, randomized, multi-center design in 34 centers in the US and Canada, began enrolling October 9, 2006 and the last subject completed the blinded portion of the trial on May 28, 2008. Thirty three clinical sites were initiated and 31 sites enrolled patients. The open label extension period is ongoing.

Figure 6: Design of Trial 0433/1 (source: Sponsor)



The trial’s protocol and statistical analysis plan presented the following procedures, outcomes and endpoints, and proposed analyses:

Clinical Assessment:

Two investigators were used at each site. One investigator was in charge of all aspects of the study except for the Jankovic Rating Scale (JRS) scoring, which was performed by the “blinded independent investigator.” For the sake of consistency, the BSDI had to be administered before the JRS was rated. Investigators who rated the JRS were trained and certified.

Primary endpoint:

- Jankovic Rating Scale (Severity Subscale): The JRS is a two item, 0-4 rating scale with anchored cut-points for severity of blepharospasm and its frequency. The primary statistical analysis is the change from baseline (Visit 2) to week 6 (Visit 4). The dependent variable in the ANCOVA model is the change from baseline in the JRS Severity subscale score assessed by the blinded independent investigator and the independent variables are treatment, baseline JRS severity subscore, sex, age, dose and trial center.

JRS is determined by interview between the rater and the patient. The patient reports their symptoms for the prior 3 days and judge the average severity and frequency, which is recorded by the rater.

Secondary criteria:

- JRS Severity Subscale Diary: The median value of the diary (a patient self-rated JRS-S) for the seven days prior to visit will be used in an analysis of covariance. The initial self-assessment is made in the week prior to the baseline injection, with the endpoint value taken from diaries prior to week 6 (Visit 4).
- Blepharospasm Disability Index: The BSDI is a self-rated scale for the assessment of impairment of specific activities of daily living caused by BEB. The scale consists of 6 items rated 0-4 with anchored cut-points, plus a choice of "not applicable to me." The 6 items are "Driving a vehicle", "Reading", "Watching TV", "Shopping", "Walking" and "Doing everyday activities".
- Patient Evaluation of Global Response: The PEGR is a single descriptive and subjective response to a self-rated scale ranging from "complete abolishment of signs and symptoms" (+4) down to "very marked worsening" (-4).
- Global Assessment of Efficacy: The investigator performed a single global assessment of the efficacy of study medication at the final visit of the double blinded phase of the trial ("Main Period"). The patient was rated on a 4-point Likert scale, ranging from "very good", "good", "moderate", to "poor".

Secondary time-based measurements (duration of effect):

- Time to Onset of Treatment Effect after Injection (subjective assessment)
Time to onset of effect was defined in weeks from the day of injection (Day 0). The patient was queried at each visit and telephone contact up to Visit 4 (Week 6, 42 ± 3 days). If the patient answered yes they were asked what day they noted the effect. An amendment to the Sponsor's SAP added that, for subjects without any reported onset of treatment effect through the trial period, the time to onset of effect will be calculated to the last visit of the trial period and censored.

- **Time to Waning of Treatment Effect after Injection (subjective assessment)**
Time to waning of effect was similarly defined in weeks from the day of injection. However no inquiry was made unless the patient was one who reported an onset of treatment effect. In this case they were asked about waning of effect at Week 3, at the earliest. An amendment to the Sponsor's SAP added that, for subjects without any reported onset of treatment effect until end of the trial period, the time to waning of effect will be set to zero weeks.

- **Duration of Treatment Effect**
For all patients who experienced a treatment effect, the duration was defined as the time period from day of injection (Day 0) until the time point for the "agreed upon" day of retreatment. This day (which ends the blinded portion of this trial for that subject) was determined by the evaluation of the JRS severity subscore assessed by the blinded investigator (score must be ≥ 2).

If a patient did not experience a treatment effect, the duration of treatment effect is set to 0 days.

Safety measurements:

Adverse Events were defined for the purposes of recording, documentation, definition of intensity, action taken and outcome. All patients who had an AE were monitored until it resolved or stabilized. The minimum period of AE related observation was defined as 20 weeks $\pm$ 3 days, or until the next injection of any BoNT. Serious Adverse Events (SAEs) were defined in the protocol using standard criteria. Reports went to the DSMB as well as the Sponsor within 24 h.

Adverse events of special interest included symptoms such as ptosis, abnormal vision, dry mouth, dysphagia, speech problems, dyspnea, respiratory infections, local weakness, facial weakness, and general body weakness which are considered to be signs of local or systemic toxin spread. These symptoms and all other signs and symptoms, which the Investigator considered to indicate toxin spread, were to be recorded as an AE and reported within 7 days to the CRO.

Other safety variables included vital signs, body weight, physical and neurological examination, electrocardiogram, a global assessment of tolerability and laboratory parameters (pregnancy testing, clinical chemistry, hematology and serum for BoNT antibodies).

Blood samples for botulinum neurotoxin antibodies are obtained at the screening visit, Visit 4 (week 6) and the final visit of the double blind period (Visit 5, up to 20 weeks). Sampling extends into the open label period at all injection visits and the final visit of the open label trial. Measurement is done by ELISA and positive samples will be confirmed using the mouse ex vivo hemidiaphragm assay. The assay is unable to discriminate between neutralizing and non-neutralizing antibodies.

Key Inclusion Criteria

- Male or female outpatients aged 18 to 80 years (inclusive) previously treated with BOTOX®
- Clinical diagnosis of bilateral BEB
- Jankovic Rating Scale Severity (JRS-S) subscore ≥ 2 at baseline
- Source documentation of the last two consecutive injection sessions with BOTOX® and a stable satisfactory therapeutic response directly prior to trial entry.
- At least 10 weeks must have been passed between the last injection with BOTOX® for BEB and baseline.

Key Exclusion Criteria

- Atypical variant of BEB caused by inhibition of levator palpebrae muscle
- Myotomy or denervation surgery in the affected muscles (e.g., peripheral denervation and/or spinal cord stimulation)
- The two injections prior to enrollment using more than 50 U BOTOX® per eye
- Hypersensitivity to human serum albumin, sucrose, or Botulinum toxin Type A
- Neuroleptic induced blepharospasm
- Diagnosis of myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant neuromuscular disease which might interfere with the trial
- Treatment with Botulinum toxins for any indication other than BEB within 4 months prior to baseline and during the trial
- Present or pre-existing blood coagulation disorders including therapeutic or prophylactic anticoagulation
- Severe hearing loss.

Concomitant Medication

Any medication not related to the treatment of BEB were allowed and recorded. Anti depressants, opioid analgesics, non-steroidal anti-inflammatory agents, anticholinergics and benzodiazepines were allowed if taken in stable doses for at least 3 months prior to entry into the study and maintained through the evaluation period.

Other drugs active at the neuromuscular junction were to be "avoided": neuroleptics, verapamil, dantrolene, quinine and peripheral muscle relaxants.

The following were contraindicated: botulinum toxin of any other serotype, phenol or alcohol injection in the part of the body under study, intrathecal baclofen, aminoglycoside antibiotics, tetracycline, polymixin, aminoquinolones, and anesthetic agents including locals.

Trial Visits

Table 5: Trial 0433/1 Visit checklist (source: Sponsor)

Trial visit	V1 (Screening)	V2 (Baseline)	V3 (Control Visit)	T1 (Telephone contact)	V4 (Control Visit)	Optional phase: At least fortnightly contacts (visits and telephone calls)*	V5 (Final Visit Main Period)
Assessment time point and time window	Day -7 (-7 days)	Day 0	Week 3 (Day 21 ± 3 days)	Week 4/5 (Day 28- 35)*****	Week 6 (Day 42 ± 3 days)	Week 8, 10, 12, 14, 16, 18 or visits on subject's request Phone call Visit	up to Week 20
Informed consent	X						
Med. His. / Conc. Dis. / Conc. Med.	X						
Demographic data	X						X
Physical/neurological examination, body weight Inclusion & exclusion criteria	X	X					
Jankovic Rating Scale/Subject Diary**	X	X	X		X	X	X
Jankovic Rating Scale/Rater Assessment	X	X	X		X	X	X
Blepharospasm Disability Index	X	X	X		X	X	X
Vital signs	X						
ECG	X						
Clinical chemistry, hematology	X						X
Antibody titer	X				X		X
Pregnancy test	X (Blood)	X (Urine)					X (Blood)
Patient Evaluation of Global Response***							X
Randomization for Main Period		X					
Injection session	X****	X			Ask for need	Ask for need	Ask for need
Adverse events		X****	X	X	X	X	X
Changes in conc. medication /conc. diseases		X	X	X	X	X	X
Global assessment of efficacy/tolerability							X
Onset (O) / Waning (W) of effect			X (O/W)	X (O/W)	X (O/W)	X (W)	X (W)
Documentation of discontinuation of Main Period							X

* The following applies to the optional phase:

- The subject was to be questioned every 2 weeks, either by phone or at a visit, about the need of an injection.
 - The interval between two visits was never to exceed 4 weeks.
 - In the event that a subject expressed via phone the need for an injection, a visit was to be scheduled immediately.
 - If the physician disagreed with the subject regarding the need for a new injection, the subject was to come for a visit every 2 weeks from that time.
- ** Instructions for electronic diary were given to the subject.
 *** Evaluation of the response to the injection at Baseline Visit.
 **** AEs occurring prior to first injection were to be recorded as baseline complaints on the AE form.
 ***** If a new AE occurred, which in the Investigator's opinion could not be sufficiently documented via telephone, the subject came to the site within the following 7 days.
 Med. His. =Medical history; Conc. Dis.=Concomitant disease; Conc. Med.=Concomitant medication; ECG=Electrocardiogram

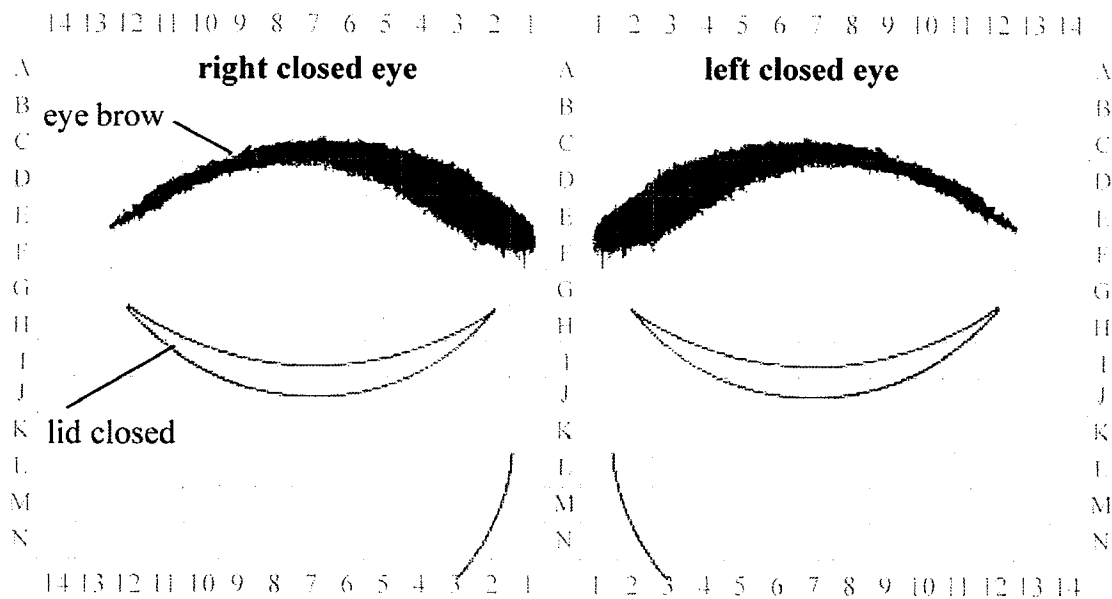
Treatments and Ancillary Management:

NT201 and placebo were provided as sterile lyophilized powder reconstituted with 0.9% saline and then injected. Sucrose and human albumin were the excipients used in the placebo vial. One unit of NT 210 corresponds to the calculated median lethal dose in mice (LD50 i.p.).

At the baseline visit (Visit 2), each subject received one dose of NT201 or placebo distributed among several injection points in both eyes. Highest dose permitted was 50 Units per eye. The treatment in both groups was to be identical (i.e.: total dose, volume, dilution, injection points per muscle, doses at each site) to what they had received in the previous two botulinum toxin sessions before entering the study. On the CRF volumes were recorded according to the following schema for documentation:

Figure 7: Case Report Form Injection site identification (source: Sponsor)

Injection Documentation



! Please mark and identify injection points with numbers.

The subject was injected only once in the blinded portion of this trial. Any new injection of NT 201 after this time automatically marked entry into the open label extension trial.

Randomization and Controls:

Subjects were randomized to NT-201 versus placebo in a 2 : 1 ratio at Visit 2. Block randomization was used but block size (3) was kept secret. The DSMB held a sealed coded list of randomized subjects.

Because blepharospasm is more prevalent in women, it was expected to have a female preponderance in the study population.

GCP:

See also **Section 3.2** above. Merz performed an internal audit of a single clinical site #1019, six subjects enrolled. They found no evidence of noncompliance with GCP.

Protocol Amendments:

(The reviewer selected the substantive changes)

Amendment 1 (August 1, 2006, prior to the start of the study):

- The site personnel were directed how to ask patients for adverse events. This served to standardize the Adverse Event elicitation.
- The sequence of the assessments, i.e. first the Blepharospasm Disability Index (BSDI) and then the Jankovic Rating Scale (JRS), was defined as “mandatory” instead of “recommended” only. This served to avoid variability in the sequence of these two assessments.
- A further sensitivity analysis on the primary efficacy endpoint was defined in the protocol: “Further sensitivity analyses of the primary efficacy parameter will be based on the comparison of response rates (OR) at Control Visit V4 (Week 6) between the treatment groups. Responders are defined as patients with an improvement of at least 1 point in the JRS severity subscore compared to the Baseline Visit (V2, Day 0)... Comparisons between the two treatment groups will be performed using logistic regression models. The dependent variable is the response to treatment (0 = no, 1 = yes) and the independent variables are identical to the independent variables in the ANCOVA models for the primary efficacy variable. Again, three models will be presented: 1) full model with all adjusting variables, 2) final model with all adjusting variables with $p < 0.2$ (backward selection), and 3) simple model including the treatment effect only. The same missing replacement strategies as for the primary efficacy variable will be applied to the JRS severity data before responder determination.”

Amendment 2 (March 26, 2007, 5 months after the first enrollment):

- The upper limit of age of patients allowed was increased to 80 years of age. The reason was that the blepharospasm population turned out to be on average of higher

age than initially expected, as assessed during screening procedures at several sites.

- The exclusion criteria “severe hardness of hearing” was added to avoid inclusion of elderly patients who are not able to handle the patient telephone diary with interactive voice recognition and response system.
- Patients with other facial dystonia were allowed to be enrolled, provided the symptoms did not interfere with blepharospasm and did not need treatment with other botulinum toxins during the study participation.
- The requirement for stable (i.e.: identical) injection schemes of the two previous injections prior to study entry was changed by adding tolerance ranges of allowed deviations (+/- 10 %). Consequently the wording requesting “identical” or “same” injections was changed to “similar”.

Method of analysis for efficacy (exposure / response):

The Sponsor defined three populations:

• **Evaluable for Safety Population [EFS]:**

The EFS Population includes all patients who received trial medication.

• **Intent-To-Treat Population [ITT]:**

All randomized patients are included in the analyses of each efficacy outcome. This group of patients, defined as the ITT Population, is the basis for confirmatory testing.

• **Treated-Per-Protocol Population [TPP]:**

The TPP Population is defined as identical to the ITT Population but excluding patients for whom major protocol deviations were identified. This population was intended to be used for sensitivity analyses.

Unless otherwise indicated, this review uses the ITT population for analysis.

Descriptive statistics were derived by the Sponsor for all efficacy outcome variables.

The Sponsor indicated that, for the primary efficacy variable,

“the confirmatory analysis of the [Jankovic Rating Scale Severity Score] will be based on the comparison of least square means from an analysis of covariance [ANCOVA] model at Visit 4 (Week 6) between the two treatment groups in the ITT Population. The dependent variable in the ANCOVA model is the change from baseline in the JRS severity subscore assessed by the blinded independent Investigator and the independent variables are treatment, baseline JRS severity subscore, sex, age, dose (cut-off: median dose), and center (or pooled center). In case of missing data for the change from baseline in the JRS severity subscore,

the last available value for the change will be used (LOCF). Type III Sum of Squares will be used for testing procedures.”

All tests in the ANCOVA models are two-sided with Type I error of $\alpha=0.05$.

Similar analyses were performed for the patient diary reporting the JRS severity subscale (for which the median score for at least 3 days prior to Visit 4 at week 6 was used) and the Blepharospasm Disability Index (BSDI).

The Patient Evaluation of Global Response (PEGR) was recorded at the final visit of the trial period. Missing data for this endpoint was given a value of 0 to indicate no effect.

Time to event variables measuring drug response and its duration are analyzed as Kaplan-Meier curves. In general, ambiguous data was treated with a “worst case” scenario to temper any undue optimism with regard to drug effect.

Sample size calculations were made based on previous JRS severity subscale data from trial MRZ 60201 – 0003. From these data a clinically relevant difference for the NT 201 treated group compared to placebo was assumed to be 0.8 points in mean change from baseline in JRS severity subscore. A two group t-test with a two-sided significance level of $\alpha = 0.05$ would have 90% power to detect such a difference assuming a common standard deviation of 1.0, when the sample size is 52 in the NT 201 group and 26 in the Placebo group (ratio 2:1). Taking into consideration a 30% drop-out rate, the Sponsor planned to randomize 75 patients in the NT 201 group and 37 in the placebo group (total $n = 112$).

Subject Enrollment:

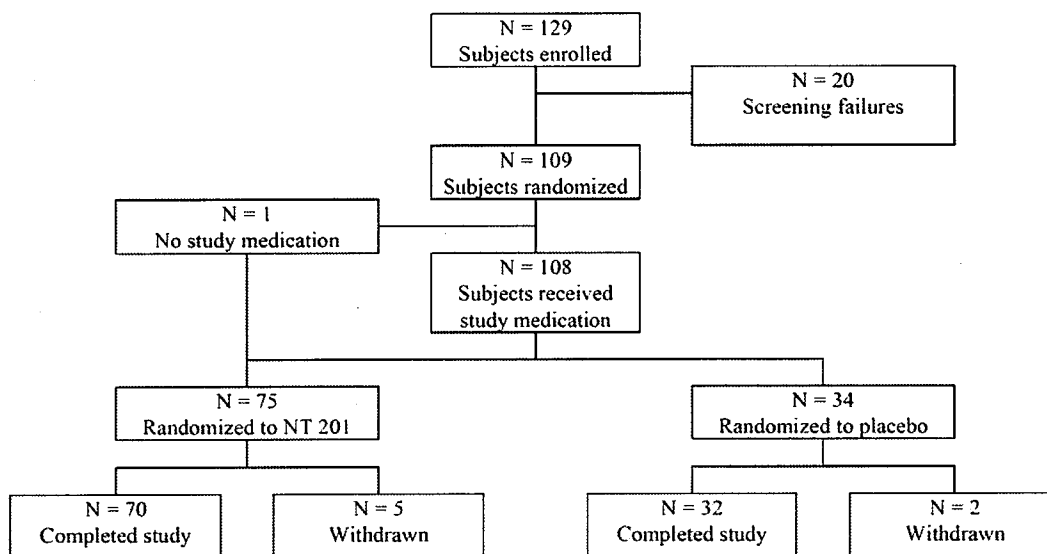
31 sites in the US and Canada enrolled subjects. The first enrollment occurred on October 9, 2006 and the date of last completion was May 28, 2008.

Figure 8: Trial 0433/1 enrollment by clinical site



Trial populations / Patient disposition:

Figure 9: Trial 0433/1 Subject disposition (source: Sponsor)



Source Data: Table 14.1.1.6

Screen Failures (20):

Most common reasons for screening failures, all of which occurred at the screening visit (Visit 1) were: missing doses from two previous BOTOX® treatments, lack of BOTOX® stable response, surgery in affected eye muscles, previous two BOTOX® injections greater than 50 u per eye, and uncontrolled medical disease.

One subject was randomized (NT 201 group) but did not receive medication; no reason was given. Seven subjects withdrew prematurely (NT 201 = 5; PCB = 2). Reasons included withdrawal of consent, lost to follow up or triggers of withdrawal criteria (see Dropouts, below).

Table 6: Trial 0433/1 Assignment by analysis population (source: Sponsor)

	NT 201 group	Placebo group	Total
Number of Subjects Randomized	75	34	109
Number (%) of Subjects in EFS	74 (98.7)	34 (100.0)	108 (99.1)
Number (%) of Subjects in ITT	75 (100.0)	34 (100.0)	109 (100.0)
Number (%) of Subjects in TPP	71 (94.7)	31 (91.2)	102 (93.6)

EFS=Evaluable for Safety; ITT=Intent-To-Treat; TPP=Treated-Per-Protocol
 Source: Table 14.1.1.7

Study Results

Demographics

Demographic characteristics did not vary within the ITT population. Consistent with the epidemiology of the syndrome, 65% of the subjects were women in both treatment arms. Average age was similar in both groups, about 63 years (range 22 to 79 years). Participants in the trial were white (83 %), Hispanic (8%), Asian (6%) or black (4%), and most were non-smokers (67%).

The median duration of blepharospasm was 84 months, the same in both treatment arms (range 6 - 468 months; mean 105 months). Length of disease after formally diagnosis was 5 years on average.

Baseline severity as quantified by the Jankovic Rating Scale and Blepharospasm Disability Rating Scale revealed no statistical difference between the two treatment arms (the baseline rating is used as covariate in the outcome analysis).

Baseline Ratings in ITT Population (source: Sponsor).

Table 7: Trial 0433/1 Baseline JRS ratings in ITT cohort (source: Sponsor)

Efficacy variable	NT 201 group N = 75 Mean (SD)	Placebo group N = 34 Mean (SD)
JRS Severity subscale (Independent Rater)	3.12 (0.734)	2.94 (0.814)
JRS Frequency subscale (Independent Rater)	2.75 (0.902)	2.82 (0.758)
JRS sumscore (Independent Rater)	5.87 (1.492)	5.76 (1.415)
JRS Severity subscale (Subject Diary)	2.61 (0.976)	2.53 (1.170)
JRS Frequency subscale (Subject Diary)	2.49 (1.004)	2.36 (1.145)
JRS sumscore (Subject Diary)	5.11 (1.862)	4.89 (2.213)
BSDI	1.60 (0.791)	1.37 (0.839)

JRS=Jankovic Rating Scale; BSDI=Blepharospasm Disability Index; SD=standard deviation

86% of subjects had a positive medical history at entry into the trial. These were usual and common illnesses and surgeries, and no disparity between the groups was noted. Depression was noted in one NT 201 subject and 3 PCB subjects; depression is known to negatively influence self ratings of illness and related disability.

Eyelid ptosis was noted in equal ratios in both groups (NT 201 = 6; PCB = 3). Ten (13%) NT 201 and 6 (18%) placebo subjects had undergone blepharoplasty or other eyelid surgery. Other dystonia phenomena were noted in a third of subjects, all but 1% in facial, cervical, perioral, or mandibular muscles.

Concomitant medications before trial medication:

All subjects by definition had had BOTOX® treatment prior to entry into the trial. The median and range of numbers of injections received prior to entry into the trial were comparable in both arms (NT 201 = 13 (0 – 104); PCB 16 (2-90); *Reviewer's note: the subject receiving "0" injections in the NT 201 group was a major protocol violation*)

Concomitant medications during the trial period:

Almost all enrollees were taking concomitant medication (96%) and these were distributed roughly equally between the arms. The most common concomitant medications were vitamins, lipid modifying agents, NSAIDs, osteopenia related treatments, aspirin, ophthalmologicals, proton pump inhibitors, and antihypertensive agents. Neurological agents included anti Parkinson drugs (levodopa preparations and trihexyphenidyl: NT 201 7%, PCB 9%), anticonvulsants (clonazepam, gabapentin, levetiracetam, primidone, and topiramate: NT 201 20%, PCB 27%), muscle relaxants including baclofen (NT 201 3%, PCB 6%), antidepressants (NT 201 20%, PCB 27%), and sedatives (benzodiazepines, barbiturates and other hypnotics: (NT 201 27%, PCB 27%). In the reviewer's opinion, none of these had any effect on the trial's outcome.

Compliance with Study Medication

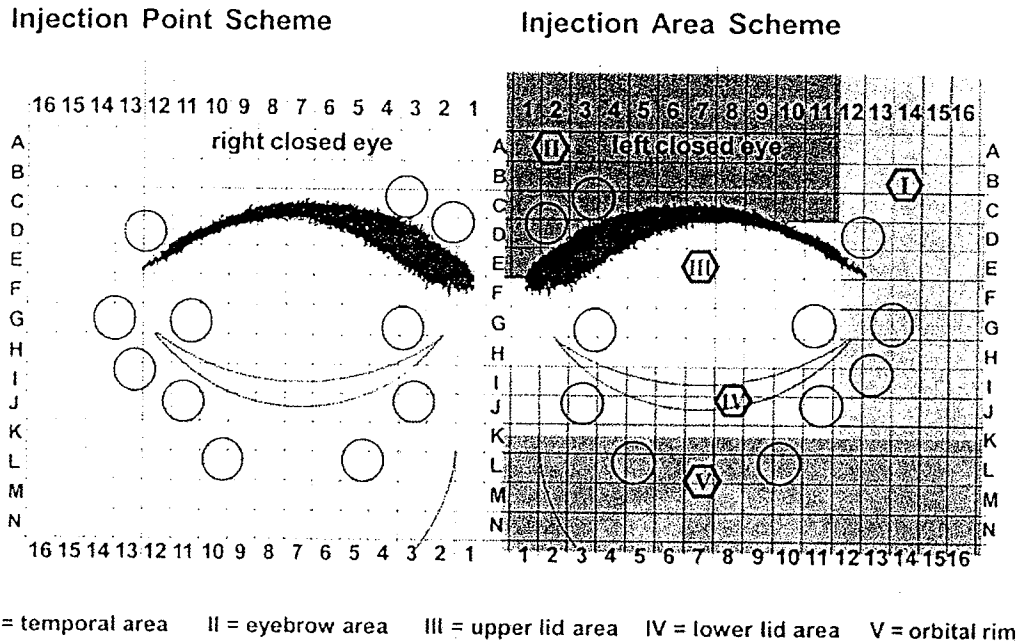
The study medication was injected by the Investigator or their designated staff at each study site. No compliance plan was specified.

Dosing Information and Exposure

Various parameters related to the dosing of NT 201 were recorded the course of this study: total dose of NT 201 by eye, number of injections around each eye, total volume of injection (sum of mL around each eye), and number of injections by anatomical site around the eye, as noted in the CRF (see Figure 7 above, page 37).

Injection points that were used in at least 10 subjects in the total ITT population for either eye are shown on Figure 10 below. It should be noted that injection sites in this trial were recorded as areas around the orbit, not individual periorcular muscles. Of interest, I reviewed the BOTOX® clinical review of July 12, 1988 (by courtesy of its author) and this is consistent with the method of data collection used for injection site location in the trials that were used to support BOTOX® approval in this indication.

Figure 10: Injection point schema (source: Sponsor)



Because the treatment of blepharospasm by botulinum toxin injection is a highly individualized and specialized clinical practice, the only possible analysis of this trial is the relationship of the total dose of NT 201 given to both eyes at the injection session to the primary outcome variable. (The rating scales used as the primary outcome do not distinguish severity or function of each individual eye alone). Medical practice dictates which muscles are appropriately injected, as it is known which determine the action of forced eye closure.

The median dose of NT 201 in 74 active treatment subjects was 65 units (range 20 to 100 units). The mean dose was 67 units (SD $\pm$ 22 units). There were no important differences between active and control groups nor right vs. left eye.

The subjects in the active arm averaged 6 injections per eye (SD $\pm$ 1.6).

The injection sites and NT 201 doses used in the active treatment arm of this trial are described in the following tables. The Sponsor does not discuss the range of dose for each injection site.

In conclusion, from the information collected, this reviewer finds that it is impossible to specify how much each periorbital muscle had been injected and with what range of NT 201 doses.

Table 8 Trial 0433/1 Summary of doses administered by injection area (source: Sponsor)

Treatment	Side	N	Nmiss	Total units of injection				
				Mean	SD	Min	Median	Max
NT 201	Right	74	0	33.5	11.07	10.0	32.30	50.0
	Temporal area	61	13	14.1	7.53	2.5	12.5	30.0
	Eyebrow area	66	8	7.9	5.98	1.3	5.0	30.0
	Upper lid area	69	5	9.4	5.11	2.5	10.0	25.0
	Lower lid area	49	25	7.3	3.66	2.5	7.5	20.0
	Orbital rim	17	57	5.6	3.32	2.5	5.0	15.0
	Left	74	0	33.4	11.32	10.0	32.50	50.0
	Temporal area	62	12	13.5	7.24	2.5	12.5	30.0
	Eyebrow area	64	10	8.1	6.07	1.3	5.0	30.0
	Upper lid area	67	7	9.6	5.01	2.5	10.0	25.0
	Lower lid area	52	22	7.4	3.85	2.5	7.3	20.0
	Orbital rim	15	59	5.7	3.40	2.5	5.0	15.0
	Total	74	0	66.9	22.32	20.0	65.00	100.0
	Temporal area	62	12	27.4	14.23	5.0	25.0	60.0
	Eyebrow area	66	8	15.7	12.00	2.5	10.0	60.0
	Upper lid area	69	5	18.7	9.79	2.5	20.0	50.0
	Lower lid area	53	21	14.0	7.60	2.5	12.5	40.0
Orbital rim	17	57	10.7	6.81	4.0	10.0	30.0	

Table 9: Trial 0433/1 Summary of injection volume and number by site (source: Sponsor)

Treatment	Side	N	Nmiss	Total Volume (mL)		Number of Injections			
				Mean	SD	N	Nmiss	Mean	SD
NT 201	Right	74	0	0.55	0.20	74	0	6.0	1.57
	Temporal area	61	13	0.24	0.13	61	13	2.3	1.03
	Eyebrow area	66	8	0.12	0.09	66	8	1.3	0.60
	Upper lid area	69	5	0.15	0.07	69	5	1.8	0.61
	Lower lid area	49	25	0.12	0.07	49	25	1.5	0.54
	Orbital rim	17	57	0.09	0.06	17	57	1.2	0.56
	Left	74	0	0.55	0.21	74	0	5.9	1.59
	Temporal area	62	12	0.24	0.14	62	12	2.2	1.03
	Eyebrow area	64	10	0.12	0.08	64	10	1.3	0.58
	Upper lid area	67	7	0.15	0.07	67	7	1.9	0.59
	Lower lid area	52	22	0.12	0.06	52	22	1.5	0.61
	Orbital rim	15	59	0.09	0.06	15	59	1.2	0.56
	Total	74	0	1.10	0.41	74	0	11.9	3.16
	Temporal area	62	12	0.48	0.27	62	12	4.4	1.95
	Eyebrow area	66	8	0.24	0.17	66	8	2.5	1.17
	Upper lid area	69	5	0.30	0.14	69	5	3.7	1.15
	Lower lid area	53	21	0.23	0.13	53	21	2.9	1.16
Orbital rim	17	57	0.17	0.12	17	57	2.3	0.99	

Protocol Deviations and Violations

Protocol deviations were classified as major and minor by the Sponsor prior to breaking the blind and these have been reviewed. The classification was appropriate. Only missing outcome evaluations (or missing visits that resulted in missing assessments) and errors in drug administration were considered major. Seven subjects were affected by major protocol deviations (NT 201 = 4; PCB = 3). Two PCB subjects and one NT 201 subject were included in the study even though they did not require injection i.e.: JRS score was 1 (too low).

Table 10: Trial 0433/1 Major protocol violations (source: Sponsor)

Major Protocol Deviation [a]	NT 201 group	Placebo group	Total
	N = 75 n (%)	N = 34 n (%)	N = 109 n (%)
Total subjects with at least one deviation	4 (5.3)	3 (8.8)	7 (6.4)
Missing assessment	4 (5.3)	1 (2.9)	5 (4.6)
Administration of study medication	3 (4.0)	1 (2.9)	4 (3.7)
Missing Visit	3 (4.0)	1 (2.9)	4 (3.7)
Early discontinuation	3 (4.0)	2 (5.9)	5 (4.6)
Inclusion criterion at baseline not met: no need for injection of Botulinum toxin	1 (1.3)	2 (5.9)	3 (2.8)
Inclusion criterion at screening not met: no clinical diagnosis of BEB	1 (1.3)	0	1 (0.9)
Randomized subjects who were not treated	1 (1.3)	0	1 (0.9)
Wrong injection procedure	1 (1.3)	0	1 (0.9)

Minor protocol deviations were numerous (one or more in each of the 109 randomized subjects) but did not lead to exclusion from analysis. The most common were: noncompliance with the JRS diary in 98 (90%) subjects, non adherence to time schedule of visits 65 (60%) of subjects, and inability to document a stable response to BOTOX® treatment given prior to entry into this trial (18 (17%) subjects). Twice as many minor deviations by percent occurred in the active treatment arm. Most had to do with missing visits and time deviations.

Efficacy Results

The population represented in this trial and its demographic features closely models the population previously treated with BoNT which would likely be encountered in clinical practice. As such, conclusions concerning the efficacy of NT 201 in blepharospasm resulting from this trial may be generalized to the target clinic population.

The dosing and exposure experience with NT 201 in the single injection session is given above. However, it is important to note that, in addition to the time based outcomes noted below, there are certain constraints which the protocol imposed. No patient would be reinjected before Visit 4 (at 6 weeks) but if needed, that evaluation could be performed simultaneously with Visit 5 which is the termination visit and evaluation. While the performance of Visit 5 would be triggered by the need for new treatment, a patient would otherwise have this visit performed at 20 weeks.

Sponsor's Efficacy Analysis

The primary statistical reviewer has evaluated the Sponsor's efficacy analysis and finds, as have I, that the primary and key secondary outcomes demonstrate NT 201 to be effective in treating blepharospasm in this population. While this reviewer makes no specific attempt to replicate the Sponsor's analysis, the calculations below closely corroborate those findings, though this reviewer's interpretation of the findings may differ.

The Sponsor, using analyses pre-specified by the SAP, finds that statistical comparisons demonstrated that the JRS Severity Subscore had a significantly greater reduction from baseline evaluation to Visit 4 in the NT 201 group (negative least squares mean change) than in the Placebo group (positive least squares mean change, i.e., a score increase) and that the score change was also influenced by gender, age, and baseline JRS Severity Subscore.

Table 11 Trial 0433/1 Logistic Regression Analysis of Response Rate in ITT-LOCF Population (source: Sponsor)

Model	Variables	p-Value	Odds Ratio Estimate	Odds Ratio 95%-CI
Full Model	Treatment	<0.001	11.29	(3.23 – 39.42)
	Gender	0.057		
	Age	0.021		
	Dose Group	0.668		
	Baseline JRS Severity subscore	0.286		
	Pooled Center	0.009		
Final Model	Treatment	<0.001	12.80	(3.65 – 44.90)
	Gender	0.044		
	Age	0.015		
	Pooled Center	0.005		
Simple Model	Treatment	<0.001	6.99	(2.44 – 20.03)

Source: Table 14.2.1.4.1.1

Primary Efficacy Endpoint

Table 12: Jankovic Rating Scale, Severity Subscale (JRS-S)

Severity	0:	None
	1:	Increased blinking present only with external stimuli (e.g. bright light, wind, reading, driving, etc)
	2:	Mild but spontaneous eyelid fluttering (without actual spasm), definitely noticeable, possibly embarrassing, but not functionally disabling
	3:	Moderate, very noticeable spasm of eyelids only, mildly incapacitating
	4:	Severe, incapacitating spasm of eyelids and possibly other facial muscles

Jankovic Rating Scale - Severity Subscale:

The JRS Severity Subscale rating performed by the independent blinded rater was available for 108 of 109 subjects at both baseline (Visit 2) and 6 weeks after the injection (Visit 4 at 42 ± 3 days). One subject was randomized but did not receive drug.

The mean difference from baseline to Visit 4 in the NT 201 arm was -0.84 (95% CI -0.56, -1.11) moving from 3.15 to 2.31 on average. In contrast, the mean difference for the placebo group was 0.21 (95% CI 0.52, -0.11) moving from 2.94 to 3.15 over the same period. There was no statistically significant difference in severity between the arms at baseline.

Figure 11: Trial 0433/1 JRS-S scores at baseline (Visit 2) by arm

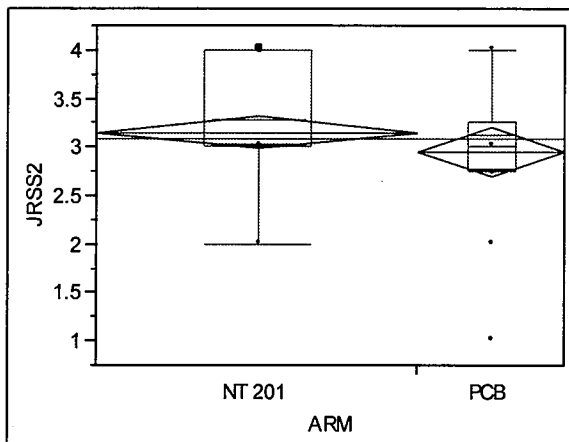
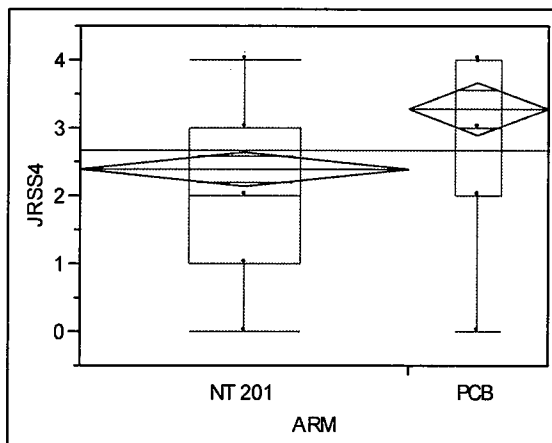


Figure 12: Trial 0433/1 JRS-S scores at 6 weeks (Visit 4) by arm



Change from baseline (Visit 4 minus Visit 2) by arm

Figure 13: Trial 0433/1 JRS-S change from baseline (Visit 4 minus Visit 2) by arm

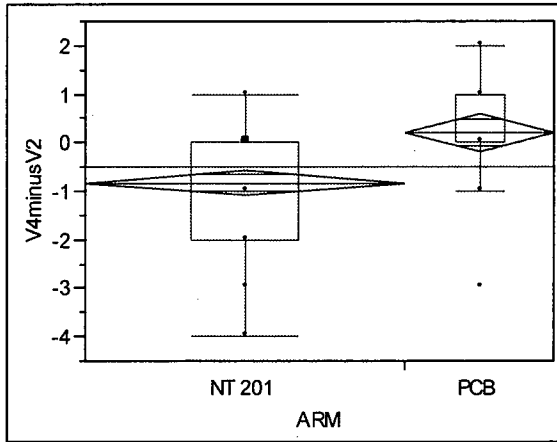


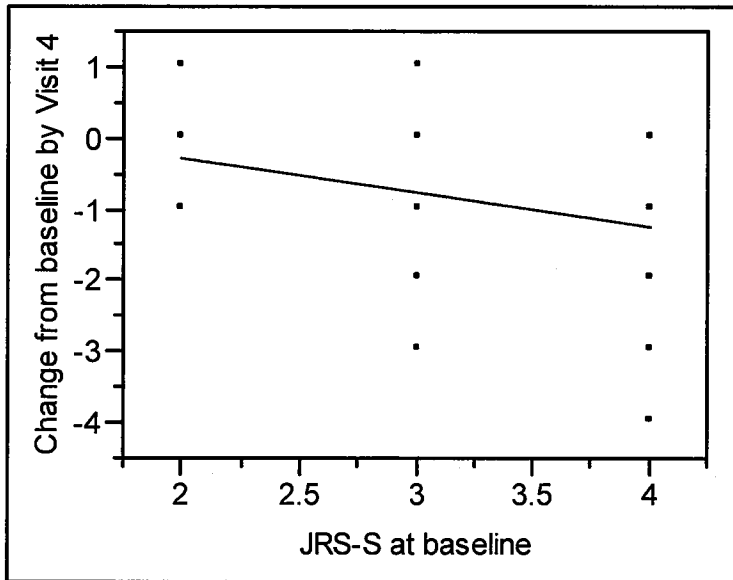
Table 13: Trial 0433/1 Change in JRS-S (Visit 4 – Visit 2)

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
NT 201	74	-0.83784	0.12855	-1.093	-0.5830
PCB	34	0.20588	0.18964	-0.170	0.5819

Using the baseline JRS-S score as a covariate strengthens the differences between the arms ($p < 0.0004$) and the reviewer thinks it is appropriate. By regression analysis, there is a clear relationship between the baseline severity and the improvement one is likely to see as a treatment outcome in the active drug arm. Of interest, there is a similar relationship in the placebo arm, though not as strong in this smaller sample ($p < 0.0426$). This could be explained by regression to the mean following multiple observations of the trial cohort or simply a poor quality metric. While the difference is statistically significant, it is quite small (0.21 points on the JRS-S) and clinically meaningless.

Stepwise regression control reveals that total dose of NT201 does not add any predictive strength to the model and doesn't contribute to the significance of the treatment effect.

Figure 14: Trial 0433/1 Regression plot of NT 201 arm (F Ratio 6.0954, p < 0.0159)



The results of multivariable analysis with the baseline JRS Severity Score as covariate reveals that there is a statistically significant improvement after treatment with NT201 (p < 0.001).

The reviewer's analysis closely corroborates the Sponsor's findings.

The JRS Frequency Subscale, while not a primary or secondary outcome showed similar movement from baseline evaluation.

Table 14: Jankovic Rating Scale, Frequency Subscale (JRS-F)

Frequency	0: None
	1: Slightly increased frequency of blinking
	2: Eyelid fluttering lasting less than 1 second in duration
	3: Eyelid spasm lasting more than 1 second, but eyes open more than 50% of waking time
	4: Functionally "blind" due to persistent eye closure (blepharospasm) more than 50% of waking time

Table 15: Trial 0433/1 Baseline JRS-F subscore at baseline (Visit 2)

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
NT 201	75	2.74667	0.09930	2.5498	2.9435
PCB	34	2.82353	0.14748	2.5312	3.1159

Figure 15: Trial 0433/1 JRS-F change from baseline to week 6 (Visit 4 - Visit 2)

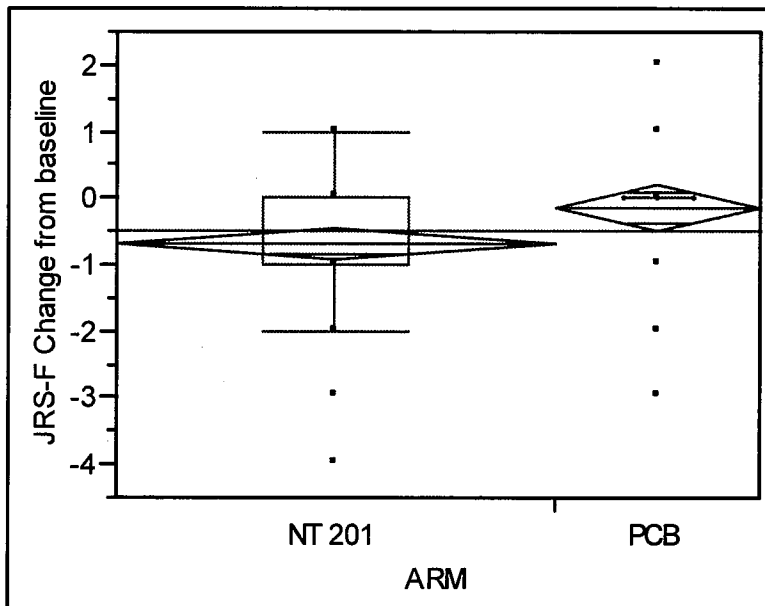


Table 16: Trial 0433/1 Change in JRS-F from baseline to week 6

Level	Mean	Std Error	Lower 95%	Upper 95%
NT 201	-0.67476	0.11899	-0.9107	-0.4388
PCB	-0.14583	0.17430	-0.4914	0.1997

The results of multivariable analysis with the baseline JRS Frequency Score as covariate reveals that there is a statistically significant improvement (change from baseline) after treatment with NT201 ($p < 0.0137$).

Secondary Efficacy Analysis

JRS Severity Subscale Diary:

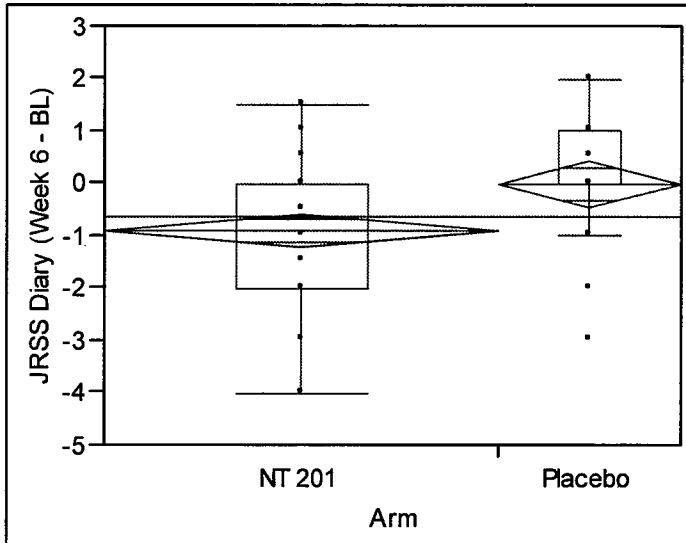
The median value of the patient self-rated JRS Severity Subscale for the seven days prior to the rating visit was used for analysis. The subject's initial self-assessment is made in the week prior to the baseline injection, with the endpoint value taken from diaries for the week prior to Visit 4 (week 6).

Multivariable analysis of the diary self-rating, using baseline measures as the covariate and LOCF for missing data reveals that there was a significant difference between the treatment groups ($p < 0.005$):

Table 17: Trial 0433/1 JRS Severity Subscale Patient Diary

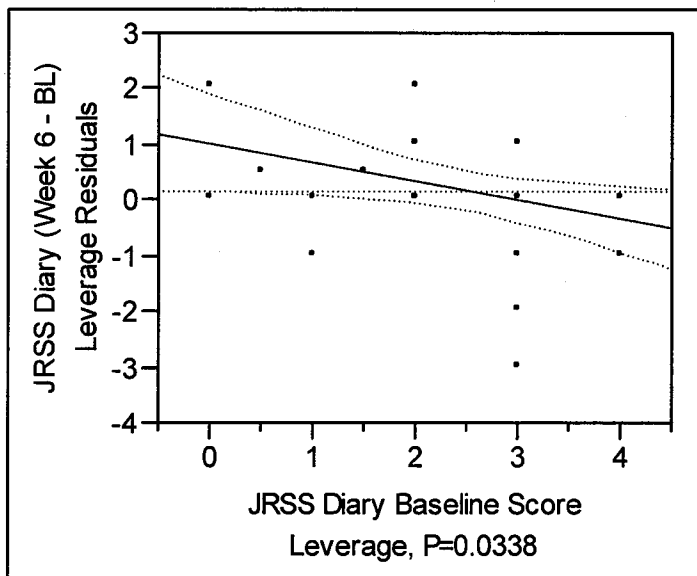
Level	JRSS Diary Mean BL ± SD	Mean Change from BL	Std Error	Lower 95%	Upper 95%
NT 201	2.61 ± 0.98	-0.90000	0.15469	-1.207	-0.5928
Placebo	2.53 ± 1.17	-0.02469	0.22737	-0.476	0.4268

Figure 16: Trial 0433/1 JRS-S Patient Diary Change from baseline to week 6



Leverage plot of the residuals from the least squares model reveals that the subject's baseline severity rating does indeed influence outcome:

Figure 17: Trial 0433/1 JRS-S Patient Diary Residuals Leverage Plot



Blepharospasm Disability Index:

The BSDI is a self-rated scale for the assessment of impairment of specific activities of daily living caused by BEB. The scale consists of 6 items rated 0-4 with anchored cut-points, plus a choice of "not applicable to me." The 6 items are "Driving a vehicle", "Reading", "Watching TV", "Shopping", "Walking" and "Doing everyday activities". Higher scores denote increasing severity of disability.

Analysis of covariance using the baseline BSDI score as the covariate revealed that there was statistically significant improvement in the active treatment group ($p < 0.0023$).

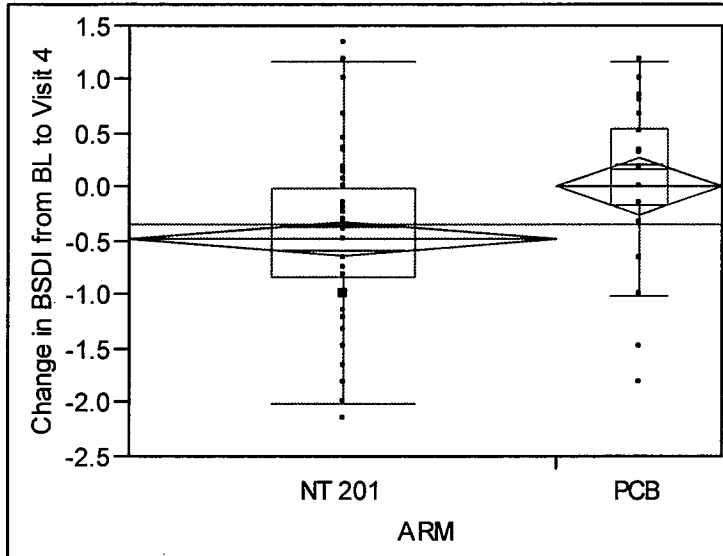
Table 18: Trial 0433/1 Baseline BSDI scores

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
NT 201	75	1.59644	0.09308	1.4119	1.7810
PCB	34	1.36863	0.13824	1.0946	1.6427

Table 19: Trial 0433/1 BSDI change from baseline to week 6

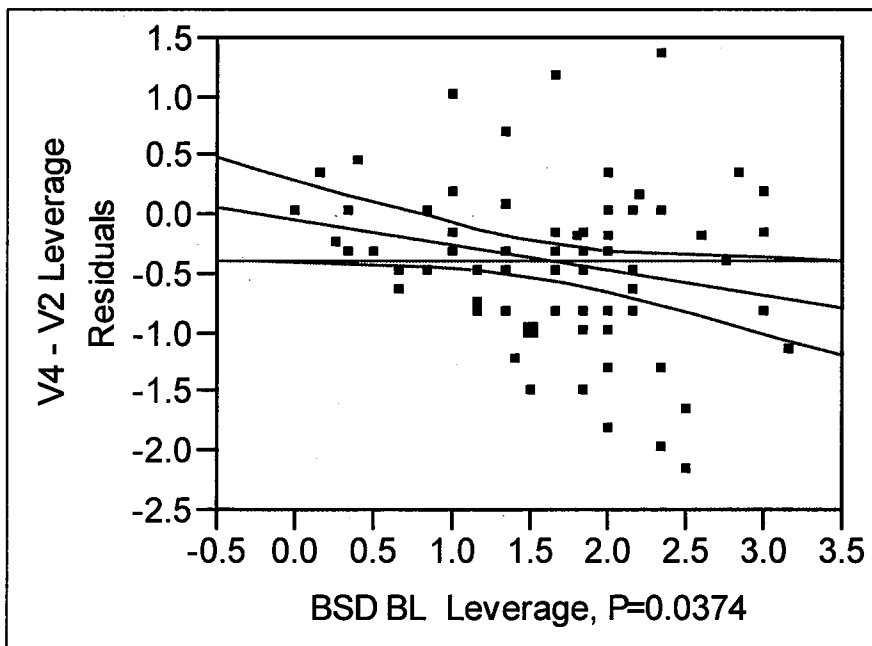
Level	Mean	Std Dev	Lower 95%	Upper 95%
NT 201	-0.47674	0.951074	-0.6500	-0.3035
PCB	0.01478	0.810885	-0.2277	0.2572

Figure 18: Trial 0433/1 Change in BSDI from baseline to week 6



Again, leverage plot of the residuals from the least squares model reveals that the subject's baseline severity rating does indeed influence outcome:

Figure 19: Trial 0433/1 BSDI Residuals Leverage Plot

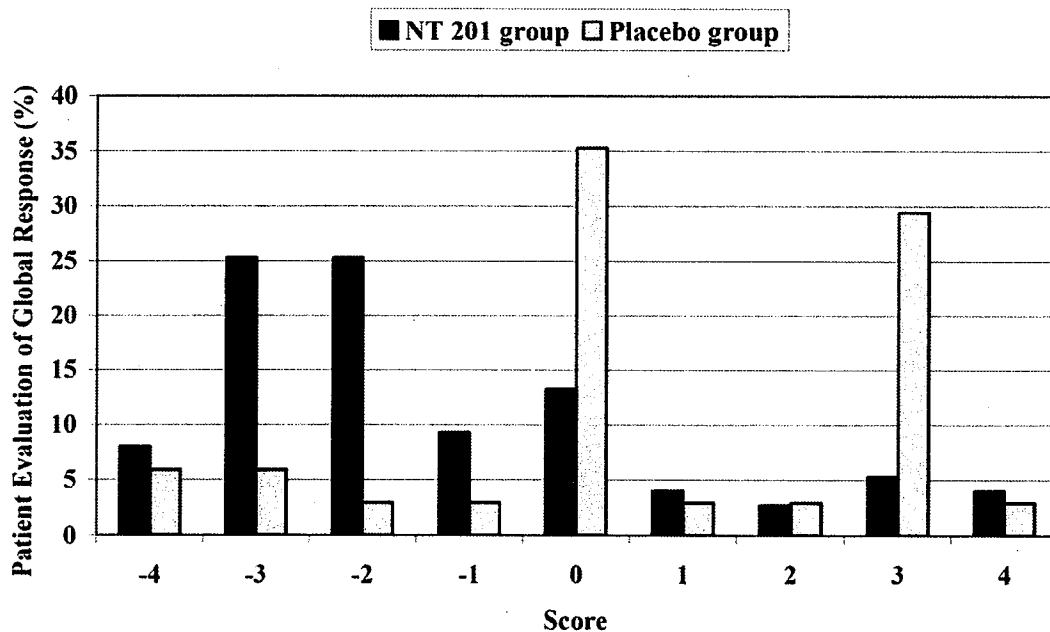


Patient Evaluation of Global Response:

The PEGR is a single descriptive and subjective response to a self-rated scale ranging from "complete abolishment of signs and symptoms" (+4) down to "very marked worsening" (-4). The patient used the scale below to answer the question, "How do you rate the effect of the last injection?"

Because this rating occurred at the last visit of the study, it is the Observed Case population as opposed to LOCF. Note that the Sponsor reversed the usual direction of the scale, i.e.: negative in the protocol designated worsening.)

Figure 20: Trial 0433/1 Patient Evaluation of Global Response (PEGR) at final visit (source: Sponsor)



-4, complete abolishment of all signs and symptoms; -3, marked improvement; -2, moderate improvement; -1, slight improvement; 0, unchanged; 1, slight worsening; 2, moderate worsening; 3, marked worsening; 4, very marked worsening

Source: Table 14.2.8.1.1

Dichotomizing the population as moderate improvement or better versus all the rest, analysis by contingency table reveals the following.

Table 20: Trial 0433/1 PEGR contingency table

Count Row %	Improved (Score 2 or better)	Not Improved	
NT 201	44 59%	31 41%	75
PCB	5 15%	29 85%	34
	49	60	109

Test	Chi Square	Prob > Chi Sq
Likelihood Ratio	19.892	<.0001
Pearson	18.270	<.0001

There was no relationship between the categories of improvement and total dose of NT 201 in the active treatment arm.

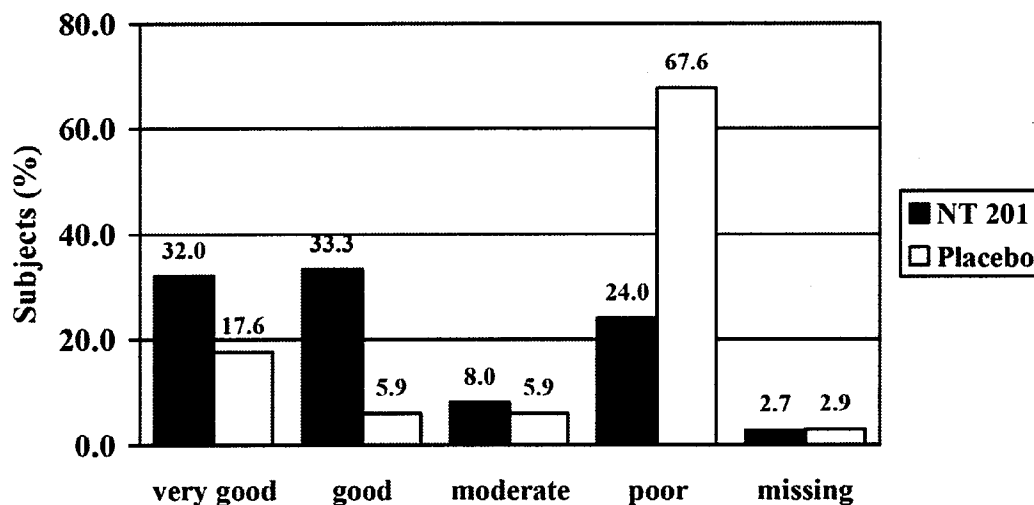
Global Assessment of Efficacy:

The trial investigator performed a single global assessment of the efficacy of study medication at the final visit of the double blinded phase of the trial. The patient was rated on a 4-point Likert scale, ranging from “very good”, “good”, “moderate”, to “poor”.

Because this rating occurred at the last visit of the study, it is the Observed Case population as opposed to LOCF.

Investigator’s Global Assessment of Efficacy at Final Visit (source: Sponsor)

Figure 21: Trial 0433/1 Investigator's Global Assessment of Efficacy at final visit (source: Sponsor)



Dichotomizing the data for assessment of efficacy by the clinical investigator between “good and very good” improvement versus “moderate and poor” reveals a statistically significant difference between the treatment arms:

Table 21: Trial 0433/1 GAE contingency table

Count Row %	Improved	Not	
NT 201	49 65%	26 35%	75
PCB	8 24%	26 76%	34
	57	52	109

Test	Chi Square	Prob > Chi Sq
Likelihood Ratio	16.972	<.0001
Pearson	16.388	<.0001

There was fairly good agreement between the patient and investigator as to their assessment of the treatment effect regardless of treatment arm.

Table 22: Trial 0433/1 Agreement between PEGR and GAE

Count Row %	Improved per patient rating	Not	
Improved per investigator rating	46 81%	11 19%	57
Not improved	3 6%	49 94%	52
	49	60	109

Test	Chi Square	Prob > Chi Sq
Likelihood Ratio	71.136	<.0001
Pearson	61.702	<.0001

Other Secondary Efficacy Analysis: Duration of Effect

The Sponsor developed two subjective patient reported time related measures: time to onset of treatment effect after injection and time to waning of treatment effect after injection.

As the table notes below, there is a difference in the number of subjects who report a perceived onset of treatment related effect. The duration to waning of effect was only ascertained only within the group that initially reported an onset.

Table 23: Trial 0433/1 Patient reported onset and waning of treatment effect

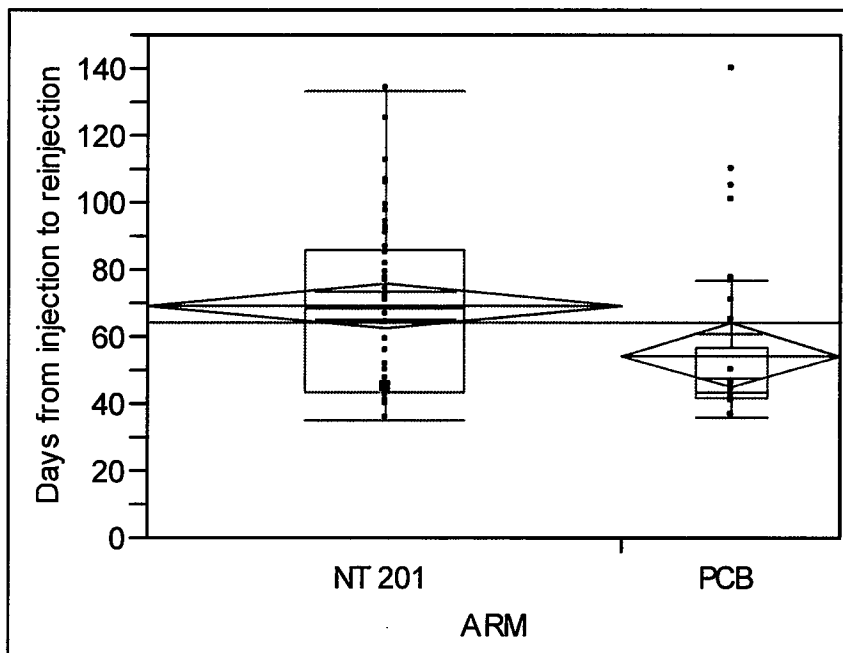
Onset to treatment effects	YES	NO	Time to onset (range)
NT 201	55 (77%)	17 (23%)	6.2 days (0 - 30)
PCB	13 (38%)	21 (62%)	6.0 days (0 -35)
Waning of treatment effects*	Reported		Time to waning (range)
NT 201	53 of 55		6.5 weeks (1 -15)
PCB	11 of 13		5.2 weeks (0-13)
* only considered if onset was also reported by the individual subject			

The reviewer thought that this was a somewhat selective and uninformative method for determining duration of effect. In its place, I looked at a usual clinical scenario where both the physician and patient agree that it is time for a reinjection for control of blepharospasm. This time point (denoted Visit 5) was pre-specified in the protocol to signal the end of participation in the double blind portion of the trial.

Visit 5, the final assessment, occurred when the patient and investigator agreed that the next injection session of NT 201 was due. This meant that the patient met pre-specified criteria for worsening by the JRS-S. The mean difference from baseline to Visit 5 in the NT 201 arm was 0.14 (95% CI 0.32, -0.05) moving from 3.15 to 3.01 on average. In the placebo group, the mean difference in JRS-S during this epoch was -0.26 (95% CI -0.002, -0.53) moving from 2.94 to 3.21 over the same period. The treated group was in essence approaching their baseline clinical state. For this reason, the interval in days from the injection visit to Visit 5 yields a valuable estimated duration of effect and of time to the need for the next injection (a point agreed upon by the patient and clinician).

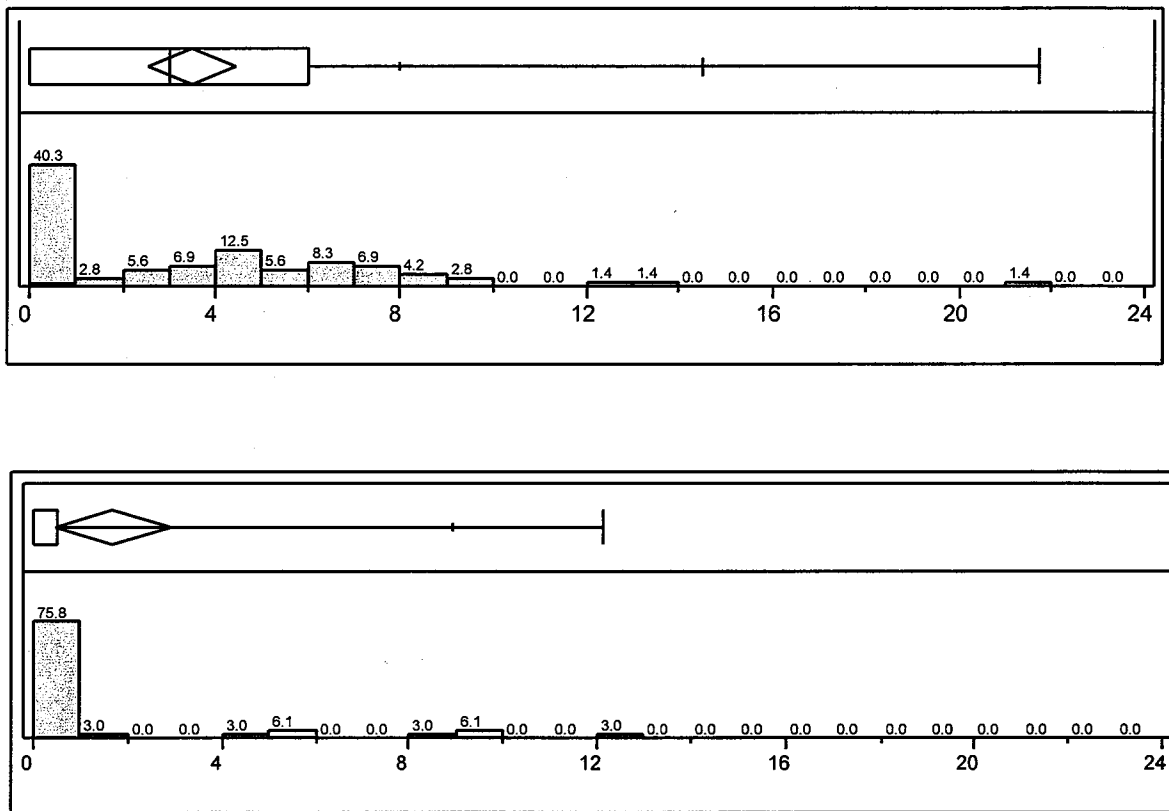
The NT 201 treated group went a mean of 69 days (95% CI: 63, 76) while the placebo arm required reinjection after a mean of 54 days (95% CI: 45, 64), ANOVA $p < 0.012$. (4 subjects missing data: NT 201 3, PCB 1)

Figure 22: Trial 0433/1 Days from injection session to retreatment



The number of subjects who required injection at the earliest allowable time (Visit 4 at 42 ± 3 days) indicates that as expected, more placebo subjects left the study sooner than those in the active treatment arm. But it also suggests that a considerable number of a subjects treated with drug were inadequately controlled. The following histograms looked at the elapsed time in weeks between Visit 4, the earliest reinjection point and Visit 5, the termination visit. For example, where elapsed time in weeks is 0, Visits 4 and 5 were performed at the same time. These illustrate that while 76% of PCB arm left the trial at Visit 4 (6 weeks), so did 40 % of the active arm. By week 10, 96% of the active treated arm had left the trial and needed retreatment (percent of subjects listed above histogram bars below).

Figure 23: Trial 0433/1 Elapsed time from Week 4 to termination visit (top: NT 201; bottom: Placebo)



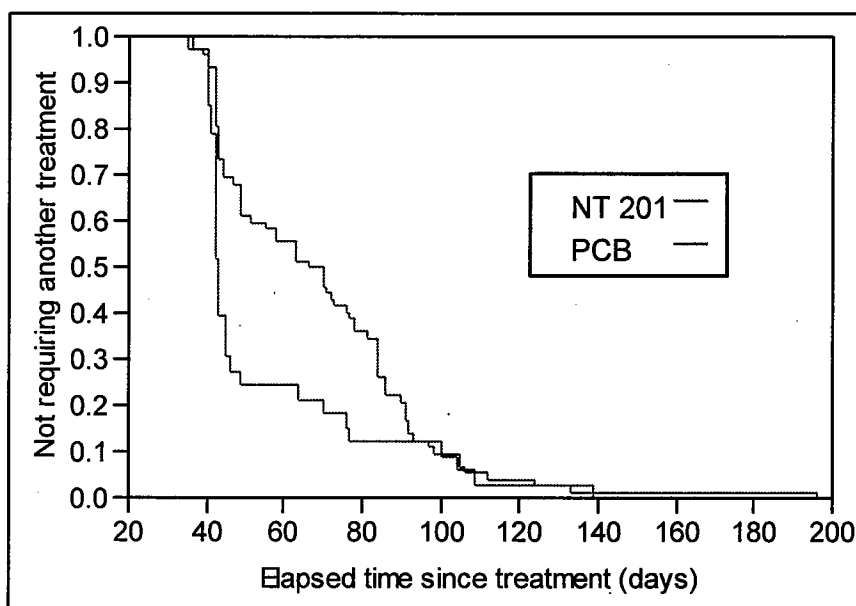
As demonstrated by survival analysis below, this difference between the arms is significant. This graph illustrates the percent of subjects "surviving" (i.e.: having continuing effectiveness of the injections).

Table 24: Trial 0433/1 Days after randomization to loss of effect (quartiles)

Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
NT 201	70	49	77	43	86
PCB	43	42	45	42	49
Combined	49	44	70	42	84

Test	Chi Square	DF	Probability > Chi Square
Log-Rank	5.5288	1	0.0187
Wilcoxon	12.0085	1	0.0005

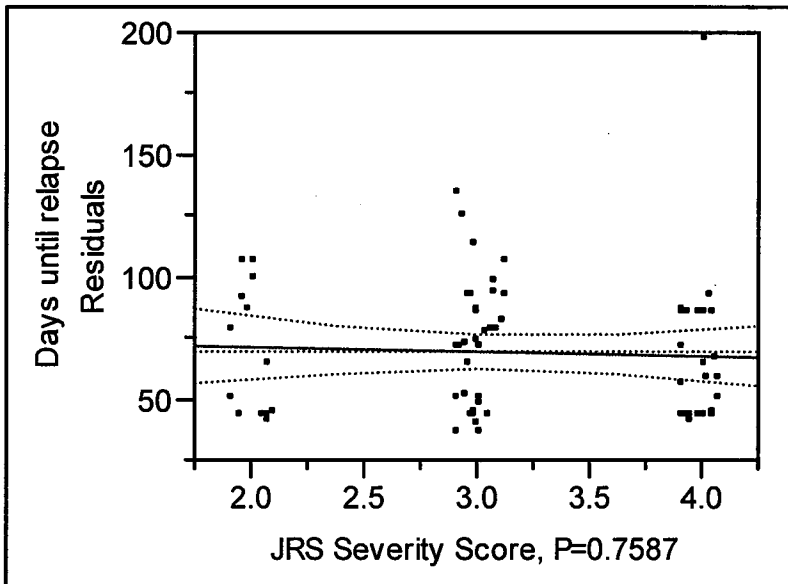
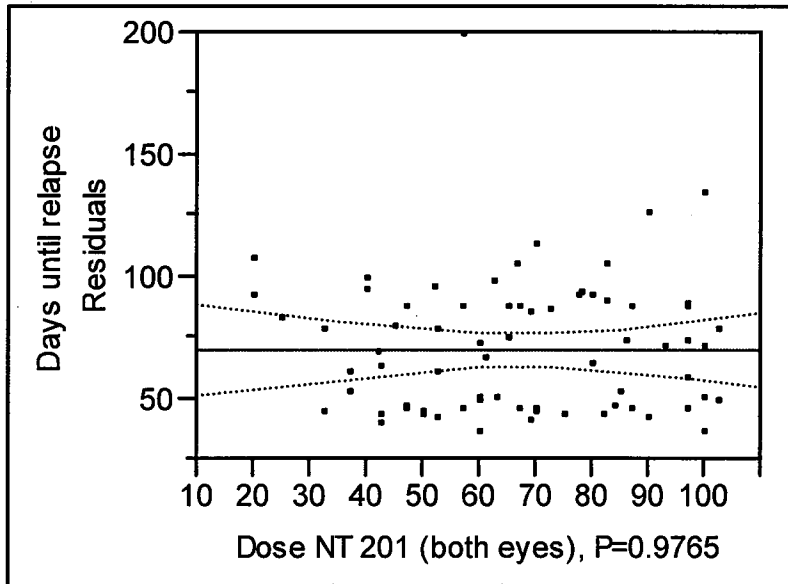
Figure 24: Trial 0433/1 Elapsed time to failure after treatment (survival model)



The question is raised whether there is a relationship between those who terminated early in the trial and a treatment factor such as dose of NT 201 or disease factor such as severity of illness.

The Cox proportional hazards model takes into account covariates which might modify the length of drug effect in either group. In this case however, neither total dose (both eyes) of NT 201 nor baseline JRS Severity score affected the outcome. This was also replicated using a linear regression model for least squares. Limiting the analysis to "best responders" by various criteria also did not reveal any dose response relationship.

Figure 25: Trial 0433/1 Elapsed time to failure: lack of covariate effect in regression model by leverage plot (top: total dose NT 201; bottom: baseline JRS-S score)



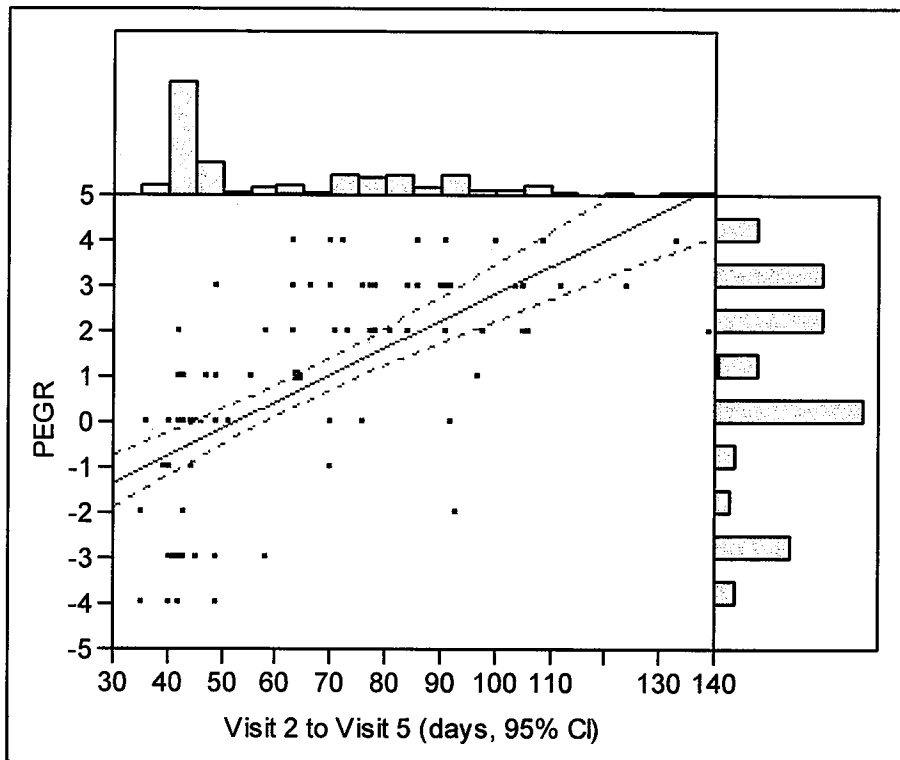
Clinical Meaningfulness

The question is posed whether the improvement in blepharospasm outcome measures noted in this trial's evaluations are internally consistent and clinically meaningful. I looked at this in two ways.

As noted above, there is agreement between the patients' assessment of their state on the JRS-S subscale with that of the blinded rater.

Furthermore, the patient's self evaluation of their improvement (PEGR) is closely related to how long they were able to last from the injection session (Visit 2) until the final evaluation (Visit 5) which marked the need for the next treatment by injection and the end of the double blind portion of the trial. (One outlier (a placebo patient who did well for 139 days) was excluded from this linear regression analysis.)

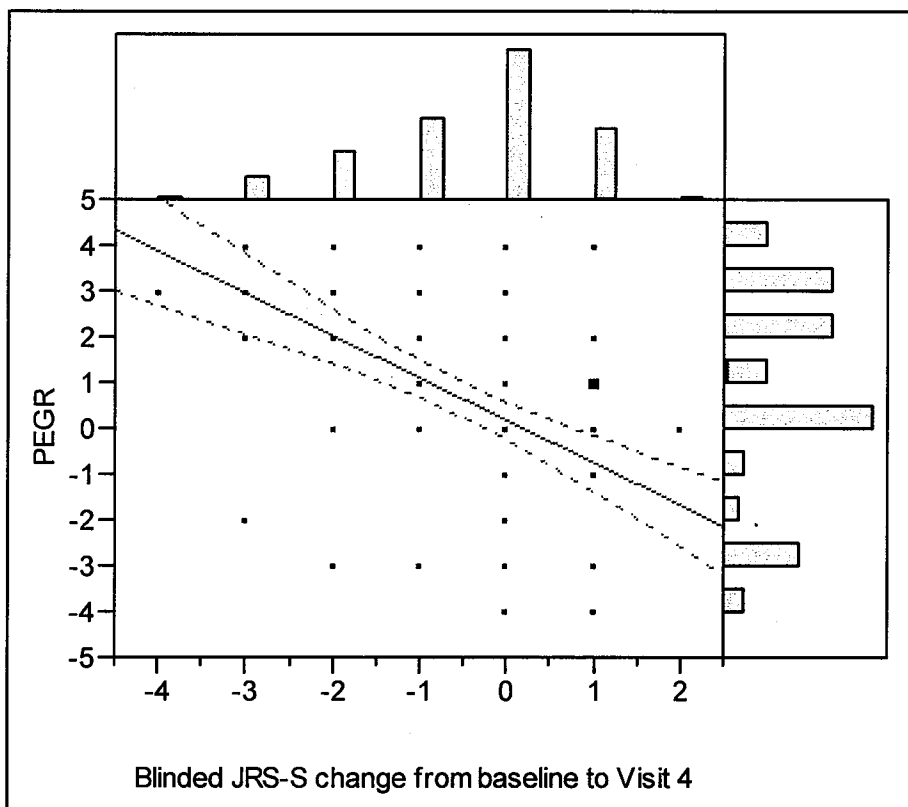
Figure 26: Trial 0433/1 Relationship of PEGR to Duration of Effectiveness



The equation for the linear fit is $PEGR = -3.1 + 0.06 * V2V5INT$, and for instance, one sees that a treatment lasting 90 days would be perceived as “2” (moderate improvement).

Analysis of the relationship of the PEGR and the change of the blinded investigator’s rating of the JRS Severity Subscore from baseline to Visit 4 reveals a similar relationship.

Figure 27: Trial 0433/1 Relationship of PEGR to JRS-S change from baseline



The equation for the linear fit is $PEGR = 0.2 - 0.9 * V4minusV2$. By this model, an improvement of 1 point would be perceived as “1” (slight improvement), and a change of 2 points on the JRS-S would be perceived as “2” (moderate improvement. (The mean change from baseline in JRS-S was -0.84 points in the treated arm.) The peer-reviewed literature suggests that this is at the bottom of the range of what has been determined to be a clinically important difference (Jankovic, et al, Mov Dis, 24 (3) 407-413, 2008). The interval (days) from injection to injection appears to be a more robust measure of patient satisfaction and this is borne out in multivariable modeling.

It should be noted that the PEGR is an ordinal scale and the residuals from this least squares method are not normally distributed (goodness of fit by Shapiro Wilk W test). For this reason, a non parametric analysis would be more appropriate to model these relationships. However, the consistency and linearity of this parametric model makes it useful and sufficient for this sort of post hoc exploration.

Safety Analysis

Because of safety concerns specific to botulinum toxins, and because human experience with NT 201 was derived from three different disease entities with a wide range of dosing regimens (blepharospasm, cervical dystonia and spasticity), this BLA submission was the subject of separate comprehensive analysis of safety performed within the Division of Neurology Products. The reader is referred to that document.

This reviewer's recommendation concerning the risk to benefit ratio and the use of NT 201 in blepharospasm is based upon that safety analysis and the efficacy analysis presented above.

5.3.2 Open label repeated injection trial for the treatment of blepharospasm (MRZ 60201-0433/2)

Trial:

Prospective, double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of blepharospasm (MRZ 60201-0433/2)

Phase: III

Purpose:

The purpose of this open label extension to the primary confirmatory trial for the indication of blepharospasm was to provide additional data concerning the efficacy of NT 201 in continuing use, as well as long term exposure and safety data. This extension provided for up to 5 additional open label injection periods following participation in the double blind portion of this trial. However, the Sponsor provided no statistical analyses of efficacy or maintenance of effect. Exposure data was received in the 120 day safety update.

The reviewer's analysis is based upon Information provided gleaned from the trial summary provided for the double blind portion of the trial. Data requests were made by the reviewer for efficacy data and these were received after the date for the 120 day safety data update submission (see Appendix 9.4). If one estimates the allowed 5 additional injection periods at intervals of 3 months each, based on the completion of the blinded trial, the extension period should have ended by the end of 2009.

Trial design

After the blinded trial (i.e., after the termination Visit 5) the patient entered the open label period.

Up to 11 visits (five injection sessions, five control visits, and one termination visit) took place. Assessment by rating scales took place at the time of injection and at the "control visit" 42 ± 3 days after the injection visit.

Patients attended the visits for injections as required. The patient was eligible to receive a new injection if the investigator agreed with the need (based on the JRS severity subscore). The minimum interval between two injections was to be at least six weeks. If the patient had a need for an injection, but did not meet the trial criteria above, the patient was not to be injected and the visit was to be documented as an optional visit. The next visit was then scheduled within 4 weeks. Optional visits were also to be performed for safety reasons.

The Termination Visit was performed no later than 20 weeks after the last injection during the open label period or when the patient received a new injection with any botulinum toxin other than study medication.

Key Endpoints:

- Duration of effect at all visits: interval between two injections sessions for patients with treatment effect.
- Global assessment of efficacy by investigator
- Change in the investigator rated JRS severity and frequency sub scores and in the JRS sum score at all visits (except Visit 6*)
- Change in the patient diary rated JRS severity and frequency sub scores and in the JRS sum score at all visits of the first treatment interval (except Visit 6*), median score of previous 7 days)
- AUC, T_{max} , and E_{max} for change in the JRS severity and frequency sub scores and in the JRS sum score (as assessed by patient diary) after the first injection session in the open label period
- Change in Blepharospasm Disability Index at all visits (except Visit 6*)
- Patient Evaluation of Global Response at all injection visits (except Visit 6*) and the Trial Termination Visit

(* Visit 6 is the first injection session of the open label extension and the termination visit of the double blind portion of the trial)

Safety Measurements:

- Adverse events
- Clinical chemistry and hematology
- Global assessment of tolerability by Investigator
- Antibodies against Botulinum neurotoxin Type A
- Physical and neurological examinations

Inclusion

Completion of the double blinded portion of the trial
Negative pregnancy test before each injection

Exclusion

The patient receives any other botulinum toxin

Concomitant Medication

No limitation

Study Visits

Table 25: Trial 0433/2 Visit checklist (source: Sponsor)

SCHEDULE OF EVENTS DURING OPEN-LABEL EXTENSION PERIOD				
Study visit	Treatment intervals (maximal 5)* V7, V9, V11, V13, V15 (Control Visit)**		Optional Visits OLEX*** (OVO)	Safety Period V16 (Trial Termination Visit)
	V6, V8, V10, V12, V14 (Injection Visit)	Day 42 ± 3 days after V6, V8, V10, V12, V14 V14 is at the latest 48 weeks (+ 1 week) after start of OLEX Period		
Assessment week Time window / (Days)	Day 0 of treatment interval, any day of OLEX Period		From Week 6 on up to Week 48 at the latest	up to Week 20 (± 3 days), after V14 (V14 = last injection visit)
Physical / Neurological examination, body weight	X (only before 3 rd injection during OLEX)			X
Jankovic Rating Scale/Investigator Assessment	X	X	X	X
Blepharospasm Disability Index	X	X	X	X
Vital signs	X	X	X	X
Patient Evaluation of Global Response**** (except V6)	X			X
Clinical Chemistry, Hematology	X			X
Antibody titer	X			X
Pregnancy test*****	X**** (urine)			X (blood)
Injection session	Only if indicated	Ask for need	Ask for need	
Adverse events	X	X	X	X
Changes in Conc. medication / Conc. Diseases	X	X	X	X
Global Assessment of Efficacy/Tolerability (except V6)	X			X
Documentation of treatment effect**** (except V6)	X	X		X
Documentation of Trial Termination				X

Treatments and other ancillary management

Administered with the same technique as the double blind portion of the trial, a maximum of 5 injection sessions of NT 201 was allowed. Dose adjustment up to 50 U per eye was permitted depending on the effect achieved with the previous injection.

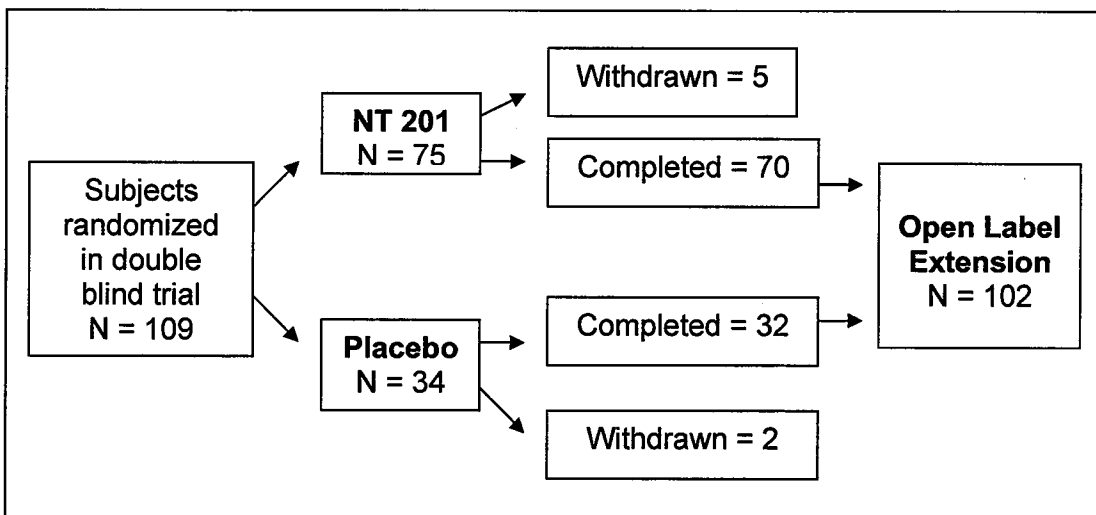
Randomization and Controls:

Not applicable

Subject Enrollment:

All 102 eligible subjects from the double blind portion of the trial enrolled in the open label extension.

Figure 28: Trial 0433/2 Subject disposition

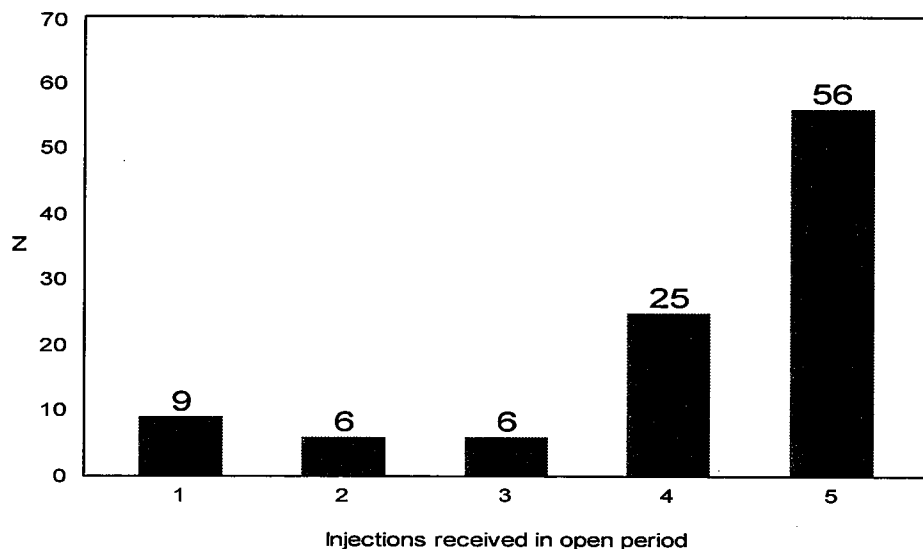


Trial populations / Patient disposition

The nature of the trial population is discussed in Section 5.3.1 covering the double blinded portion of the trial.

The histogram below illustrates the number of open label injections received by the trial cohort in the open label period. It is unknown if any of this data is censored by an incomplete time period of observation. Given the date of the last completed double blind subject, this analysis should encompass a completed open trial and the reviewer operates on this assumption. 89% of subjects received 4 or 5 open label injections.

Figure 29: Trial 0433/2 Number of subjects by number of treatment sessions in open label extension trial



Method for determining the outcome of efficacy analysis (exposure / response):

No statistical analysis plan for the open label trial was pre-specified.

Study Results

Patient Compliance, Protocol Deviations and Violations

No data submitted.

Sponsor's Exposure Data

In the 120 day safety update, the Sponsor submitted exposure information in tabular form, combining both the double blind and open label portion of the 0433 trial. These tables draw broad strokes regarding dosing and exposure. The reviewer, using requested datasets (see appendix) provides a more detailed description following these tables and in Section 6 of this review.

Table 26 Trial 0433/1 and /2: NT 201 exposure by injection (source: Sponsor)

Injection Number	N	Mean Dose (±SD) (Units)	Median Dose (Units)	Minimum, Maximum (Units)
First Injection	106	61 (23.4)	60	20, 100
Second Injection	98	53 (20.8)	50	10, 100
Third Injection	91	54 (20.5)	50	10, 100
Fourth Injection	86	55 (20.5)	50	10, 100
Fifth Injection	76	55 (22.5)	50	8, 100
Sixth Injection	36	59 (23.1)	50	23, 100

OLEX: open-label extension; SD: standard deviation.

Source: Table 1.1.1, ISS Appendix K.

Table 27 Trial 0433/1 and /2: NT 201 by dose group and length of exposure (source: Sponsor)

Observation Period	Dose Group		Overall
	10 - 40 U	>40 U	
2 to <7 weeks	1 (0.9%)	2 (1.9%)	3 (2.8%)
7 to <13 weeks	1 (0.9%)	2 (1.9%)	3 (2.8%)
13 to <21 weeks	2 (1.9%)	3 (2.8%)	5 (4.7%)
21 to <24 weeks	1 (0.9%)	1 (0.9%)	2 (1.9%)
24 to <48 weeks	1 (0.9%)	11 (10.4%)	12 (11.3%)
48 to <72 weeks	17 (16.0%)	49 (46.2%)	66 (62.3%)
72 to <96 weeks	4 (3.8%)	11 (10.4%)	15 (14.2%)
Overall	27 (25.5%)	79 (74.5%)	106 (100%)

Data are presented as number of subjects (percent of subjects).

OLEX: Open-label Extension Period; U: units.

Source: Table 1.5, Section 5.3.5.3, Appendix K.

Table 28 Trial 0433/1 and /2: NT 201 length of exposure by number of injections (source: Sponsor)

Observation Period	Number of Injections						Overall
	1	2	3	4	5	6	
2 to <7 weeks	3 (2.8%)	-	-	-	-	-	3 (2.8%)
7 to <13 weeks	2 (1.9%)	1 (0.9%)	-	-	-	-	3 (2.8%)
13 to <21 weeks	3 (2.8%)	2 (1.9%)	-	-	-	-	5 (4.7%)
21 to <24 weeks	-	1 (0.9%)	1 (0.9%)	-	-	-	2 (1.9%)
24 to <48 weeks	-	1 (0.9%)	1 (0.9%)	1 (0.9%)	6 (5.7%)	3 (2.8%)	12 (11.3%)
48 to <72 weeks	-	2 (1.9%)	2 (1.9%)	8 (7.5%)	28 (26.4%)	26 (24.5%)	66 (62.3%)
72 to <96 weeks	-	-	1 (0.9%)	1 (0.9%)	6 (5.7%)	7 (6.6%)	15 (14.2%)
Overall	8 (7.5%)	7 (6.6%)	5 (4.7%)	10 (9.4%)	40 (37.7%)	36 (34.0%)	106 (100%)

Data are presented as number of subjects (percent of subjects).

"-" indicates category not applicable. OLEX: Open-label Extension Period.

Source: Table 1.10, Section 5.3.5.3, Appendix K.

Reviewer’s Aim

The reviewer’s analysis of this open label trial extension is focused upon determining that the patient’s response to continued treatment is sustained. To this end, the following parameters are analyzed:

- Dose and exposure: For those subjects who continue receiving open treatment, there should be no evidence for an increased in dose requirement.
- Magnitude and duration of drug effect: The robustness of efficacy as measured by JRS-S, BDSI and PEGR should approximate that found in the double blind portion of the trial. Duration of effect is demonstrated by absence of shortening of the interval between injection sessions.

Dose and Exposure

As seen above, half the subjects (56 of 102) received 5 treatments, the maximum possible under the protocol. Of the remainder, 25 received 4 injections and 21 received 3 or less.

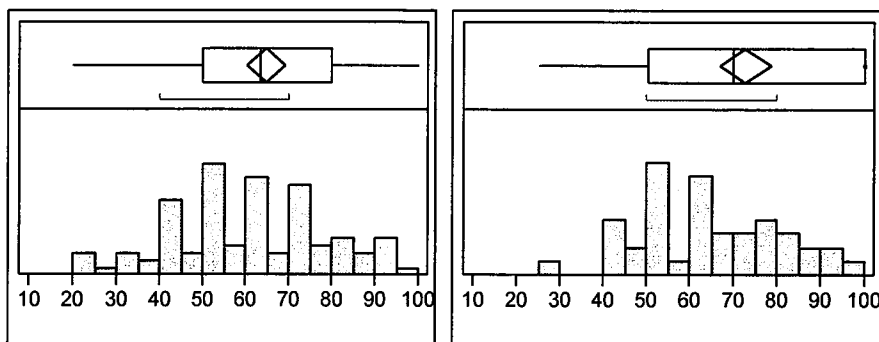
An analysis of matched pairs of data for individual subjects, uncorrected for multiple comparisons, revealed no significant change over the course of the entire trial, i.e.: there was no significant increase or decrease in dose of NT 201 injected from the start of the trial.

For example, compared below are the first open label injection (n = 102) with the fourth (n=81) and fifth injection (n=56), which are not statistically different.

Table 29: Trial 0433/2 Injected dose of NT 201 by treatment session

Open label: NT 201 injection dose: units, combined eyes			
	First	Fourth	Fifth
Mean	64.8	66.5	72.7
Std Dev	22.3	23.1	22.0
Std Err Mean	2.2	2.6	2.9
upper 95% Mean	69.2	71.6	78.6
lower 95% Mean	60.4	61.3	66.8
N	102	81	56

Figure 30: Trial 0433/2 Distribution of total NT 201 doses (units, both eyes) administered at first (left) and fifth (right) treatment sessions



Robustness of Effect

JRS-S

Table 30: Trial 0433/2 JRS-S by number of treatments received

JRS Severity Score (95% CI) by the number of injections subject received in OL period															
Injections received in OL Trial	First OL Injection			Second OL Injection			Third OL Injection			Fourth OL Injection			Fifth OL Injection		
	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%
1 (n=9)	-1.7	-2.6	-0.8	.	.	.	.	.	.	.	.	.	.	.	.
2 (n=6)	-1.3	-2.4	-0.1	-0.9	-2.0	0.1	.	.	.	.	.	.	.	.	.
3 (n=6)	-1.5	-2.5	-0.5	-0.3	-1.2	0.7	-0.4	-1.2	0.5	.	.	.	.	.	.
4 (n=25)	-1.8	-2.3	-1.3	-1.0	-1.5	-0.5	-1.5	-2.0	-1.1	-1.3	-1.8	-0.9	.	.	.
5 (n=56)	-1.3	-1.6	-0.9	-1.3	-1.6	-1.0	-1.0	-1.3	-0.6	-1.0	-1.3	-0.7	-0.9	-1.2	-0.6

There are two ways to look at the OL JRS Severity subscore. First, would be to see if there is waning of drug effect within an individual over multiple injection periods. The second would be to see whether differences in efficacy resulted in subjects wishing to take fewer injections in the open label period.

As is evident from the table above, neither of these appear to be the case. Multivariable analysis using the baseline JRS-S subscore as the covariant for each respective period reveals that there are no statistically significant intra-individual or intra-period differences of severity. The one exception is for the group receiving 3 injections in their final injection period (JRSS: -0.4, CI -1.2, 0.5). This is likely the result of multiple

uncorrected comparisons; the n is small and there is no obvious explanation for this single finding.

Also of reassuring interest is that the magnitude of effect of NT 201 upon the JRS-S subscore is very consistent with that seen in the double blind portion of the trial (for the Trial 0433/1 arm receiving active drug : JRSS: -0.84, CI -1.1, 0.6).

BSDI

Table 31: Trial 0433/2 BSDI by number of treatments received

BSDI (95% CI) by the number of injections subject received in OL period															
Injections received in OL Trial	First OL Injection			Second OL Injection			Third OL Injection			Fourth OL Injection			Fifth OL Injection		
	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%
1 (n=9)	-0.5	-1.0	0.1	.	.	.	.	.	.	.	.	.	.	.	.
2 (n=6)	-0.1	-0.9	0.7	0.0	-0.6	0.7	.	.	.	.	.	.	.	.	.
3 (n=6)	-0.6	-1.2	0.0	-0.1	-0.7	0.4	-0.1	-0.4	0.3	.	.	.	.	.	.
4 (n=25)	-0.6	-0.9	-0.2	-0.5	-0.8	-0.3	-0.6	-0.8	-0.5	-0.2	-0.5	0.1	.	.	.
5 (n=56)	-0.7	-0.8	-0.5	-0.4	-0.6	-0.3	-0.3	-0.4	-0.1	-0.5	-0.6	-0.3	-0.3	-0.4	-0.1

As with the JRS-S there are no statistically significant intra-individual or intra-period differences of severity. Once again, the magnitude of effect of NT 201 upon the BSDI is very consistent with that seen in the double blind portion of the trial (for the arm receiving active drug: BSDI: -0.48, CI -0.65, -0.3).

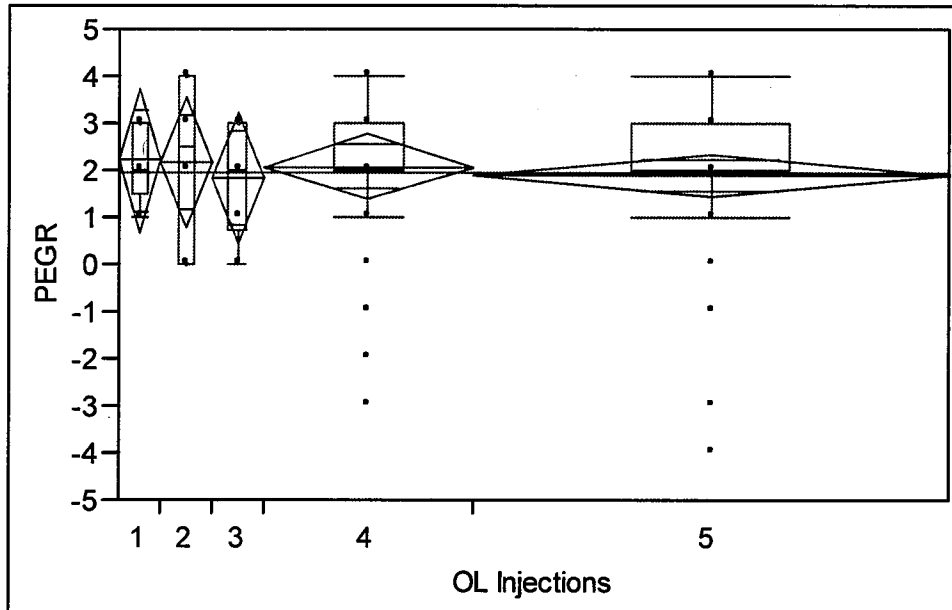
PEGR

The final patient reported assessment of efficacy for the open label period was analyzed. This is the PEGR score for the subject's last open label injection. Four subjects (all of whom received only one injection in the open label extension) were excluded for lack of data. Perceived efficacy at the end of the open label trial did not distinguish among the groups regardless of the number of injections they received (p = 0.98)

Table 32: Trial 0433/2 PEGR by number of treatments received

OL Injections	N	Mean	Std Error	Lower 95% CI	Upper 95% CI
1	5	2.2	0.77	0.7	3.7
2	6	2.2	0.70	0.8	3.6
3	6	1.8	0.70	0.4	3.2
4	25	2.1	0.34	1.4	2.8
5	56	1.9	0.23	1.4	2.3

Figure 31 Trial 0433/2 PEGR Box plot by number of treatments received



The overall magnitude of effect of open label NT 201 upon the PEGR is very consistent with that seen for the arm receiving active drug in the double blind portion of the trial: With improvement considered a score of 2 or better, the open label trial performed at least comparably or better.

Table 33: Trial 0433/2 PEGR from blinded and open label trials compared

Count Row %	Improved (Score 2 or better)	Not Improved	Total N
NT 201 Double Blind	44 59%	31 41%	75
Open label	75 77%	23 23%	98

Duration of effect

In order to look at duration of effect, the reviewer adopted a naturalistic approach as used in the double blind portion of the trial. The interval analyzed was the time from injection to the time when the patient and investigator agreed that criteria were met for the next injection session. Due to missing data, intervals were only calculated for subjects receiving 3, 4 or 5 open label treatments with NT 201. In these 87 patients, 364 injection treatments were administered. The mean interval between treatments was 82 days (95% CI 80, 85) range 39 to 238 days.

In examining what determined the number of injections a subject received in open label follow-up, it was apparent that the duration of effect was the major determinant of this.

Table 34: Trial 0433/2 Interval between treatments by number received

Time interval in days between NT 201 injection sessions									
Injections received in OL Trial	Second to Third OL Injection			Third to Fourth OL Injection			Fourth to Fifth OL Injection		
	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%	Mean	Lower 95%	Upper 95%
3 (n=6)	122	101	143						
4 (n=25)	94	83	104	103	95	110			
5 (n=56)	77	70	84	78	72	83	77	73	82
	p < 0.001			p < 0.001					

This would indicate that the number of injections received in the extension trial may be related to the length of time that it was perceived to be successful, and that time ran out in the extension trial, curtailing treatment availability for patients. Multiplying the interval (mean number of days) from the second to third injection by the number of injections the group received in the trial equals 366, 376, and 385 days, respectively.

Dose Received

Finally, it was possible that the duration of treatment effectiveness was related to the dose administered. This appears not to be the case. For example, the chart below of mean total NT 201 dose for both eyes demonstrates that dose appears to have no relationship to length of effectiveness, and in fact, long intervals were associated with smaller doses in some groups. One possible explanation is that there are individual differences in the sensitivity of blepharospasm to treatment with BoNT and that some subjects have the biologic capacity to go further with less.

Table 35: Trial 0433/2 Total NT 201 dose by number of treatments received

NT 201 Dose (total units, both eyes) by the number of injections received															
Injections received in OL Trial	1st OL Inj			2nd OL Inj			3rd OL Inj			4th OL Inj			5th OL Inj		
	Mean	Low 95%	Up 95%	Mean	Low 95%	Up 95%	Mean	Low 95%	Up 95%	Mean	Low 95%	Up 95%	Mean	Low 95%	Up 95%
1 (n = 9)	44*	31	59	.	.	.	.	.	.	.	.	.	.	.	.
2 (n = 6)	70	52	87	66	49	83	.	.	.	.	.	.	.	.	.
3 (n = 6)	66	48	83	67	50	85	68	51	85	.	.	.	.	.	.
4 (n = 25)	60	52	69	60	51	68	60	51	68	54†	46	63	.	.	.
5 (n = 56)	70	64	75	71	65	76	72	66	77	72	66	78	73	67	79

* differs significantly from others in column (ANOVA, p < 0.0215)
 † differs significantly from others in column (ANOVA, p < 0.0015)

Discussion of findings and conclusion

The exploratory post hoc analyses presented above suggest that there is sustained effectiveness of NT 201 in the treatment of blepharospasm in this open label extension trial. The magnitude of effect in the investigator and patient based rating scales are of similar magnitude to those seen in the double blind portion of the trial. There was a wide range of duration of effectiveness of treatment among individuals and this appears not to be related to the dose administered but rather individual differences in biologic response to therapy or other unmeasured factor outside the scope of this trial.

5.3.3 Supportive trial of NT 201 compared to BOTOX® in blepharospasm (MRZ 60201-0003)

Trial:

Safety and efficacy of NT 201 (highly purified Botulinum Neurotoxin A) compared to BOTOX® (purified Botulinum Neurotoxin A-complex) in blepharospasm.

Phase: III

Purpose:

The Sponsor's stated objective for this trial was to demonstrate non-inferiority in safety and efficacy of NT 201 compared to BOTOX® in patients with blepharospasm.

Trial design

This trial was a randomized double-blind parallel active-controlled multicenter trial performed in 42 centers in Europe and Israel. It began enrollment in March 2001 and was completed January 2002. A total of 304 patients were enrolled. All subjects had had a stable therapeutic response to BOTOX® injection on at least two previous occasions. The primary outcome was the change from baseline in the Jankovic Rating Scale from the time of injection to 3 weeks later. Secondary measures included a patient assessment of efficacy and measures of the duration of clinical response.

During the baseline visit (day 0), each eligible patient was randomized to NT 201 or BOTOX®. At this visit, the trial medication was administered in randomized, double-blind fashion and the patients were observed for a period of up to 16 weeks after injection session. Each patient was injected with a dosage of up to 35 units of NT 201 or BOTOX® per eye, equivalent to the previous two injection sessions directly prior to trial entry and according to the randomization.

A "control" visit for evaluation of efficacy was performed at day 21 ± 1. From this visit on, if the patient felt the need for a new injection session, they were to return at any time up to day 112 for an optional visit. If both the physician and the patient agreed upon the necessity of a new injection session after the control visit (day 21), all assessments required for the final visit were performed and the trial was terminated for this patient.

Primary endpoint:

Jankovic Rating Scale is the sum of the ratings for two single items judging severity and functional impairment of blepharospasm.

Secondary criteria:

The Function Scale for Patients with Blepharospasm is an earlier version of the Blepharospasm Disability Index used in Trial 0433/1 above. It is almost identical to the BSDI. This self-rating scale assesses the impairment for specific activities of daily living caused by blepharospasm. The scale includes 6 items (0-4 points per item): "Driving a vehicle", "Reading", "Watching TV", "Shopping", "Getting about on foot" and "Doing everyday activities"

Patient Evaluation of Global Response is a 9-point scale for self-rating the blepharospasm from "complete abolishment" to "very marked worsening".

Duration of Treatment is defined as the interval between the day of the injection session and the date when both the patient and the physician have agreed upon the necessity of a new injection. The trial ended at 112 days. Amendment 1 to the trial also added estimations by the patient as to time to onset and waning of treatment effect.

Safety endpoints:

These include physical examination, vital signs, clinical chemistry and hematology, antibodies against botulinum toxin A,

Inclusion

- Male or female outpatients between 18 and 75
- A clinical diagnosis of blepharospasm with a need for injection
- Patients with documented stable therapeutic response to BOTOX® as a result of the last two previous injection sessions directly prior to trial entry
- (Stability was defined as injecting at least two times the same injection points, administering the same doses and volumes in the same interval resulting in the same satisfactory therapeutic response as evaluated by the investigator and assessed by the patient)
- Source documentation of the last two injection sessions prior to trial entry
- Patients must be on a stable dose of other medications (if any) used for focal dystonia treatment (e. g. anticholinergics and benzodiazepines) for 3 months prior to and throughout the trial
- Negative pregnancy test at entry

Exclusion

- No neurotoxin treatment other than BOTOX®.
- Atypical syndrome
- Hypersensitivity to human serum albumin
- Will need anesthesia during the trial

Concomitant Medication

Medications for other conditions were allowed. Psychotropic medications were allowed if the subject was on a stable dose for 3 month prior to entry into the trial. Drugs affecting the neuromuscular junction were prohibited.

Study Visits (Checklist)

This version of the study checklist is from the original protocol. Amendment 1 added a global assessment by the investigator at the end of the trial.

Table 36: Trial 0003: Visit checklist (source: Sponsor)

Trial visit	Baseline/ Injection	Trial period		
	Baseline visit	Control visit	Optional visits **	Final visit
Assessment week Time Window (days)	Week 0 (Day 0)	Week 3 (Day 21 ± 1 day)	Visits on patient's request	Up to week 16 (Day 109-112)
Informed consent	X			
Medical history	X			
Physical examination	X			X
Neurological examination	X			X
Inclusion & exclusion criteria	X			
Jankovic Rating Scale	X	X	X	X
Function Scale for Patients with Blepharospasm	X	X		X
Patient Evaluation of Global Response		X		X
Vital signs	X	X	X	X
ECG	X	X		X
Blood sampling	X	X		X
Antibody titer	X			X
Pregnancy test (urine)	X			
Pregnancy test (blood)	X			X
Randomisation	X			
Injection session	X			
Adverse Events	X*	X	X	X
Concomitant medication	X	X	X	X
Documentation of trial termination				X

Treatments and other ancillary management

Injection points and the dose of botulinum toxin (specified as volume in the protocol) were chosen on the basis of the patient's previous BOTOX® experience. BOTOX® and NT 201 were considered equipotent unit for unit.

Randomization and Controls:

Balanced block randomization was used in a 1:1 ratio.

GCP:

The trial was performed in accordance with GCP, was in compliance with the Declaration of Helsinki and operated according to requirements of local IECs. Copies of IEC approvals were provided as well as sample informed consent.

The trial sites were monitored and the Sponsor's quality assurance unit audited 13 clinical sites. Two of the sites were audited twice for reasons unknown.

Protocol Amendments

Amendment 1 (February 20, 2001):

Prior to the start of the trial, this amendment refined the use of the outcome parameters, added duration measures for the treatment effect, and added a global assessment by the investigator. Most importantly, the statistical analysis plan was changed with regard to the non-inferiority margin. These changes are incorporated into the Sponsor's Statistical Analysis Plan, discussed below.

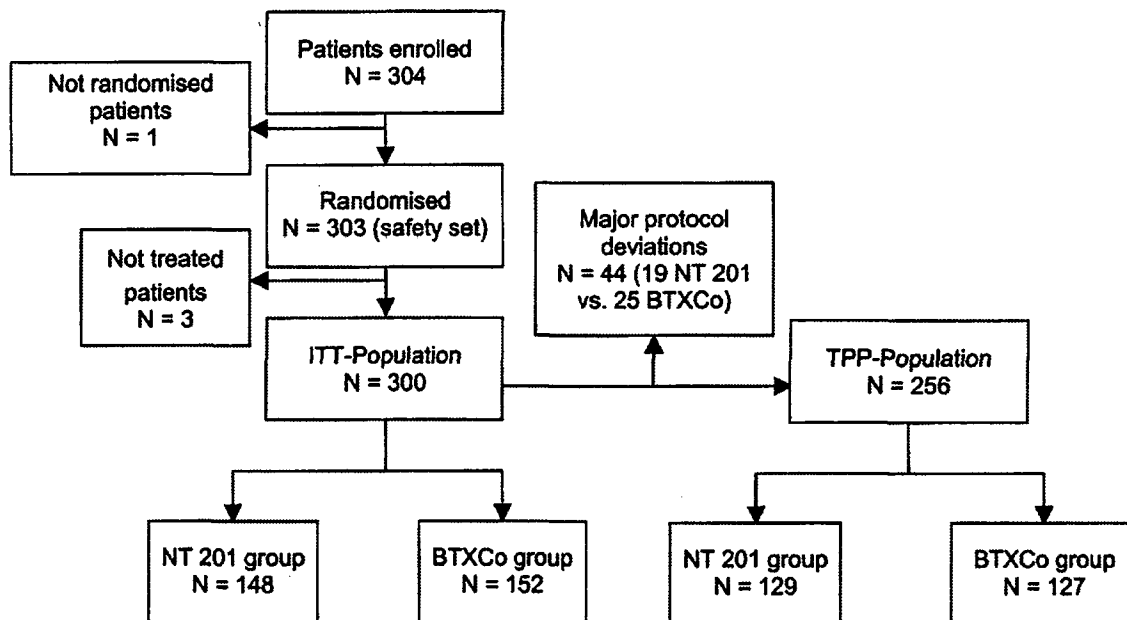
Amendment 2 (July 10, 2001):

This amendment prolonged the enrollment period due to slower than expected recruitment.

Trial populations / Patient disposition

The safety population was considered everyone who was randomized. The Intent to Treat (ITT) population is everyone who was randomized and received medication.

Figure 32: Trial 0003 Subject disposition (source: Sponsor)



Data Source: Table 14.1.1.1.1, Table 14.1.1.3.1

Method for determining the outcome of efficacy analysis (statistical analysis plan):

The SAP from the original protocol was only finalized and signed on August 20, 2002 well after the start of the trial. There is a statement affirming that “the statistical analysis plan was finalized after data base closure and before unblinding.” It does not differ substantively from that proposed in the protocol and amendments.

The method for replacing missing data was use of LOCF.

JRS total score, the primary efficacy parameter, was to be analyzed using an analysis of covariance model with baseline, treatment, baseline*treatment and total dose. The interaction is taken as fixed effect, and the baseline value and total dose as covariate. The baseline value is defined as the value at the baseline visit. If there is a significant baseline treatment interaction, an analysis of variance model was to be used instead. The treatments would be considered clinically equivalent if the mean difference between treatments (NT 201 - BOTOX®) is less than Δ . The therapeutically “irrelevant difference” (a term taken by the reviewer to mean non-inferiority margin) was defined as 1 point based on the clinically supported suggestion by physicians derived from an internal expert meeting and from results of a field study conducted by the Sponsor. The hypothesis of NT 201 being the same or better than BOTOX® was to be tested by comparing the 95% upper confidence limit for the adjusted treatment group means (NT 201 - BOTOX®) with Δ , the value of clinical irrelevance. If this upper limit is less than Δ ,

then the Sponsor believes the treatments may be declared equivalent. If this upper limit is less than 0, then NT 201 may be declared superior to BOTOX®. In situations where the basic model assumptions are violated, a suitable transformation or a non-parametric procedure would be used.

The sample size calculation was based on the assumption that the irrelevant difference of the two treatments for the change of the Jankovic rating scale is $\Delta = 1$ point. From previous trials the standard deviation of the change was estimated to be 2.0 by the Sponsor. Cohort size was calculated using a significance level of 2.5% and a power of 90%.

This, however, was adjusted by Amendment 1. At that time the irrelevant difference was changed to $\Delta = 0.8$ point to maintain less power, with $\alpha = 0.025$ (1 sided) and with $1 - \beta = 0.85$. The Sponsor did not provide a rationale for justification of the non-inferiority margin or change in power. The effect size of BOTOX® was not calculated or estimated from review of published trials and there is no discussion of why such a clinical margin would be acceptable.

Only the primary efficacy variable (Jankovic Rating Scale) was tested as confirmatory by the Sponsor. "All other statistical tests will be interpreted in an exploratory sense," (SAP, p 10, Version 20.08.2002). Exploratory survival analyses were used to look at time based effects.

Also of note, it is only in the trial's final report that it is indicated that the Treatment Per Protocol (TPP, NT 201 n = 129; BOTOX® n = 127), not the ITT cohort, was used by the Sponsor to analyze the primary efficacy variable.

The SAP strategy for missing data in the primary outcome was as follows: For the confirmatory analysis, only observed cases were used and those subjects with missing date were dropped. For the ITT analysis, baseline evaluations were used for the follow-up evaluation (LOCF), but no imputation was made for the one subject with missing baseline data. For secondary outcomes, no imputations were made and only the TPP population was used.

Study Results

Reviewer's note:

In the submission's proposed label (version 3/1/2010) the Sponsor makes the following statement in Section 2.3. General Dosage and Administration: (b) (4)

This is restated in Section 14, Clinical Studies (14.2 Blepharospasm). As a result this reviewer has focused upon the primary efficacy variable which was used to support this claim (JRS total score) and the secondary

outcomes which provide some comparability to the confirmatory study in Section 5.3.1 (JRS severity subscore).

Demographics and Concomitant Medications

In the ITT population, 73% were women, commensurate with the syndrome. Only four subjects were not white. They had comparable medical histories and concomitant medication use. Mean age was 63. Subjects had 6 to 7 years of blepharospasm prior to entry into the trial. They had had on average 15 to 16 treatments with botulinum toxin before enrolling. There were no significant differences in demography between the arms.

Upon entry into this trial they had comparable passage of time since the previous BOTOX® treatment (13-14 weeks). The subjects had comparable perceptions of how long that previous treatment had lasted (10 weeks).

The two arms had comparable severity of blepharospasm at the randomization visit:

Table 37: Trial 0003 Baseline total JRS score

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
BOTOX®	149	5.54362	0.12572	5.2962	5.7911
NT 201	144	5.21528	0.12788	4.9636	5.4670

Compliance with Study Medication

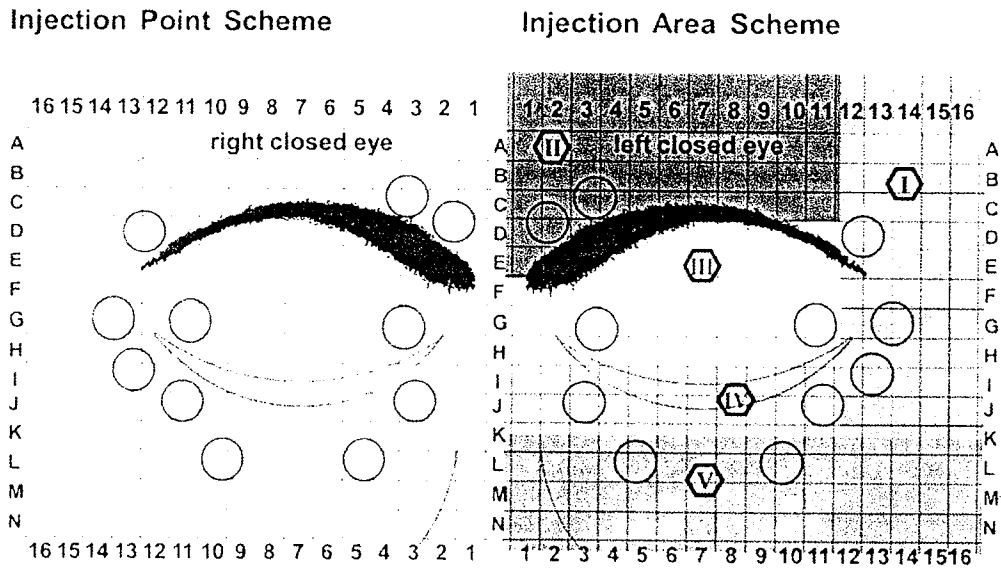
The study medication was injected by the clinical investigator at each study site. No compliance plan was specified.

Dosing Information and Exposure

One unit of NT 201 corresponds to the calculated median lethal intra peritoneal dose (LD₅₀) in mice. Each vial contained 100 units, approximately 600 picograms (Sponsor's range 400-800 pg).

The injection scheme followed that of usual clinical practice with regard to target sites and dose injected. Volume of NT 201 injected solution was recorded on the CRF by area, not dose in units or by muscle injected.

Figure 33: Trial 0003 Injection point schema (source: Sponsor)



I = temporal area II = eyebrow area III = upper lid area IV = lower lid area V = orbital rim

Table 38: Trial 0003 Dose of trial medications administered (source: Sponsor)

TREATM.	SEX	AREA	N	Nmiss	Mean	Std	Min	25%	Median	75%	Max
NT 201	Total	temporal area	130	18	16.27	10.091	2.50	10.00	15.00	20.00	40.00
		eyebrow area	108	40	9.14	4.599	2.50	5.00	10.00	10.00	26.00
		upper lid area	111	37	10.41	6.094	2.50	5.00	10.00	12.00	30.00
		lower lid area	99	49	9.55	5.019	2.00	5.00	10.00	10.00	30.00
		orbital rim	81	67	10.13	5.179	1.25	5.33	10.00	12.00	20.00
BTXCo	Total	temporal area	125	27	17.19	10.072	2.50	10.00	15.00	20.00	40.00
		eyebrow area	98	54	9.15	4.198	2.50	5.00	10.00	10.00	20.00
		upper lid area	115	37	11.58	7.165	2.50	5.00	10.00	15.00	40.00
		lower lid area	105	47	11.11	7.054	2.50	5.00	10.00	10.00	40.00
		orbital rim	77	75	10.23	4.871	2.50	6.00	10.00	10.00	20.00

Data source: Table 14.1.3.29.1.1

Table 39: Trial 0003 Dose comparison (ITT cohort, total units for both eyes)

Amount of medication received (units)									
Treatment	N	Nmiss	Mean	SD	Min	25%	Median	75%	Max
NT 201	148	0	40.69	14.55	15.0	30.0	40.0	50.0	95.0
BTXCo	152	0	41.65	15.94	15.0	30.0	40.0	50.0	100.0

Data source: Table 14.1.3.25.1.1

Protocol Deviations and Violations

Protocol violations were equally distributed between the treatment arms. If subjects had been randomized they were allowed to continue in the trial. Half the subjects had minor violations and 15% of subjects had major violations. Major violations included time window violations, violations of exclusion criteria, errors in injected dose and lack of safety examination and missing evaluations of outcome variables.

Efficacy Results

Primary Efficacy Endpoint

Jankovic Rating Scale –Total Score

The analysis dataset provided listings for 303 of 304 enrolled subjects (NT 201 n = 148; BOTOX® n = 155). One subject had been randomized but not treated. Outcome evaluations were missing on ten patients (NT 201 n = 4; BOTOX® n = 6). Three subjects in this group also had no injection dose recorded (all were in the BOTOX® arm). This efficacy analysis used the available data on the rest of the subjects.

Both arms were treated with virtually identical dose distributions (t –test, p = 0.585): NT 201: mean 41 units (95% CI 38, 43); BOTOX® mean 42 units (95% CI 39, 44).

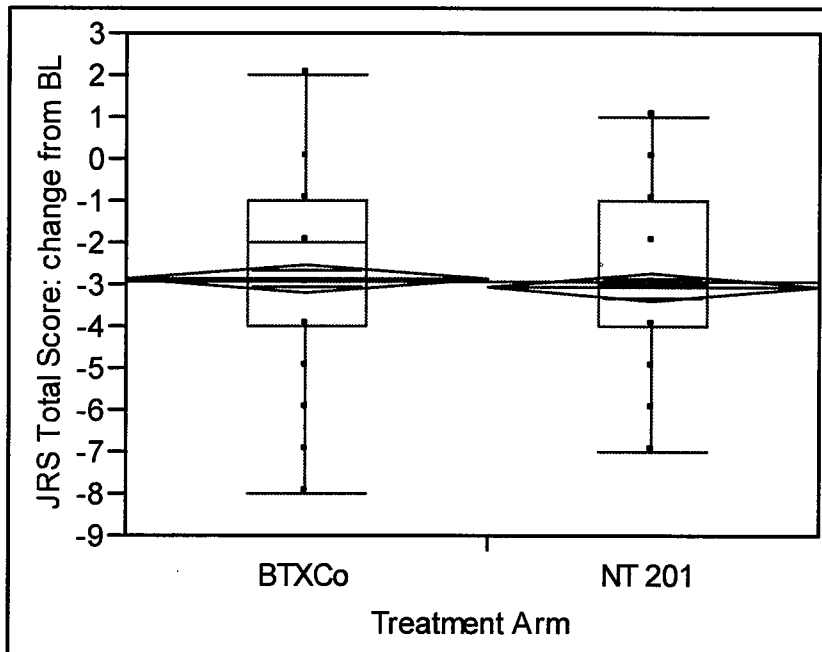
Using the baseline value of the total JRS score as a covariate in multivariable analysis, there is no difference in effect between the treatment arms (p = 0.362):

Table 40: Trial 0003 JRS change from baseline analysis of covariance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
TREATC	1	17.9793	17.9793	0.8334	0.3620
Error	288	6212.8133	21.5723		
C. Total	289	6230.7926			

Level	Mean	Std Error	Lower 95%	Upper 95%
BOTOX	-2.8608	0.16161	-3.179	-2.543
NT 201	-3.0746	0.16948	-3.408	-2.741

Figure 34: Trial 0003 JRS change from baseline box plot



Dose response exploration revealed no observable dose-response relationship for the entire cohort or by treatment arm.

Secondary Efficacy Analysis: Jankovic Rating Scale – Severity Subscore

JRS severity subscale ratings were available on the same patients as those used in the total score analysis.

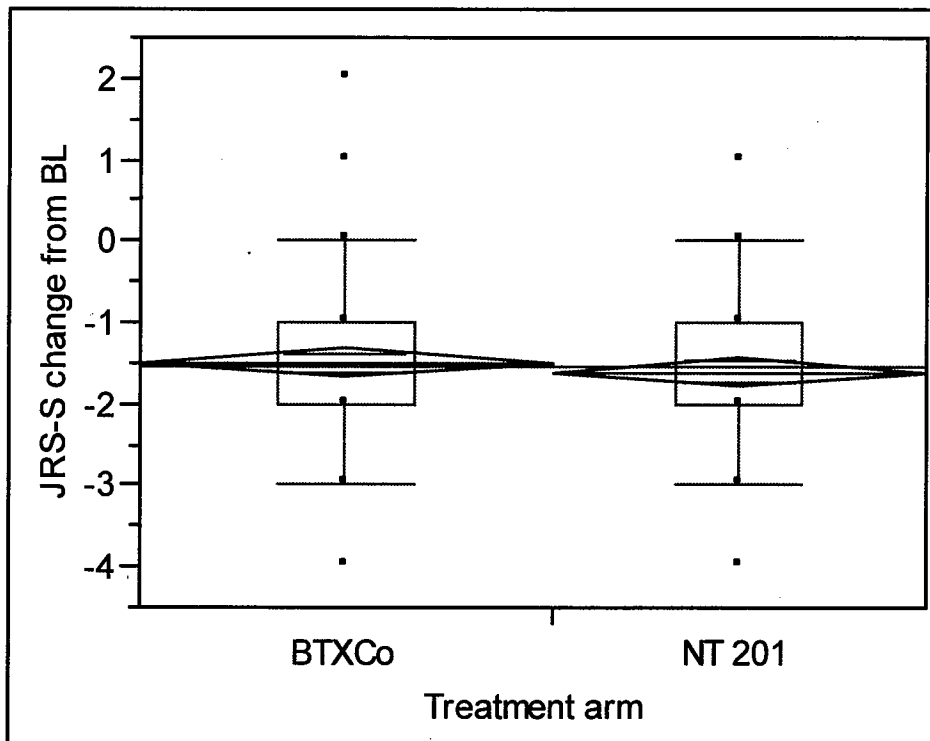
Using the baseline value of the JRS-S subscore as a covariate in multivariable analysis, there is no difference in effect between the treatment arms ($p = 0.3931$). Once again, dose response exploration revealed no observable dose-response relationship for the entire cohort or by either treatment arm.

Table 41: Trial 0003 JRS-S change from baseline analysis of covariance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
TREATC	1	2.40132	2.40132	0.7316	0.3931
Error	287	942.00267	3.28224		
C. Total	288	944.40399			

Level	Mean	Std Error	Lower 95%	Upper 95%
BOTOX	-1.4988	0.08851	-1.673	-1.325
NT 201	-1.6084	0.09257	-1.791	-1.426

Figure 35: Trial 0003 JRS-S change from baseline box plot



Comparability of JRS-S to placebo controlled Trial MRZ 60201-0433/1

Even though the prespecified primary outcome in this active comparator trial was the total JRS score, the JRS Severity subscale data makes it possible to evaluate the comparability of the effect size in this trial to that of the double blind placebo controlled confirmatory Trial MRZ 60201-0433/1. The patient populations in these two trials were comparable with regard to gender, race, age, BMI, and disease duration. As noted below in Table 44 they were judged to have different baseline severity.

Change from baseline of the JRS severity subscore at 6 weeks was the primary outcome in that trial, but a rating was also performed at 3 weeks making a comparison to this active control trial possible for the purpose of looking at effect size of NT 201 and making an assessment of assay sensitivity for this trial.

By analysis of covariance using the baseline severity subscale score as the covariate, the change in JRS-S from baseline at 21±3 days in Trial 0433/1 was significantly different from placebo, as expected ($p < 0.0043$):

Table 42: Trial 0433/1 JRS-S change from baseline at 3 weeks

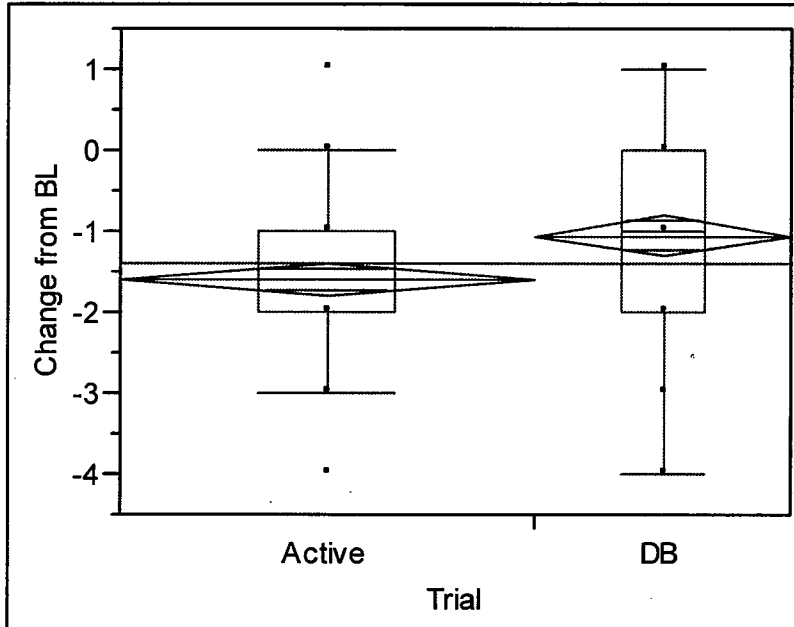
Level	Mean	Std Error	Lower 95%	Upper 95%
NT 201	-1.0558	0.13272	-1.319	-0.7927
PCB	-0.3500	0.20258	-0.752	0.0516

A comparison of the change from baseline of the JRS-S score at three weeks for the NT 201 groups in both studies reveals that the measured change was significantly different between these two studies, 50% less effect in the placebo controlled trial than the active comparator trial (ANCOVA, $p < 0.0006$):

Table 43: Trial 0003 vs. Trial 0433/1 JRS-S change from baseline at 3 weeks

Level	N	Mean	Std Error	Lower 95%	Upper 95%
Active	144	-1.6084	0.09859	-1.803	-1.414
DB	75	-1.0513	0.12613	-1.300	-0.803

Figure 36: Trial 0003 vs. Trial 0433/1 JRS-S change at 3 weeks box plot



At baseline these populations also had different blepharospasm severity ($p < 0.0001$):

Table 44: Trial 0003 vs. Trial 0433/1 JRS-S at baseline

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Active	144	2.65972	0.06934	2.5231	2.7964
DB	75	3.12000	0.09608	2.9306	3.3094

It is of interest that, as shown in the analysis of the placebo controlled trial above, more severe disease at baseline was related to greater change from baseline following treatment. In this trial, NT201 also had a smaller effect when compared to placebo, in a population more severely affected by blepharospasm. This suggests that the rating scales were applied in different fashion in the two trials. Without a placebo arm in the active comparator trial it is difficult to know which trial represents greater estimation of drug effect, but interpretation would favor the smaller effect size as blindly measured against placebo. In support of this is the Duration of Treatment Effect analysis which follows below.

Patient Evaluation of Global Response (PEGR)

The patient's own impression of their clinical response was evaluated at the outcome visit at three weeks but also at the final visit of the trial. (This contrasts to Trial 0433/1 the placebo controlled trial in which the PEGR was only obtained at the trial's final termination visit.)

There were no significant differences among PEGR scores within and between arms at either of these visits:

Table 45: Trial 0003 PEGR at 3 week outcome evaluation

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
BOTOX	149	1.9	0.1	1.7	2.1
NT 201	144	2.2	0.1	2.0	2.5

Table 46: Trial 0003 PEGR at trial final visit

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
BOTOX	151	2.0	0.1	1.7	2.2
NT 201	146	2.2	0.1	2.0	2.4

If one looks at the PEGR at the Final Visit in the NI trial versus the NT 201 arm in Trial 0433/1 there is a significant difference with subjects perceiving as doing less well in the placebo controlled trial (ANOVA, $p < 0.0001$):

Table 47: Trial 0003 vs. Trial 0433/1 PEGR at final visits compared for NT 201 arms

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
DB	75	1.3	0.2	0.9	1.6
NI	146	2.2	0.1	1.9	2.5

If one dichotomizes the score to moderately improved (2 or better) versus 1 or less, the results are also significantly better in the NI trial (X^2 , $p < 0.0076$).

Table 48: Trial 0003 vs. Trial 0433/1 PEGR scored “moderately improved” or better compared for NT 201 arms

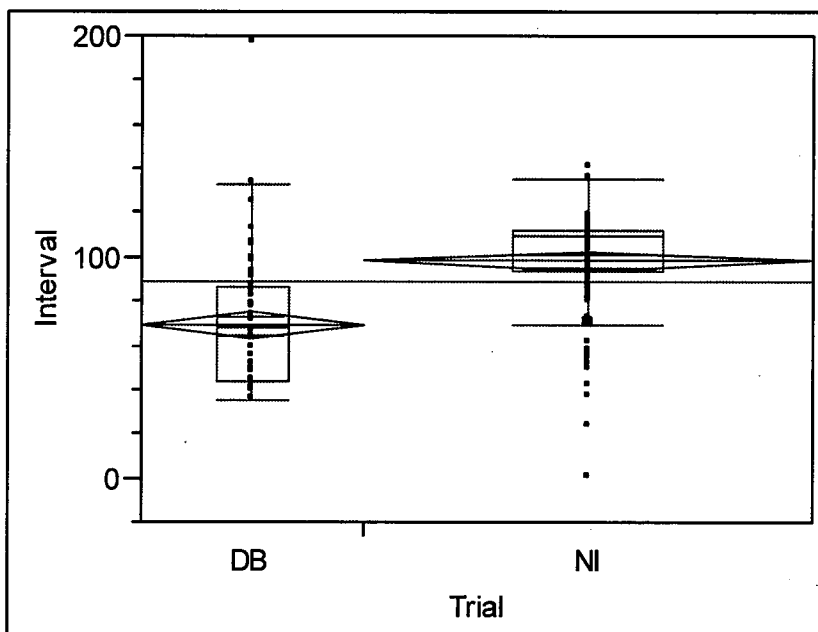
Count Row %	No	Yes	
DB	31 41%	44 59%	75
NI	35 24%	111 76%	146
	66	155	221

There is also a significant difference in the length of the intervals between the injection and the time of the final trial visit for the NT 201 treated arms in both trials; it is considerably shorter in the placebo controlled trial (ANOVA, $p < 0.0001$): Given the shorter interval to the end of the treatment period in the placebo controlled trial, it follows logically that the subjects would be unhappier with the outcome. In any case it makes this patient reported outcome difficult to compare between trials.

Table 49: Trial 0003 vs. Trial 0433/1 Interval from treatment session to final visit for NT 201 treated arms

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
DB	72 days	69	3	63	75
NI	146 days	98	2	94	102

Figure 37: Trial 0003 vs. Trial 0433/1 Interval from treatment to final visit box plot



Duration of Treatment Effect

Duration of Treatment was defined in the protocol as the interval (days) between the day of the injection session and the date when both the patient and the physician have agreed upon the necessity of a new injection. The trial ended at 112 days, and the date of the final visit (often past day 112) was the number used if this point had not yet been reached. There was no difference between the arms but fully 25 percent of subjects in both arms had duration of treatment less than 3 months.

Table 50: Trial 0003 vs. Trial 0433/1 Duration of treatment effect for NT 201 treated arms

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
BOTOX	151	98	2.2	93	102
NT 201	146	98	2.3	94	103

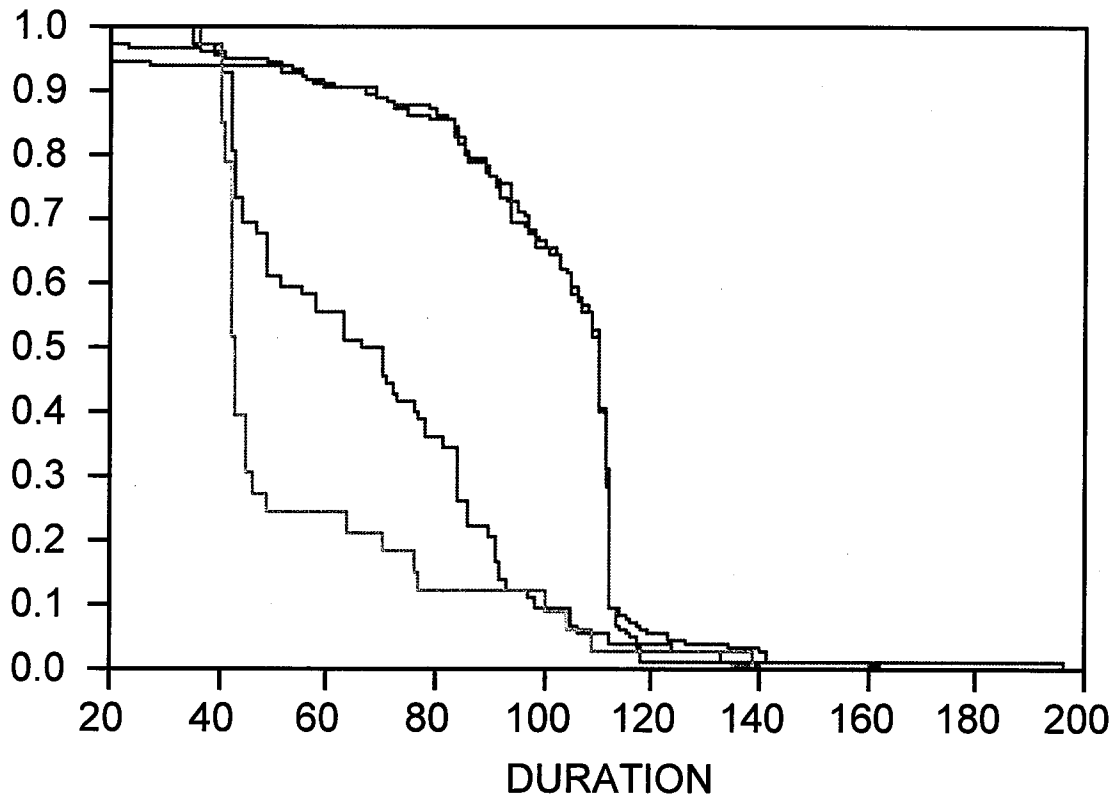
By way of contrast, the graphic below show the treatment arms from the placebo controlled and this active control trial. Treated as a survival analysis, the graph shows

as DURATION the interval in days from the injection session to the final blinded trial visit, as defined by the need for retreatment. "BTXCo" and "NI NT201" represent the arms from this trial while "NT201" and "PCB" represent the arms from Trial 0433/1. The difference between the two NT 201 arms is statistically significant (X^2 , $p < 0.0001$).

Table 51: Trial 0003 vs. Trial 0433/1 Interval to next injection quantiles in days for all treatment arms

Arm	Median Time (days)	Lower 95%	Upper 95%	25% Failures	75% Failures
BOTOX	110	106	110	91	112
NI NT201	110	105	110	94	112
NT 201	70	49	77	43	86
PCB	43	42	45	42	49

Figure 38: Trial 0003 vs. Trial 0433/1 Interval to next injection survival plot



BTXCo	—
NI NT201	—
NT 201	—
PCB	—

Patient reported Waning of Effect was added by protocol Amendment 1. This time-based outcome was the patient's own evaluation of when the treatment's effect wore off. The interval from the injection session to this point was recorded in weeks by the investigator.

Table 52: Trial 0003 Patient reported waning of treatment effect (weeks)

Level	Minimum	10%	25%	Median	75%	90%	Maximum
BOTOX	0	4.1	8	11	13	15	20
NT 201	0	6	8	11	14	16	17

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
BOTOX	150	10	0.33	9.6	11.0
NT 201	145	11	0.34	10.0	11.3

The patient reported length of effect for NT 201 in this active comparator trial was 11 weeks on average. This is very consistent with the 77 day reported in the placebo controlled trial. The investigator guided assessment of duration of effect, when both the investigator and patient "agreed" the next treatment was needed, appears to show a bias towards an optimistic assessment of duration of effect for both active agents.

Exploration of dose and responses

No dose response relationship was found in this trial.

Outcome of Safety Analysis

The reader is referred to the separate clinical safety review being performed for this BLA submission.

Discussion of findings and conclusion

As a non-inferiority design, this trial has deficiencies that affect its interpretation.

It is difficult to estimate from prior experience what the effect size of the primary outcome variable should be. No discussion was presented regarding the rationale for the size of the non-inferiority margin, how much effect one was willing to give up (which changed from 95 to 90% by Amendment 1) and the historical constancy of the effect. In fact, the JRS has not been previously used in an adequately controlled and blinded trial of blepharospasm. The difference in effect size of the JRS for the NT 201 arms in the placebo controlled and active controlled trial graphically demonstrates the difficulty this poses.

Even if the margin had been adequately prespecified, the population in this trial is not the same as other populations used in blepharospasm trials which have led to market approval. A precondition to entry in this trial was an adequate and stable response to a marketed BoNT A product, which is, in effect, enrichment. This parceling of the real world population of subjects with blepharospasm would eliminate those with small drug effect size, treatment resistant blepharospasm, and patients who respond well for very long intervals of time. All these factors preselect a population which resulted in the response to treatment pattern elicited in these this trial. We have no data as to the effect of NT 201 in a population of treatment-naïve subjects with blepharospasm, ultimately the population of subjects who will most often be offered this agent.

While the subject's estimation of the duration of treatment effect was consistent in both this and the placebo controlled trial, the investigators' assessment of the duration of treatment effect in the active control trial appears considerably more favorable, and not consistent with the experience of neurological clinics specialized in the treatment of blepharospasm. (It would have been even longer had the interval not been limited by the ending of the trial period at 112 days). There are few controlled trials which look at the duration of efficacy of botulinum toxin preparations but it is generally considered that clinical efficacy falls off after 60 days and 10 weeks is the average duration of action (Simpson, et al. Neurology 70: 1699-1706, 2008).

The source of the discrepancy in the investigators' assessment is not clear. Certainly, knowing that every subject in the trial was treated with an active BoNT product would bias the clinicians towards an optimistic assessment of the treatment they administer. Training for assessing the primary outcome did occur. Given that this trial was performed in Europe and Israel, whilst the confirmatory trial was performed in North America raises the possibility of cultural effects or practice differences among the investigators.

Both the investigators' rated improvement of severity and the patients' assessment of satisfaction are more favorable in this trial compared to the placebo controlled trial. A placebo arm in the active comparator trial would have established the ability of the trial to sensitively detect the magnitude of drug effect (i.e. establish assay sensitivity).

Failing that, the consistency of the patient reported outcome for time to the waning of treatment effect seems to offer the only support as to the comparability of these two treatment trials.

6 Review of Efficacy

Efficacy Summary

The proposed indication for NT 201 is the treatment of benign essential blepharospasm.

In this application the treatment of blepharospasm was studied in a population of adult subjects who had previously responded in a favorable and stable fashion to BOTOX®, another BoNT Type A product approved for blepharospasm.

Three Phase III trials were performed: a double blind trial which demonstrated superiority to placebo in a single treatment session (NT 201, n = 75; PCB, n = 34), an open label extension of that trial which demonstrated the maintenance of drug effect over 1 year (n = 102), and a blinded active control trial using a single treatment session which was intended as a non-inferiority comparison trial to BOTOX® (NT 201, n = 144; PCB, n = 149).

All three trials used the Jankovic Rating Scale (JRS) which is composed of a severity and a frequency subscale. The non-inferiority trial used the total JRS score while the other two trials used only the severity subscale (JRS-S) for the primary outcome. Secondary measures included the Blepharospasm Disability Index (BSDI) and global ratings of improvement by the investigator and patient. Multivariable analyses were performed using the baseline measure as a covariate.

The selected treatment dose for NT 201 in each subject was the same as that previously used for the BOTOX® product prior to entering the trial and given in the same periorbital sites. Dose ranging studies, per se, were not performed as the source and manufacture of the drug product and Phase I data suggested that its physiological effect should approximate that of BOTOX®. A maximum of 50 units per eye was administered in the development program. The average total dose delivered to both eyes for the double blind and the open label extension trial was 67 units, with no side to side difference.

In the placebo controlled trial at 6 weeks following treatment, NT 201 was superior to placebo injection in the periorbital muscles ($p < 0.0004$). The JRS-S score improved (moved negatively) by -0.84 points (95%CI -1.09, -0.58), compared to placebo which worsened (moved positively) by 0.21 points (95%CI -0.17, 0.58).

The level of functional disability at six weeks following treatment as measured by the BSDI also improved significantly in the active treatment arm ($p < 0.0023$). The BSDI improved (moved negatively) by -0.48 points (95%CI -0.65, -0.30), compared to the placebo arm which worsened (moved positively) by 0.15 points (95%CI -0.23, 0.26).

Other secondary measures, of which there were many, moved consistently in the direction favoring the active treatment group.

The duration of treatment effect was assessed in both the double blind and open label trials. In the double blind trial waning of effect was best determined by the interval from treatment until meeting the predetermined criteria for retreatment. The time to the need for retreatment was a median of 70 days (95% CI 49, 77).

In the open label trial which lasted over a year, the number of injections the subject received was determined by how long the treatment effect was adequate. As a result, 89% of subjects received either 4 or 5 treatment sessions. The average interval for 87 evaluable subjects receiving 364 treatments in the open label trial was 82 days (95% CI 80, 85; range 39 to 238 days).

The active control trial yielded little additional useful information. As indicated in the trial review in **Section 5.3.3**, the reviewer had concern about the validity of the results of that trial due to deficiencies in its design.

6.1 Indication

The treatment of benign essential blepharospasm is the proposed indication for NT 201. This chronic syndrome occurs exclusively in adults beginning on average in the fifth or sixth decade of life. Disability is the result of uncontrollable forced eye closure. While this is a clinical syndrome, blepharospasm, may occur by itself or in combination with other movement disorder phenomena such as other dystonias and Parkinsonism. It can be expected that NT 201 will have considerable off label use just as the other BoNT preparations do.

6.1.1 Methods

The confirmatory double blind trial compared a single treatment of NT 201 to placebo. The enrolled cohort was randomized 2:1, active: placebo. The range of doses given is summarized in this table:

Table 53: Trial 0433/1 Range of doses administered (source: Sponsor)

Treatment	Side	N	Nmiss	Total units of injection				
				Mean	SD	Min	Median	Max
NT 201	Right	74	0	33.5	11.07	10.0	32.30	50.0
	Left	74	0	33.4	11.32	10.0	32.50	50.0
	Total	74	0	66.9	22.32	20.0	65.00	100.0
	≤ 61.25 U [a]	33	0	46.4	11.74	20.0	50.00	60.0
	> 61.25 U [a]	41	0	83.4	13.19	63.0	85.00	100.0
Placebo	Right	34	0	30.2	10.87	10.0	28.30	50.0
	Left	34	0	30.0	10.85	10.0	27.50	50.0
	Total	34	0	60.2	21.68	20.0	56.50	100.0
	≤ 61.25 U [a]	21	0	46.4	10.60	20.0	50.00	60.0
	> 61.25 U [a]	13	0	82.6	15.01	62.5	80.00	100.0
Total	Right	108	0	32.5	11.07	10.0	30.00	50.0
	Left	108	0	32.3	11.23	10.0	30.00	50.0
	Total	108	0	64.8	22.24	20.0	61.25	100.0
	≤ 61.25 U [a]	54	0	46.4	11.21	20.0	50.00	60.0
	> 61.25 U [a]	54	0	83.2	13.51	62.5	82.50	100.0

[a] 61.25 is the exact calculated median dose; Nmiss=Number of subjects with missing data; SD=standard deviation; U=units

Source: Table 14.3.1.1

The average total dose delivered to both eyes in the double blinded trial was 67 units. In addition, doses in the open label extension did not change over the course of the trial and the mean total dose for both eyes remained 67 units.

The effect of treatment was rated by a blinded investigator at six weeks following treatment. The patient was followed after that to a maximum of 20 weeks. At the time where the patient and investigator agreed that retreatment was needed and the patient met predetermined criteria for worsening, they ended the trial. The patient was then offered treatment in the open label extension trial.

The severity subscale of the Jankovic Rating Scale was the primary efficacy measure. This is a single item, 0-4 rating scale, with anchored cut-points for the severity of blepharospasm. The planned statistical analysis was the change from baseline (Visit 2) to week 6 (Visit 4). The dependent variable in the ANCOVA model is the change from baseline in the JRS Severity subscale score assessed by the blinded independent investigator and the independent variables are treatment, baseline JRS severity subscore, sex, age, dose and trial center. The trial was powered to demonstrate a one point change from baseline, thought to represent a clinically meaningful change by the Sponsor.

The most important secondary criteria were: duration of treatment effect, change from baseline of the JRS-S from the patient's diary and the blepharospasm disability index (BSDI), the patient evaluation of global response (PEGR) and the investigator's global assessment of efficacy.

6.1.2 Demographics

In the double blind trial, 109 patients were randomized and 108 received medication (NT 201, n = 75; PCB, n = 34). Seven patients withdrew leaving 70 NT 201 and 32 placebo subjects completing the trial. All 102 subjects entered the open label extension of this trial which demonstrated the maintenance of drug effect over 1 year. The blinded active control non-inferiority trial which is not discussed further in this section randomized 293 patients for a single treatment session (NT 201, n = 144; BOTOX®, n = 149).

Demographic characteristics did not vary between treatment arms. Consistent with the epidemiology of the syndrome, 65% of the subjects were women. Average age was 63 years (range 22 to 79 years). Participants in the trial were white (83 %), Hispanic (8%), Asian (6%) or black (4%), and most were non-smokers (67%). Medical illness and concomitant medications were as expected for a cohort of this age.

The median duration of blepharospasm was 84 months, the same in both treatment arms (range 6 - 468 months; mean 105 months). The length of disease after formally diagnosis was 5 years on average. A third of subjects had other dystonic phenomena, all but 1% in the contiguous segments of face, neck, mouth, and mandible.

6.1.3 Subject Disposition

Of the 109 subjects randomized and receiving medication. One dropped out and never received medication. The rest completed the trial. Seven (NT 201 = 4; PCB = 3) were subject to major protocol violations (assessments out of window, errors in medication administration) but were evaluated in the ITT population.

6.1.4 Analysis of Primary Endpoint(s)

Jankovic Rating Scale (Severity Subscale):

The mean difference from baseline to week 6 (Visit 4) in the NT 201 arm was -0.84 (95% CI -0.56, -1.11) moving from 3.15 to 2.31 on average. In contrast, the mean difference for the placebo group was 0.21 (95% CI 0.52, -0.11) moving from 2.94 to 3.15 over the same period. There was no statistically significant difference in baseline severity between the arms.

Table 54: Trial 0433/1 JRS-S change from baseline to outcome visit (week 6)

Arm	Number	Mean	Std Error	Lower 95%	Upper 95%
NT 201	74	-0.83784	0.12855	-1.093	-0.5830
PCB	34	0.20588	0.18964	-0.170	0.5819

6.1.5 Analysis of Secondary Endpoints(s)

JRS Severity Subscale Diary: The median value of the diary (a patient self-rated JRS-S) for the seven days prior to visit was used in an analysis of covariance. The initial self-assessment is made in the week prior to the baseline injection, with the endpoint value taken from diaries prior to week 6 (Visit 4). Multivariable analysis of the diary self-rating, using baseline measures as the covariate and LOCF for missing data reveals that there was a significant difference between the treatment groups ($p < 0.005$):

Table 55 Trial 0433/1 JRS-S patient diary change from baseline to outcome visit

Arm	JRSS Diary Mean BL ± SD	Mean Change from BL	Std Error	Lower 95%	Upper 95%
NT 201	2.61 ± 0.98	-0.90000	0.15469	-1.207	-0.5928
Placebo	2.53 ± 1.17	-0.02469	0.22737	-0.476	0.4268

Blepharospasm Disability Index: The BSDI is a self-rated scale for the assessment of impairment of specific activities of daily living caused by BEB. The scale consists of 6 items rated 0-4 with anchored cut-points, plus a choice of "not applicable to me." The 6 items are "Driving a vehicle", "Reading", "Watching TV", "Shopping", "Walking" and "Doing everyday activities". Baseline disability scores were equivalent between the arms: NT 201: 1.60 (95% CI: 1.41, 1.78) PCB: 1.37 (95% CI 1.09, 1.64). Analysis of covariance using the baseline BSDI score as the covariate revealed that there was statistically significant improvement in the active treatment group ($p < 0.0023$).

Table 56: Trial 0433/1 BSDI change from baseline to outcome visit

Arm	Mean	Std Dev	Lower 95%	Upper 95%
NT 201	-0.47674	0.951074	-0.6500	-0.3035
PCB	0.01478	0.810885	-0.2277	0.2572

Patient Evaluation of Global Response: The PEGR is a single descriptive and subjective response to a self-rated scale ranging from "complete abolishment of signs and symptoms" (+4) down to "very marked worsening" (-4). This was dichotomized to differentiate between those with moderate improvement or better versus all the rest. Analysis by contingency table revealed a significant result by X^2 , $p < 0.0001$):

Table 57: Trial 0433/1 PEGR at end of trial

Count (Row %)	Improved	Not Improved	
NT 201	44 (59%)	31 (41%)	75
PCB	5 (15%)	29 (85%)	34
	49	60	109

Global Assessment of Efficacy: The investigator performed a single global assessment of the efficacy of study medication at the final visit of the double blinded phase of the trial. The patient was rated on a 4-point scale, ranging from “very good”, “good”, “moderate”, to “poor”. For assessment of efficacy by the clinical investigator, the data was dichotomized between “good and very good” improvement versus “moderate and poor.” This reveals a statistically significant difference between the treatment arms: (X^2 , $p < 0.0001$):

Table 58: Trial 0433/1 GAE at end of trial

Count (Row %)	Improved	Not Improved	
NT 201	49 (65%)	26 (35%)	75
PCB	8 (24%)	26 (76%)	34
	57	52	109

6.1.6 Other Endpoints

The duration of treatment effect was defined as the time period from day of injection (Day 0) until the time point for the “agreed upon” day of retreatment. This day (which ends the blinded portion of this trial for that subject) was determined by the evaluation of the JRS severity subscore assessed by the blinded investigator (score must be ≥ 2). The duration of treatment effect was assessed in both the double blind and open label trials.

In the double blind trial waning of effect and the need for retreatment was after a median of 70 days (95% CI 49, 77). In the open label trial which lasted over a year, the number of injections the subject received was determined by how long the treatment effect was adequate. As a result, 89% of subjects received either 4 or 5 treatment sessions. The average interval for 87 evaluable subjects receiving 364 treatments in the open label trial was 82 days (95% CI 80, 85) range 39 to 238 days.

The JRS Frequency Subscale, while not a primary or secondary outcome showed similar movement from baseline evaluation. The results of multivariable analysis with the baseline JRS Frequency Score as covariate reveals that there is a statistically

significant improvement (change from baseline) after treatment with NT201 ($p < 0.0137$). The mean difference from baseline to week 6 (Visit 4) in the NT 201 arm was -0.67 (95% CI -0.91, -0.43). In contrast, the mean difference for the placebo group was 0.15 (95% CI -0.49, 0.20). There was no statistically significant difference in baseline severity between the arms NT 201: 2.75 (95% CI 2.55, 2.94) PCB 2.82 (95% CI 2.53, 3.12).

6.1.7 Subpopulations

The effects of gender and age upon outcome of treatment with NT 201 were investigated by the Sponsor. Age (above and below 60) had no effect in the group receiving active treatment. In the placebo group lower age was associated with slight worsening of symptoms over the evaluation period: a gain of 0.43 points on the JRS-S vs. 0.05 points in older subjects. Women achieved higher mean score reductions in response to treatment than male subjects: (- 1.02 vs. - 0.46 points). It is to be emphasized that this exploration is retrospective on a small number of subjects and should be viewed in that light. The low number of non-white subjects precludes any conclusion on the effect of race.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor wishes to demonstrate that the effective dose of NT 201 is roughly equivalent to that of a population that has previously responded to BOTOX® treatment for blepharospasm. It is not clear, however, how a BoNT naïve population may respond. For this reason, prudence suggests a lower starting dose, 25 units per eye, with individual injections sites initially receiving 1.25 -2.5 units, and increasing to a maximum recommended dose as clinically needed and tolerated. The Sponsor suggests (b) (4) units per eye as a maximum dose.

Single dose exposure to higher doses (45 to 50 units per eye) of NT 201 is considerable. In Trial 0003, the active control trial, the maximum dose was limited by protocol to no more than 35 units per eye (70 u total dose).

In Trial 0433/1, the double blind trial, 16 subjects in the NT 201 arm received 90 units total dose or greater. In Trial 0433/2, the open label extension, 5 additional subjects from the placebo arm subjects received 90 units total dose or greater. This brings the total to 21 unique individuals who received 90 u total dose or greater (i.e.: 45 u /eye). If one takes into account the multiple treatment sessions in the double blind and open label extension trials, as opposed to individuals, then there were 114 treatment sessions at 90 u total dose or greater.

However, because NT 201 is intended as a chronic treatment, the chronic exposures in the clinical trials bear careful examination.

Using the datasets for Trials 0433/1 and 0433/2, the intervals between sequentially administered treatments (numbers of days from one injection to the next injection) were summed. The interval of exposure to active drug in the double blind trial was carried over into the open label extension as these patients were rolled over without interruption in treatments.

This summed exposure for each subject was converted to weeks to get total duration of exposure. The rounding was downward in direction, e.g. 7 weeks and 6 days was considered 7 weeks. If a subject was lost to follow-up and had no final visit for that treatment session, that injection dose and its interval were dropped from the exposure data set.

Subjects with at least 24 weeks and 48 weeks continuous observation were taken to be supportive of exposure to the lowest dose in that interval. I looked at all combinations to see if a given dose exposure might be supported at some middle interval over the course of a subject's treatment. For example one subject received 4 injections of 100, 100, 60, and 55 units at intervals over a year. As a result this patient was supportive of 100 units at 6 months exposure, but also 50 units at 48 weeks exposure. (The doses are expressed as deciles, e.g.: a dose between 50 and 59 units supported a 50 unit dose).

Table 59 NT 201 Cumulative dose exposure at 24 and 48 weeks

NT 201 cumulative dose exposure at 24 and 48 weeks					
Total dose NT201 (both eyes)	Considered supportive of this dose level	24 Weeks		48 Weeks	
		N	Cumulative N at or exceeding this dose level	N	Cumulative N at or exceeding this dose level
100 Units	100 Units	15	15	13	13
90 - 99 Units	90 Units	5	20	4	17
80 - 89 Units	80 Units	11	31	5	22
70 - 79 Units	70 Units	14	45	12	34
60 - 69 Units	60 Units	16	61	14	48
50 - 59 Units	50 Units	17	78	18	66
40 - 49 Units	40 Units	8	86	8	74
30 - 39 Units	30 Units	3	89	3	77
29 Units or less	20 Units	3	92	3	80

This then would suggest that there is insufficient exposure data to support the Sponsor's proposed (b) (4) maximum total dose and indicates that 70 units (35 units per eye) may be more appropriate.

The clinical literature suggests that frequency of usage may have a long term effect upon efficacy. More frequent treatment (intervals less than every 10 weeks) may contribute to the formation of blocking antibodies. Because drug concentrations were not measured it is impossible to propose a response relationship. There does not appear to be one related to injected dose. Subjects taking concomitant medications which affect the neuromuscular junction were excluded from trials so specific drug-drug interactions are unknown. It is apparent that the degree of improvement obtained by treatment with NT 201 may also be related to the baseline severity of disease.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The open label extension trial demonstrates by three criteria that tachyphylaxis to drug effect did not occur that over the time of the trial: there was no need for increasing doses of NT 201 over time, there was no loss of duration of treatment effect, and there was no loss of effect as measured by the JRS-S.

6.1.10 Additional Efficacy Issues/Analyses

The clinical reviewer, in looking at the magnitude and direction of change in the primary and secondary outcome measures, has found a credible relationship between scales rated by the investigators and patients rated outcomes of efficacy. On the basis of the concordance and the quantifiable relationship between investigator and patient derived measures, it is fair to state that the magnitude of improvement as assessed by the JRS-S is clinically meaningful to the patient.

7 Review of Safety

Safety Summary

Because of safety concerns specific to botulinum toxins, and because human experience with NT 201 was derived from three different disease entities with a wide range of dosing regimens (blepharospasm, cervical dystonia and spasticity), this BLA submission was the subject of separate comprehensive DNP safety analysis. The reader is referred to that document.

After discussion with the safety reviewer, it appears that no new or unexpected adverse events were discovered in the course of the development program for NT 201. However, review of the safety data suggests that there is the same possibility of unintended paralytic effects in both contiguous and remote parts of the body as is seen in other BoNTs.

Two safety subsections are retained here for discussion: the issues of spread of toxin after injection (7.3.5) and immunogenicity (7.4.6)

7.3.5 Submission Specific Primary Safety Concerns

Spread of neurotoxin effect to non-target tissues:

The potential for spread of botulinum toxin into tissues adjacent to the target muscles or more remotely via tissue planes or even the blood stream is a source of concern for this class of agents. Because Xeomin® is a smaller biologic by virtue of its size, it is cogent to raise the concern that, precisely because of the nature of the preparation, greater diffusion is possible.

The Sponsor's Periodic Safety Update Report No. 6, covering the period up to July 1, 2009, reports 90 cases of potential spread from their spontaneous reporting system. Using a list of sentinel terms (including, e.g. dysphagia, aspiration, ptosis, muscle weakness) that signal adverse events of special interest, 3 cases considered serious were found. One was ptosis in association with a cosmetic use in the glabellar region. One case with respiratory failure and one case with dyspnea were associated with off label use. Two additional cases of speech disorder were considered to be evidence of systemic or local toxin spread, documenting that this phenomenon occurs with NT 201 just as with the other BoNTs.

Only Trial 0433/1 lends an opportunity to judge spread in an NT 201 treated group as compared to placebo. The table below looks at reported AEs by Preferred Term selected for the potential that it could reflect spread, either local or distant.

Table 60: Trial 0433/1 Subjects reporting AE of special interest

Individuals reporting the AE (Preferred Term)	NT 201 (n=75)		Placebo (n=34)	
	N	%	N	%
Facial paresis	2	2.7	0	0.0
Dry mouth	12	16.0	2	5.9
Dysphagia	4	5.3	2	5.9
Dyspnea	4	5.3	1	2.9
Muscular weakness	1	1.3	2	5.9
Asthenia	3	4.0	0	0.0

Dry mouth, presumably a result of local diffusion, appears to exist more commonly in the active arm. Other local (facial weakness) and more distant phenomena (dysphagia, dyspnea, and generalized weakness) are present but appear less commonly in the NT 201 treated arm. The open label extension corroborates these findings but they must be considered preliminary information from a very small sample. Individuals reporting these preferred terms at any time in the open label treatment extension are as follows:

Table 61: Trial 0433/2 Subjects reporting AE of special interest

Individuals reporting the AE (Preferred Term) during Open Label Treatment	NT 201 (n = 102)	
	N	%
Facial paresis	3	2.9
Dry mouth	10	9.8
Dysphagia	4	3.9
Dyspnea	6	5.9
Muscular weakness	6	5.9
Asthenia	3	2.9

Nevertheless, it suggests that NT 201 is not immune from the AEs observed for the class of BoNT agents.

A paucity of AE reports from the Trial 0003 NT 201 vs. BOTOX® comparison trial suggests that events were poorly captured. For example, in 297 BoNT treated subjects, there was only one report of dry mouth which suggests poor “assay sensitivity” for the collection of AEs in this trial. In Trial 0433/1 a specific checklist of potential side effects was employed while in Trial 0003 the CRF contained only one general question as to whether anything new had occurred health-wise.

7.4.6 Immunogenicity

Because botulinum toxin products are biological proteins which are chronically administered on an intermittent schedule, they are obvious sources of activation for the human immune system. Blocking antibodies have been described but their relationship to the loss of clinical efficacy is not clear cut. (b) (4)

An early series, investigating 559 BoNT type A treated patients between 1984 and 1992, found 24 (4.3%) with antibodies by mouse assay. Some had had only one or two injection sessions. Eight of 76 patients with follow-up (10.5%) developed resistance to drug effect. As a rule, they had had been treated with larger doses and had injections at closer intervals, especially booster injections 2 to 3 weeks after the initial session (Greene, et al. Mov Dis 9(2): 213-217, 1994).

However, well-documented cases of antibodies developing after a single injection or with low dose (as in the treatment of glabellar lines) exist.

Another study (by far the largest in the literature) looked at the correlation between the presence of neutralizing antibodies and non-responsiveness to treatment (Lange, et al.

Clin Neuropharm 32(4)213-218, 2009). Serum samples were taken from 503 patients with a variety of diagnoses treated by BoNT-A (Dysport® or BOTOX®). The selected subjects were secondary nonresponders, i.e.: initially responded but then lost the responsiveness to therapy. Fewer than half of the subjects (n = 224, 44.5%) had neutralizing antibodies. The authors concluded that non-responsiveness is not well correlated with the presence of antibodies and that non responsiveness may not reliably be used as a surrogate for the presence of antibodies. They confirmed that the presence of antibodies in these non-responders was associated with higher doses and shorter intervals between injections (for example, only 6 of 38 subjects (16%) with blepharospasm, but 175 of 362 subjects (48%) with cervical dystonia).

The authors found the presence of antibodies to be unrelated to the commercial preparation used, but found that cumulative doses higher than 6000 units were associated with a higher proportion of patients with antibodies. Of note, the mean duration of therapy until secondary nonresponsive was 41 months (Dysport®) and 45 months (BOTOX®). This also suggests that formulation differences among BoNT agents may not be relevant to the formation of antibodies or the development of non-responsiveness.

An alternative plausible explanation for the loss of efficacy to BoNT products could be that actual muscle fiber damage results from the use of toxin. This has been documented by biopsy in humans (Schroeder, et al. *Mov Dis* 24 (10)1494-1503, 2009).

In the NT 201 development program, antibodies were investigated (Goschel, et al *Exp Neurol* 147:96-102, 1997) and the Sponsor argues that antibodies were present in all non-responders, stating that non-responders who were not antibody positive subsequently responded to retreatment. However, in this paper, no study design specifications or clinical data are presented. The Sponsor demonstrated antibody development to high doses of BOTOX® but not NT 201 after biweekly injections for 12 weeks in rabbits. In a 33 week study comparing Dysport®, BOTOX® and NT 201, one animal did develop antibodies in the NT 201 group.

In Trial 0433/1 (placebo controlled) and Trial 0003 (active control with BOTOX®), the Sponsor screened antibodies by ELISA and confirmed with the mouse hemidiaphragm bioassay. Antibody titers > 3.58 mU/mL and hemidiaphragm paralysis times > 64 minutes were considered positive. In these two trials, 2 of 222 patients (1%) had antibodies at baseline (2 others were "borderline"). In Trial 0433/1 two subjects developed transient "borderline" antibodies which were not present at the final visit. In Trial 0003, one NT 201 subject became positive and another "borderline" at the final visit. In Trial 0003, two subjects developed antibodies in the BOTOX® arm; they had had 21 and 31 previous injection sessions, respectively. There were no clinical phenomena which could be attributed to this development. The Sponsor's tally from all trials in the development program for all indications reveals that 0.7% of 1048 NT 201 patients and 0.8% of 354 BOTOX® patients developed anti BoNT antibodies (ISS, p. 84).

Results of antibody screening in the 52 week open label follow-up to Trial 0433/1 have not been reported.

The most recent Periodic Safety Update Report (PSUR No. 6, submitted August 2009) reports 36 cases of ineffective or no response to treatment. The report also states "It has not been investigated whether secondary non-response due to the development of antibodies is less frequent under Xeomin® therapy than under treatment with conventional preparations containing the Botulinum toxin type A complex."

The Sponsor proposes the following for the label:

(b) (4)



This reviewer thinks that none of this is warranted. (b) (4)



8 Postmarket Experience

This source of this post market information for NT 201 is the Sponsor's Periodic Safety Update Report No. 6, covering the period up to July 1, 2009.

During the year covered by this PSUR, (b) (4) vials of Xeomin® were sold. Assuming 1 vial per patient and injections every 3 to 4 months, the Sponsor estimates (b) (4) patients exposed. An additional 1031 subjects in clinical trials were also exposed to NT

201. Cumulative exposure in clinical trials and since the first marketed use of Xeomin® on May 31, 2005 is estimated at (b) (4) vials and about (b) (4) patients.

No marketing authorizations have been withdrawn or suspended.

The occurrence of adverse drug reactions is the subject of a separate DNP safety review, except for the discussion in **Section 7.3.5. Submission Specific Safety Concerns**, above.

9 Appendices

9.1 Literature Review/References

References are cited within the body of this report.

9.2 Labeling Recommendations

Preliminary review by DMETS indicates that the USAN and proposed trade name for NT 201 are acceptable.

Recognizing the complex regulatory process for the creation of REMS and PMCs, the reviewer offers these few observations for consideration:

The Sponsor's proposed risk management plan (dated March 1, 2010) contains the appropriate elements though they are in places lacking in detail, e.g. dosing units and specific information about distant spread. In addition the Sponsor proposes the first report at (b) (4)

Review of the Dear Healthcare Provider Letter uses phrases suggesting

(b) (4)

Verbiage warning of distant spread includes the notice that this may result from the use of BoNT in spasticity, the situation which may predispose to this phenomenon presumably due to larger doses used for larger muscles. (b) (4)

As a result, I think it is appropriate to acknowledge this use, emphasizing both its off label status and the increased potential for serious treatment related adverse events from distant spread.

A survey or other instrument for the evaluation of the effectiveness of the REMS was not submitted.

Suggested label changes:

A preliminary review of the label (version of March 1, 2010) by this reviewer prompts the following preliminary suggestions for change by label section:

1.2 Benign Essential Blepharospasm - suggested change to Blepharospasm

Because the clinical phenomenon of blepharospasm is often found accompanied by other movement disorder phenomena (one third of the subjects in this trial had other craniofacial dystonia), it is recommended that an indication be granted for the treatment of blepharospasm as a symptom in addition to the syndrome of BEB. This makes the indication consistent with the BOTOX® label in which a similar population was studied.

(From the BOTOX® label: **1.4 Blepharospasm and Strabismus BOTOX** is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.)

NT 201 was tested in subjects who had had previous successful treatment with BOTOX®. It is reasonable to view this as enrichment of the study population. As a result, it is unknown what the magnitude of drug effect might be in a treatment naïve population with blepharospasm. However, there is no clinical *a priori* evidence to suggest that the response in these two populations would differ greatly. The potential exceptions would be for a subgroup of poor responders, who would have been excluded from this trial, and treatment naïve subjects who could have a more robust response to initial treatment. A conservative approach erring on the side of safety would be to indicate NT 201 only for blepharospasm patients previously treated with BOTOX®.

2.2 Benign Essential Blepharospasm

Trials defined the areas of injection topically in diagrams, not by anatomical names of location. It may be clearer to illustrate the sites of injection, the frequency and the dose used, using the illustration like that in the study report (see Figure 10 and Table 8 in this review).

2.3 General Dosage and Administration Information

This reviewer suggests that the claim of (b) (4) is not substantiated. The cited reference, Roggenkämper, et al, 2006, is a published report of Trial 003 reviewed above in Section 5.5.3 of this review.

Dose and exposure data suggests a maximum dose of 35 units NT 201 per eye.

2.3.2 Administration

No data was submitted to support the statement that (b) (4) I am concerned that employing this strategy in blepharospasm would likely lead to more unintended treatment emergent adverse effect because of the small size of the targeted muscles.

5 Warnings and Precautions

In 5.2, consider changing [REDACTED] (b) (4) to narrow angle glaucoma or other more common term.

5.3.5 Immunogenicity

(b) (4)

14 Clinical Studies

The statements about [REDACTED] (b) (4) are unsubstantiated.

In 14.2, the legend for Table 4 describes muscle sites but the table lists periorbital regions. Again an illustration may serve to clarify.

The change from baseline in JRS-S in the NT 201 group was -0.84. To describe the difference in Section 14.2 as -1.0 which is the combined change of the improvement in active treatment arm plus the decline in the placebo group is a bit of sophistry that may not be exactly accurate. I suspect it is written this way because the literature suggests that a change of one point in the JRS-S was the prespecified margin for a clinically significant difference.

9.3 Advisory Committee Meeting

No advisory committee consideration was sought for this application.

9.4 Dataset Requests to Sponsor

The datasets from the confirmatory blepharospasm trial and its open label follow-up extension trial were uninterpretable as submitted. The datasets originally submitted electronically to the eCTD did not adhere to a standard structure i.e.: they were neither CDISC SDTM nor ADaM compliant and they lacked a XML backbone or a useable key to interpretation of the variable domains. For this reason a request for restructuring of the eCTD analysis datasets were made at the time of acceptance of the submission for filing. This request (which follows) was answered promptly and satisfactorily allowing the review to proceed.

To the Sponsor: Trial MRZ 60201- 0433 (Blepharospasm) dataset request

This is a request for datasets to be provided in a particular structure that will make review efficient and timely. Please create the files, and the variables in them, using the names supplied in the tables below.

The requested dataset files that describe demographics for the double blind and open label portions of the trial (named **DMDB.xpt** and **DMOLEX.xpt**, respectively) are typical SDTM format with one row per subject. The datasets that describe adverse events for the double blind and open label portions of the trial (named **AEDB.xpt** and **AEOLEX.xpt**, respectively) are typical SDTM format with one row per AE. Most of the key variable names in these tables will also appear familiar to users of SDTM.

The other requested datasets provide a particular structure for the outcome variables of interest in the double blind and open label portion of the trial. Note that it is one line per subject with all visits for that subject occupying the same row. In the open label datasets, depending upon how many additional Xeomin treatments the subject received in that extension period, not all cells will be filled.

Provide days, dates, units, etc in a format that may be used for calculation in SAS. The same format should be used in all the requested tables. For each of the 13 requested files, provide a definition table indicating from which of your eCTD datasets each variable's data was taken including the source filename and source variable name. Provide this in .xml format.

A. In a file named **DMDB.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of this trial. In this file, there should be just 1 row for each subject.

STUDYID	602_0433/1
USUBJID	A unique identifier for each patient in this trial. The identifier should be the same for each patient in both the double blind and open label portions of the trial. We ask that it be used in all datasets we request (at this time and in future requests).
SITE	Site number
INVNAME	Principal investigator's last name
AGE	Age in years
GENDER	Gender (M or F)
ARM	NT201 or PCB
ITTOPP	Patient is in ITT Population (Y/N)

NAIVE	Received other BoNT within 1 year of enrollment in 4033 (Y/N)

B. In a file named **DMOLEX.xpt**, create a dataset which includes the following variables for all patients in the open label extension portion of this trial. In this file, there should be just 1 row for each subject.

STUDYID	602_0433/2
USUBJID	A unique identifier for each patient in this trial. The identifier should be the same for each patient in both the double blind and open label portions of the trial. We ask that it be used in all datasets we request (at this time and in future requests).
SITE	Site number
INVNAME	Principal investigator's last name
AGE	Age in years
GENDER	Gender (M or F)

C. In a file named **AEDB.xpt**, create a dataset which includes the following variables for all patients in only the double blind portion of the trial: The table should appear that for a given patient (USUBJID) each AE has a unique sequence number (AESEQ); one AE per row.

STUDYID	602_0433/1
USUBJID	Unique patient identifier
AESEQ	Number each AE consecutively for each patient
ARM	NT201 or PCB
AETERM	Verbatim description of AE
AEDECOD	Preferred Term
AEBODSYS	SOC
AESEV	AE severity (mild/moderate/severe)
AEOUT	Resolved (Y/N)
DISCONT	Patient discontinued from trial (Y/N) due to AE
LATENCY	Number of days after injection that AE began
DURATION	Duration of AE (in days)
AESER	AE seriousness criteria

D. Create a file named **AEOLEX.xpt** which includes the following variables for all patients in only the open label blind portion of the trial. The table should appear that for a given patient (USUBJID) each AE has a unique sequence number (AESEQ); one AE per row.

STUDYID	602_0433/2
USUBJID	Unique patient identifier
AESEQ	Number each AE consecutively for each patient
AETERM	Verbatim description of AE
AEDECOD	Preferred Term
AEBODSYS	SOC
AESEV	AE severity (mild/moderate/severe)
AEOUT	Resolved (Y/N)
DISCONT	Patient discontinued from trial (Y/N)
LASTINJ	Date of the open label injection after which AE began
RTEYE	Units of NT201 injected around RIGHT eye at this injection session
LEFTEYE	Units of NT201 injected around LEFT eye at this injection session
BOTHEYES	Units of NT201 injected around BOTH eyes at this injection session
LATENCY	Number of days after injection that AE began
DURATION	Duration of AE in days
AESER	AE seriousness criteria

E. In a file named **DBJRSSEV.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602_0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTPOP	Patient is in ITT Population (Y/N)

RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
JRSS2	JRS Severity score at baseline (Visit 2)
DATEV3	Date of Visit 3
JRSS3	JRS Severity score at Visit 3
DATEV4	Date of Visit 4
JRSS4	JRS Severity score at Visit 4
DATEV5	Date of Visit 5
JRSS5	JRS Severity score at Visit 5
JRSSDIFF	JRS Severity change from baseline to Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5

F. In a file named **DBJRSFRQ.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602_0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTPOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
JRSF2	JRS Frequency Score at baseline (Visit 2)
DATEV3	Date of Visit 3
JRSF3	JRS Frequency Score at Visit 3
DATEV4	Date of Visit 4

JRSF4	JRS Frequency Score at Visit 4
DATEV5	Date of Visit 5
JRSF5	JRS Frequency Score at Visit 5
JRSFDIFF	JRS Frequency change from baseline to Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5

G. In a file named **DBJRSBDI.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602_0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
BDI2	BDI baseline score at Visit 2
DATEV3	Date of Visit 3
BDI3	BDI score at Visit 3
DATEV4	Date of Visit 4
BDI4	BDI score at Visit 4
DATEV5	Date of Visit 5
BDI5	BDI score at Visit 5
BDIDIFF	BDI change from baseline to Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5

H. In a file named **DBJRSCGI.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602_0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
DATEV3	Date of Visit 3
PNEED3	Patient feels need for injection at Visit 3 (Y/N)
INEED3	Investigator feels need for injection at Visit 3 (Y/N)
V2V3INT	Number of days between Visit 2 injection and Visit 3
DATEV4	Date of Visit 4
PNEED4	Patient feels need for injection at Visit 4 (Y/N)
INEED4	Investigator feels need for injection at Visit 4 (Y/N)
V2V4INT	Number of days between Visit 2 injection and Visit 4
V2INJINT	Number of days between Visit 2 and follow-up injection, if performed
DATEV5	Date of Visit 5
PNEED5	Patient feels need for injection at Visit 5
INEED5	Investigator feels need for injection at Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5
PEGR5	PEGR at Visit 5
IGAE5	Investigator global assessment of efficacy (1-4) at Visit 5
IGAT5	Investigator global assessment of tolerability (1-4) at Visit 5

I. In a file named **OLBONT.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602_0433/2

USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
RTEYE1	Number of units of NT201 injected around RIGHT eye 1st open label injection
LEFTEYE1	Number of units of NT201 injected around LEFT eye 1st open label injection
BOTHEYE1	Number of units of NT201 injected around BOTH eyes 1st open label injection
V6V7INT	Days from 1st open label injection session until Control Visit (Visit7)
V6V8INT	Days from 1st open label injection session until Visit 8
V8DATEOL	Date of 2nd open label injection session (Visit 8)
RTEYE2	Number of units of NT201 injected around RIGHT eye 2nd open label injection session
LEFTEYE2	Number of units of NT201 injected around LEFT eye 2nd open label injection session
BOTHEYE2	Number of units of NT201 injected around BOTH eyes 2nd open label injection session
V8V9INT	Days from 2nd open label injection session until Control Visit (Visit 9)
V8V10INT	Days from 2nd open label injection session until Visit 10
V10DATE	Date of 3rd open label injection session (Visit 10)
RTEYE3	Number of units of NT201 injected around RIGHT eye 3rd open label injection session
LEFTEYE3	Number of units of NT201 injected around LEFT eye 3rd open label injection session
BOTHEYE3	Number of units of NT201 injected around BOTH eyes 3rd open label injection session
V10V11NT	Days from 3rd open label injection session until Control Visit (Visit 11)
V10V12NT	Days from 3rd open label injection session until Visit 12
V12DATE	Date of 4th open label injection session (Visit 12)
RTEYE4	Number of units of NT201 injected around RIGHT eye 4th open label injection session
LEFTEYE4	Number of units of NT201 injected around LEFT eye 4th open label injection session

BOTHEYE4	Number of units of NT201 injected around BOTH eyes 4th open label injection session
V12V13NT	Days from 4th open label injection session until Control Visit (Visit 13)
V12V14NT	Days from 4th open label injection session until Visit 14
V14DATE	Date of 5th open label injection session (Visit 14)
RTEYE5	Number of units of NT201 injected around RIGHT eye 5th open label injection session
LEFTEYE5	Number of units of NT201 injected around LEFT eye 5th open label injection session
BOTHEYE5	Number of units of NT201 injected around BOTH eyes 5th open label injection session
V14V15NT	Days from 5th open label injection session until Control Visit (Visit 15)
V16DATE	Date of termination visit (Visit 16)
V14V16NT	Days from 5th open label injection session until Termination Visit (Visit 16)
V6V16NT	Days from 1st open label injection session until Termination Visit (Visit 16)

In a file named **OLJRSSEV.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602_0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
JRSS1	JRS Severity score at 1st open label injection session
V7DATEOL	Date of 1st open label injection session Control Visit (Visit7)
JRSS1C	JRS Severity score at 1st open label injection session Control Visit
V8DATEOL	Date of 2nd open label injection session (Visit 8)
JRSS2	JRS Severity score at 2nd open label injection session
V9DATEOL	Date of 2nd open label injection session Control Visit (Visit 9)
JRSS2C	JRS Severity score at 2nd open label injection session Control Visit

V10DATE	Date of 3rd open label injection session (Visit 10)
JRSS3	JRS Severity score at 3rd open label injection session
V11DATE	Date of 3rd open label injection session Control Visit (Visit 11)
JRSS3C	JRS Severity score at 3rd open label injection session Control Visit
V12DATE	Date of 4th open label injection session (Visit 12)
JRSS4	JRS Severity score at 4th open label injection session
V13DATE	Date of 4th open label injection session Control Visit (Visit 13)
JRSS4C	JRS Severity score at 4th open label injection session Control Visit
V14DATE	Date of 5th open label injection session (Visit 14)
JRSS5	JRS Severity score at 5th open label injection session
V15DATE	Date of 5th open label injection session Control Visit (Visit 15)
JRSS5C	JRS Severity score at 5th open label injection session Control Visit
TERMDATE	Date of termination visit (Visit 16)
JRSS6	JRS Severity score at termination visit

K. In a file named **OLJRSFRQ.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602_0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
JRSF1	JRS Frequency Score at 1st open label injection session
V7DATEOL	Date of 1st open label injection session Control Visit (Visit7)
JRSF1C	JRS Frequency Score at 1st open label injection session Control Visit
V8DATEOL	Date of 2nd open label injection session (Visit 8)
JRSF2	JRS Frequency Score at 2nd open label injection session
V9DATEOL	Date of 2nd open label injection session Control Visit (Visit 9)
JRSF2C	JRS Frequency Score at 2nd open label injection session

	Control Visit
V10DATE	Date of 3rd open label injection session (Visit 10)
JRSF3	JRS Frequency Score at 3rd open label injection session
V11DATE	Date of 3rd open label injection session Control Visit (Visit 11)
JRSF3C	JRS Frequency Score at 3rd open label injection session Control Visit
V12DATE	Date of 4th open label injection session (Visit 12)
JRSF4	JRS Frequency Score at 4th open label injection session
V13DATE	Date of 4th open label injection session Control Visit (Visit 13)
JRSF4C	JRS Frequency Score at 4th open label injection session Control Visit
V14DATE	Date of 5th open label injection session (Visit 14)
JRSF5	JRS Frequency Score at 5th open label injection session
V15DATE	Date of 5th open label injection session Control Visit (Visit 15)
JRSF5C	JRS Frequency Score at 5th open label injection session Control Visit
TERMDATE	Date of termination visit (Visit 16)
JRSF6	JRS Frequency Score at termination visit

L. In a file named **OLBDI.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602_0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
BDI1	BDI score at 1st open label injection session
V7DATEOL	Date of 1st open label injection session Control Visit (Visit7)
BDI1C	BDI score at 1st open label injection session Control Visit
V8DATEOL	Date of 2nd open label injection session (Visit 8)
BDI2	BDI score at 2nd open label injection session
V9DATEOL	Date of 2nd open label injection session Control Visit (Visit 9)

BDI2C	BDI score at 2nd open label injection session Control Visit
V10DATE	Date of 3rd open label injection session (Visit 10)
BDI3	BDI score at 3rd open label injection session
V11DATE	Date of 3rd open label injection session Control Visit (Visit 11)
BDI3C	BDI score at 3rd open label injection session Control Visit
V12DATE	Date of 4th open label injection session (Visit 12)
BDI4	BDI score at 4th open label injection session
V13DATE	Date of 4th open label injection session Control Visit (Visit 13)
BDI4C	BDI score at 4th open label injection session Control Visit
V14DATE	Date of 5th open label injection session (Visit 14)
BDI5	BDI score at 5th open label injection session
V15DATE	Date of 5th open label injection session Control Visit (Visit 15)
BDI5C	BDI score at 5th open label injection session Control Visit
TERMDATE	Date of termination visit (Visit 16)
BDI6	BDI score at termination visit

M. In a file named **OLCGI.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602_0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
PEGROL2	PEGR at 2nd open label injection session
PEGROL3	PEGR at 3rd open label injection session
PEGROL4	PEGR at 4th open label injection session
PEGROL5	PEGR at 5th open label injection session
PEGROLT	PEGR at termination visit
IGAEOL2	Investigator global assessment of efficacy (1-4) at 2nd open label injection session

IGAEOL3	Investigator global assessment of efficacy (1-4) at 3rd open label injection session
IGAEOL4	Investigator global assessment of efficacy (1-4) at 4th open label injection session
IGAEOL5	Investigator global assessment of efficacy (1-4) at 5th open label injection session
IGATOL2	Investigator global assessment of tolerability (1-4) at 2nd open label injection session
IGATOL3	Investigator global assessment of tolerability (1-4) at 3rd open label injection session
IGATOL4	Investigator global assessment of tolerability (1-4) at 4th open label injection session
IGATOL5	Investigator global assessment of tolerability (1-4) at 5th open label injection session

Addendum to:

5.3.1 Confirmatory trial of NT 201 for the treatment of blepharospasm (MRZ 60201-0433/1)

Efficacy Results (on page 47)

Calculation for the outcome for the primary efficacy outcome:

Using the LOCF method for replacement of missing values, the mean (SD) change in the JRS Severity subscore from the Baseline Visit to Visit 4 (Week 6) in the ITT population was -0.83 (1.18) points in the NT 201 group and 0.21 (0.91) points in the Placebo group. JRS Severity subscore values decreased in the NT 201 group from 3.12 points at baseline to 2.29 points at Visit 4 and increased in the Placebo group from 2.94 points to 3.15 points. Adjusted treatment difference: 1.0 (95% CI= [-1.4; 0.5]), p<0.001 for simple model with no covariates beyond baseline JRSS score.

Using the LOCF model in IT population with additional covariates, as shown in **the Sponsor's table below**, the p values for the model are:

Model[b]	Variables	p-Value	LS-Mean (SE) (95% CI)		LS-Mean Treatment Difference (95% CI)
			NT 201	Placebo	
Full Model	Treatment	<0.001	-0.8 (0.13) (-1.0, -0.5)	0.2 (0.18) (-0.1, 0.6)	-1.0 (-1.4, -0.5)
	Gender	0.059			
	Age	0.123			
	Dose Group	0.698			
	Baseline JRS Severity Subscore	0.006			
	Pooled Center	0.061			
Final Model	Treatment	<0.001	-0.8 (0.12) (-1.0, -0.5)	0.2 (0.18) (-0.1, 0.6)	-1.0 (-1.4, -0.6)
	Gender	0.057			
	Age	0.108			
	Baseline JRS Severity Subscore	0.005			
	Pooled Center	0.055			

This demonstrates the effectiveness of NT 201 in blepharospasm for the primary outcome variable using the model prespecified in the Sponsor's statistical analysis plan.

Addendum to:

5.3.3 Supportive trial of NT 201 compared to BOTOX® in blepharospasm (MRZ 60201-0003)

Efficacy Results (on page 90)

Calculation for the outcome of the primary efficacy outcome and its relationship to the prespecified non-inferiority margin:

As noted above in the statistical analysis plan, the non-inferiority margin was defined (after Amendment 1) as irrelevant difference $\Delta = 0.8$ points with $\alpha = 0.025$ (1 sided) and with $1 - \beta = 0.85$.

As is evident in the Sponsor's Table 11 below, the change in JRS sum score from baseline in the two treatment arms have substantially overlapping confidence intervals and fall within the parameters set by the sponsor. Failing to achieve a significant difference between the arms allows rejection of the null hypothesis that the two responses are different and fulfills the prespecified non-inferiority conditions.

The change in the JRS sum score at the control visit was entered as the dependent variable in an analysis of covariance, with JRS sum score at baseline, treatment group, total dose, sex, age, number of injections since diagnosis of blepharospasm, pooled country, and treatment*pooled country as the independent variables. The results from the full ANCOVA model are presented in the Sponsor's Test Table 11 below:

Text Table 11 Full ANCOVA Model of the Change from Baseline in JRS Sum Score to the Control Visit (TPP)

Treatment	LSMean	95% Confidence Interval		p-value
		Lower Limit	Upper Limit	
NT 201	-2.779725	-3.208636	-2.350814	<0.0001
BTXCo	-2.528504	-2.963093	-2.093915	<0.0001
NT 201-BTXCo	-0.251221	-0.719848	0.217407	0.2920

Data source: Table 14.2.1.1.3.1

The final ANCOVA model (Sponsor's Text Table 12, below) included only those variables having an influence on the primary efficacy variable of $p < 0.2$. These covariates were: baseline mean JRS sum score (F value=27.66, $p < 0.0001$), pooled country (F value=3.62, $p = 0.007$), and dose (F value=6.81, $p = 0.01$). From this model, the least squares mean decrease in the JRS sum score from baseline was -2.90 in the NT 201 group and -2.67 in the BOTOX group. Both values represent a significant change from mean baseline values ($p < 0.0001$), indicating

that the two treatments effectively improved blepharospasm symptoms as assessed by the JRS, while still fulfilling the non-inferiority margin.

Text Table 12 Final ANCOVA Model of the Change from Baseline in JRS Sum Score to the Control Visit (TPP)

Treatment	LSMean	95% Confidence Interval		p-value
		Lower Limit	Upper Limit	
NT 201	-2.902866	-3.223365	-2.582368	<0.0001
BTXCo	-2.670338	-2.993025	-2.347651	<0.0001
NT 201-BTXCo	-0.232528	-0.684247	0.219191	0.3116

Data source: Table 14.2.1.1.3.2

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

BLA: 1235360 and 125360 (Supplement 1)
Drug: Botulinum Toxin (Xeomin)
Indication: Cervical Dystonia and Blepharospasm
Sponsor: Merz
Submission Date: 7/2/09
Review Date: 7/2/10
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Neurology Drug Products, HFD-120

1. Background

Xeomin (NT 201; incobotulinumtoxinA) is a purified formulation of Botulinum neurotoxin Type A that according to the sponsor is free from complexing proteins. According to the sponsor, (b) (4) is the active substance in NT 201. NT 201 includes the excipients sucrose and albumin (b) (4) respectively, according to the Sponsor. The mechanism of action is thought to be due to blockade of acetylcholine release at cholinergic nerve terminals. The original BLA for Xeomin was submitted for (b) (4) indications: cervical dystonia, blepharospasm, (b) (4)

However, the safety review includes the safety data from the spasticity (b) (4). Clinical studies conducted to evaluate the use of Xeomin to treat glabellar frown lines and crow's feet contribute to the safety review.

FDA and the sponsor developed a list of Adverse Events of Special Interest (AESIs) based on adverse events observed with previously developed botulinum toxin products, and these were a focus of the safety review. These included AEs such as dysphagia, speech problems, facial weakness, general body weakness, and dyspnea or other respiratory problems associated with spread of toxin effect.

This memorandum primarily summarizes the findings of Dr. Lisa Jones' primary safety review of the Xeomin BLA. Please refer to Dr. Jones' review for more detail.

2. Summary of Findings from the Safety Review

2.1 Sources of Data

The clinical data evaluated in the safety review are from studies submitted as part of the BLA, and include studies in patients treated for cervical dystonia (CD), benign essential blepharospasm (BEB), and spasticity (SP) that were included in

Safety Team Leader Memo
BLA 125360

the Sponsor's pooled database, as well as glabellar frown lines (GFL), and crow's feet (CF). Dr. Jones includes analyses of pooled studies in order to adequately capture all deaths and serious adverse events (SAEs) and to increase the number of patients for subgroup analyses. However, due to limitations of pooling, she has also considered the safety populations for cervical dystonia, blepharospasm, and spasticity separately. There were 6 placebo-controlled trials included in the ISS as well as 3 active control studies using Botox as the active control and there was also 1 controlled study with different dilutions of NT201 that contributed to the pooled safety database. In addition, Studies 0520/1 and 0527 were placebo controlled studies in Glabellar Frown Lines, (GFL) and Study 0617 was a placebo controlled study in Crow's feet (CF) that Dr. Jones reviewed for deaths and SAEs. Dr. Jones has also considered the postmarketing experience in her review. The placebo and active controlled studies in BEB, CD and SP are shown below, as extracted from Dr. Jones' review.

BENIGN ESSENTIAL BLEPHAROSPAM				
PHASE 2				
Study Name	Treatment Groups	Study Description	Dosing/ Length of Study	Purpose/ Location
0703	NT 201: 8	Phase 2, Open-label, Single-arm Trial	Up to 100 U IM (up to 50 U per eye) for up to 8 injections within 70 weeks	Discontinued "due to slow enrollment"
PHASE 3				
Study Name	Treatment Groups	Study Description	Dosing/ Length of Study	Purpose/ Location
0433/1 Main Period	NT 201: 74 Placebo: 34	Phase 3, prospective, double-blind, randomized, placebo-controlled, multicenter study	One IM injection (up to 50 U per eye) with follow-up for up to 20 weeks.	Efficacy and safety of NT 201 compared with placebo in pre-treated subjects with BEB Location: North America
0433/2 OLEX Period	NT 201: 102	Open-label, Extension Study	Up to 5 IM injections (up to 50 U per eye) at least 6 weeks apart over 48 weeks, with 20 weeks of follow-up	Assessed longer term safety and efficacy Location: North America
0003	NT 201: 148 Botox: 152	Phase 3, double-blind, randomized, active-controlled, multicenter, non-inferiority study comparing NT 201 and Botox ®	One IM injection (≤ 35 U per eye NT 201 ≤ 35 U per eye BOTOX®) at baseline with follow-up for up to 16 weeks	Subjects with BEB, successfully pretreated with Botox on a stable dose Location: Multiple European countries and Israel

CERVICAL DYSTONIA				
PHASE 2				
Study Name	Treatment Groups	Study Description/ Location	Dosing/ Length of Study	Site of Administration
9801	NT 201 10/20: 14 NT 201 20/40: 13 NT 201 30/60: 14 BOTOX 30/60: 12	Open-Label, Randomized, Active-Controlled Trial in Location: Germany	Single dose with 14 days follow-up, re-injection with 106 days of follow-up	Splenius capitis (SPL); sternocleidomastoid (SCM)

Safety Team Leader Memo
BLA 125360

PHASE 3				
Study Name	Treatment Groups	Study Description	Dosing/ Length of Study	Site of Administration
0408/1 Main Period	NT 201 120 U: 78 NT 201 240 U: 81 Placebo: 74	Phase 3 Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Trial Location: United States	Single dose with 8 to 20 weeks of follow-up Dose range: 120 or 240 U	Splenius capitis/semispinalis; trapezius; sternocleidomastoid; levator scapulae; scalene; other spinal/semispinal muscles; suboccipital triangle; platysma/other
0408/2 Extension Period	NT 201: 217	Phase 3 Open-Label Extension Study Location: United States	Up to 5 injections at least 6 weeks apart over 48 weeks, with 20 weeks of follow-up Dose range: 120 or 240 U	Splenius capitis/semispinalis; trapezius; sternocleidomastoid; levator scapulae; scalene; other spinal/semispinal muscles; suboccipital triangle; platysma/other
0013	NT 201: 231 BOTOX: 232	Phase 3 Double-Blind, Randomized, Active-Controlled Trial Location: Europe and Israel	Single dose with up to 16 weeks follow-up Dose range: 70 to 300 U IM	Splenius capitis/semispinalis; trapezius; levator scapulae; sternocleidomastoid; scalenus; other muscles in the neck region
0605/1 Main Period	NT 201: 76	Phase "4" Main Period: Open-label, Single-arm Trial Location: Germany	Main Period: 1 injection with 4 weeks of follow-up Dose range: Up to 300 U	Sternocleidomastoid; levator scapulae; scalenus; splenius capitis; trapezius
0605/2 OLEX Period	NT 201: 76	Ongoing Extension: Study Location: Germany	OLEX Period: Up to 5 additional injections over up to 121 weeks Dose range: Up to 300 U	Sternocleidomastoid; levator scapulae; scalenus; splenius capitis; trapezius

SPASTICITY				
PHASE 2				
Study Name	Treatment Groups/ Location	Study Description	Dosing/ Length of Study	Site of Administration
(b)	NT 201: 8 Placebo: 6 Location: Germany	Phase 2 Double-blind, Randomized, Placebo -controlled Pilot Trial. Discontinued	Single injection with 84 day follow-up Dose Range: Up to 400 U IM	Upper limb
(b)	NT 201: 6 Placebo: 4 Location: Germany	Phase 2, placebo-controlled pilot Trial. Discontinued	Up to 4 injection cycles in 48 weeks Dose Range: Up to 300 U IM	Wrist and elbow flexors
PHASE 3				
Study Name	Treatment Groups	Study Description	Dosing	Site of Administration
0607	NT 201 20 U/mL: 97 NT 201 50 U/mL: 95 Location: Europe	Phase 3, Observer-Blind, Randomized, Active-controlled, Parallel-group Trial	Single dose with 12 to 20 weeks follow-up Dose Range: Up to 400 U, at either 20 U/mL or 50 U/mL	Upper limb

Safety Team Leader Memo
BLA 125360

0410/1 Main	NT 201: 73 Placebo: 75 Location: Poland, Hungary Czech. Rep.	Phase 3 Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Trial	Single dose with 12 to 20 weeks of follow-up Dose Range: Up to 400 U	Upper limb
0410/2 OLEX	NT 201: 145 Location: Poland, Hungary, Czech. Rep.	Phase 3 Open-label, Single-arm Extension Period Completed	Up to 5 injs. at least 12 weeks apart over up to 48 weeks, with up to 21 weeks of follow-up Dose Range: 170 to 400 U IM	Upper limb

NT201 is approved in Argentina, Canada, Mexico, Uruguay, and several European countries for the indications of blepharospasm and cervical dystonia, in Canada for post-stroke upper limb spasticity, and in Argentina also for a variety of indications including strabismus and temporary improvement of glabellar frown lines.

Exposure - ICH guidelines recommend that 1500 patients should be treated overall in a drug development program, 300-600 for 6 months, and 100 for at least 1 year at the dose or dose range believed to be efficacious. During the pre-BLA period, FDA discussed appropriate exposure guidelines with Merz (b) (4)

For BEB and for CD, there were no explicit guidelines for exposure stated in pre-BLA minutes, although it was stated that 85 patients with cervical dystonia will have been treated for one year at 240 units. In total, 1313 subjects received NT201 in the pooled studies. This included 431 for CD and 222 for BEB, as well as the subjects exposed at the higher doses given for spasticity.

For BEB, the proposed initial dose is up to (b) (4) per eye, and the recommended total Xeomin dose is up to (b) (4)/eye. In Study 003 (n=148), the dose was a single IM injection of ≤ 35 U per eye. In study 0433/1 (Main period) patients received a single dose of up to 50 U per eye and in 0433/2 (OLEX) patients received up to 5 IM injections of up to 50 U per eye at least 6 weeks apart over 48 weeks. In 0433 (n=106 for Main period and OLEX), 54 patients received 5 or 6 injections over 24 to 48 weeks, according to Table 11 in Dr Jones' review. While the total exposures may give an indication of overall safety, particularly

when including higher doses used in spasticity, I note that for specific doses in blepharospasm there were few patients with long-term exposure to a doses of 50 U/eye (100 U for both eyes total) for blepharospasm. As extracted from Dr.

NT 201 cumulative dose exposure at 24 and 48 weeks					
Total dose NT201 (both eyes)	Considered supportive of this dose level	24 Weeks		48 Weeks	
		N	Cumulative N at or exceeding this dose level	N	Cumulative N at or exceeding this dose level
100 Units	100 Units	15	15	13	13
90 - 99 Units	90 Units	5	20	4	17
80 - 89 Units	80 Units	11	31	5	22
70 - 79 Units	70 Units	14	45	12	34
60 - 69 Units	60 Units	16	61	14	48
50 - 59 Units	50 Units	17	78	18	66
40 - 49 Units	40 Units	8	86	8	74
30 -39 Units	30 Units	3	89	3	77
29 Units or less	20 Units	3	92	3	80

Jones' review (and prepared by Dr. Bergman), the following table shows the small database with cumulative exposures over 24 and 48 weeks to Xeomin doses greater than 50-70 U.

In a 6/17/10 response to an FDA information request, the Sponsor has also performed this analysis for the data from the combined NDA filing and 120 day safety update. Excluding subjects with dosing intervals greater than 12 weeks, the Sponsor reports that only 2 subjects had 4 or more doses of 75 to $\leq$ 99 U of Xeomin over 48 weeks and 4 subjects had 4 or more doses of 50 to $\leq$ 74 U of Xeomin over 48 weeks. In fact, the largest exposure in blepharospasm was for subjects who had 3 or more injections of 50 to $\leq$ 74 Units every 12 weeks or less (n=22) with an additional 12 who had 3 or more injections of 1 to $\leq$ 49 Units every 12 weeks or less over 24 weeks. Thus, the exposure data for doses greater than 50 or 70 units is sparse.

For CD the proposed initial dose is 120 (b) (4) U. For previously treated patients with CD, (b) (4) The proposed recommended maximum dose is (b) (4) In a May 27, 2010 response to an information request, the Sponsor reported that at the time of NDA submission 91 subjects had received a dose of $\geq$ 240 U. This included data from single dose study 0013 and 0408/1 that had single doses of $\geq$ 240 U. The Sponsor provided the following information regarding total exposure to specific doses at specific visits in the combined NDA and 120 day safety update.

Table 3: Combined NDA and 120 day Safety Update

Dose	Combined NDA and 120 day safety update					
	1 st injection	2 nd injection	3 rd injection	4 th injection	5 th injection	6 th injection
<120	3	2	3	1	0	0
≥120 to <240	78	75	62	54	38	21
≥240	85	71	63	55	45	22
Total N	166	148	128	110	83	43

I have examined the analysis dataset OLEFCD.xpt from 0408/2 and have found that 71 total subjects had a dose of 240 U, the maximum dose in that study. Of those, 38 subjects had 4 or 5 doses of 240 U, confirming the results in the Sponsor's table, above. The Sponsor's 6/17/10 response to the FDA's information request regarding exposure shows that 8 subjects had 4 or more injections (every 12 weeks or less) of 240 U or more over 48 weeks, and 4 subjects had 4 or more injections of 120 to ≤ 239 U (every 12 weeks or less) over 48 weeks. The largest experience for injections every 12 weeks or less was for subjects who had 3 or more injections over 6 months (n=36 for doses of 240 U or more, and n=31 for doses of 120 to ≤ 239 U).

Capture of Adverse Events - Dr. Jones has evaluated the methods used to elicit adverse events and finds that they were adequate but not ideal. The majority of studies, with the exception of BEB study 0433, appeared not to have used checklists to ask specifically about known adverse events associated with botulinum toxin. She is concerned that some patients may not mention certain adverse events associated with botulinum toxin to investigators believing that because this is already a known event it does not need to be tracked further. I agree with Dr. Jones' recommendation to use checklists to more adequately capture adverse events in future studies.

2.3 Significant Safety Findings

2.3.1 Deaths

Dr. Jones notes that there were 6 deaths in the Xeomin development program for all indications. Two were in placebo treated patients (1 in whom the cause of death was myocardial infarction and 1 in whom the cause of death was intracranial hematoma), 1 was in a Botox-treated patient who died of metastatic colon cancer diagnosed within months of entering the study, and 3 were in patients treated with NT 201. The deaths in patients on NT 201 all occurred in the spasticity studies during the OLEX period and are described as follows.

Subject 1054 was a 72 y.o. male with a history of multiple cardiovascular risk factors (CAD, hypertension, prior aortic aneurysm, former smoker), with a history of CVA prior to the study and a second CVA 1 week prior to death, who died in his sleep 136 days after the last dose of NT 201; there was no autopsy. I agree with Dr. Jones given the patient's past medical history, recent CVA, and the

event occurring approximately 19 weeks after the last dose of NT 201 (outside of the expected duration of effect of NT201), it seems unlikely related to NT201.

Subject 1058 was a 67 y.o. male who died as a consequence of a “severe cardiac arrest” 44 days after an injection of 400 U of NT 201. He had a past medical history significant for hypertension, CVA 2.5 years prior, and was a former smoker. Dr. Jones notes that laboratory and diagnostic tests were not done and an autopsy was not performed. I agree with Dr. Jones’ assessment that the cause of death is unknown.

Subject 1169 was a 71 y.o. male who died of a severe CVA (according to communication from the subject’s wife to the investigator) 21 days after his last dose of NT201. He had a history of prior CVA and hypertension and was a former smoker. There was no post-mortem examination.

I agree with Dr. Jones’ assessment that there does not appear to be a pattern clearly suggesting that the deaths were drug-related.

2.3.2 Nonfatal Serious Adverse Events

Overview of SAEs in the pooled safety population (including non-neurologic indications) – Dr. Jones notes that 2.9% (43/1476) of subjects who received NT 201 in the pooled and ongoing studies had a SAE compared to 5/356 (1.4%) of subjects who received placebo and 12/471 (2.5%) who received Botox. In the pooled studies, the System Organ Class (SOC) groupings with the most SAEs after exposure to NT 201 (n=1313) were Nervous system disorders (0.6%), Gastrointestinal disorders (0.5%) and Infections and Infestations (0.5%). Dr. Jones further considers the SAEs by indication as discussed below.

No subjects exposed to NT 201 experienced SAEs of hepatic failure, hepatitis, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, rhabdomyolysis, or aplastic anemia.

SAEs in BEB – There were no SAEs in the Phase 2 study 0703. There was only 1 SAE in the placebo controlled BEB trials, a case of dyspnea in a patient who received placebo. In the OLEX trial, there were 16 SAEs that included one case each of pancreatitis, dyspnea, convulsion, and bronchitis. No SAEs occurred in more than one patient. The case of dyspnea occurred in a 78 y.o. man in the setting of congestive heart failure 4 months after the last dose of NT 201. I agree with Dr. Jones that this does not appear to be a spread of toxin effect after administration of Xeomin. The SAE of convulsion (tonic-clonic seizure, followed by a grand mal seizure after arrival at the hospital) occurred in a 22 y.o. female (subject 2174) approximately 12 weeks following administration of 20 U NT 201; the subject was treated with Ativan and oxygen and was released from the hospital 2 days after the event. This event does not seem likely to be related to NT 201.

In BEB study 003, 3/148 subjects (2%) in the NT 201 study and 5/152 (3.3%) in the Botox group experienced SAEs. The 3 SAEs in the NT201 group were abdominal pain, enterocolitis, and hemorrhagic diverticulum. Dr. Jones notes that in placebo-controlled studies in all indications, there was only 1 gastrointestinal SAE.

SAEs in CD - In the Main Period of Study 408/1, 4 subjects in the NT 201 group (2.5%) experienced SAEs compared with no subject in the placebo group. These were appendicitis, asthma exacerbation, COPD exacerbation, and staphylococcal infection. The case of COPD exacerbation occurred in a 58 y.o. male (subject #1128) with concomitant diseases that included COPD/asthma treated with albuterol and with fluticasone/salmeterol inhalers, intermittent bronchitis, and Parkinson's disease. The subject received a single 240 U dose of NT 201 IM on 06-Mar-2007. On (b) (6), the subject presented to the ER complaining of progressive shortness of breath and cough over the previous 4 days, with occasional sputum production and one episode of blood-streaked sputum. The subject was hospitalized and treated with medications including IV Solu-Medrol, Levaquin, albuterol/Atrovent nebulizer, and Advair Discus. The event was considered resolved on (b) (6). It is difficult to know how Xeomin may have contributed to the event. Dyspnea has been reported in patients treated for cervical dystonia with Botox, Dysport, and Myobloc, according to the approved labeling for those drugs.

In the CD OLEX study 0408/2, Dr. Jones reports that 11 subjects experienced 16 SAEs. Dr. Jones notes that the SAEs generally occurred in only 1 patient and no pattern was apparent. She notes 1 case of respiratory failure that occurred following surgery for possible intra-abdominal bleeding, 6 weeks after the dose of NT 201. I agree with Dr. Jones that the event appeared related to the surgery, rather than the NT 201 administration. There were 2 cases of pancreatitis, one that occurred in the setting of calculi blockage of the gall bladder and common bile duct approximately 3 months after the dose of NT 201, and one that occurred approximately 1 month after the last dose of NT 201 in a patient with high alcohol consumption (12 cans of beer per day over the past 3 months). In the other CD studies, there were 30 SAEs in 23 subjects, 17 of whom had received NT 201 and 6 had received Botox.

Overall, in the CD studies, Dr. Jones notes that the SAEs which occurred in more than 1 patient were neoplasm (7 patients), myocardial infarction (2 patients¹), transient ischemic attacks/CVA (2 patients on Botox; 1 on NT 201 that was a 50

¹ Subject 1007 was a 66 y.o. male with a history of smoking; MI 25 days after last dose; occlusion of left coronary artery was diagnosed and stent was placed; other treatment included aspirin, bisoprolol, ramipril, simvastatin. Subject 1020 was a 65 y.o. male with a history of diabetes mellitus and hyperlipidemia; event occurred approximately 10 weeks after last dose. Dr. Jones noted 3 patients with myocardial infarction in her review. However, further discussion by email on 6/24/10 clarified that subject 1007 was counted twice in her review.

y.o. male with a history of hypertension, angina, diabetes, and depression, who had a concussion following a fall after mild positional vertigo) and pancreatitis (2 patients). Dr. Jones notes that with the exception of pancreatitis, these are generally prevalent events in the population.² Human carcinogenicity is discussed in section 2.3.13 of this memo.

SAEs in Spasticity – In the placebo controlled spasticity study 0410/1 Main period, 4/73 subjects (5.5%) in the NT 201 group and 1/75 (1.3%) subjects in the placebo group experienced SAEs. In the NT 201 group these included bronchitis chronic; cellulitis; epilepsy, paraparesis, status epilepticus; and hypertension, vertigo. Intracranial hematoma occurred in a placebo treated patient. In the OLEX period of 0410/2, 26/145 subjects (17.9%) experienced SAEs. This included 1 patient with inadequate control of diabetes mellitus 13 weeks after the last dose of NT 201 in a patient with a history of diabetes. There did not appear to be a pattern to the events in the OLEX period. In the other spasticity studies, a total of 17 subjects experienced a total of 23 SAEs. Dr. Jones finds that SAEs in the spasticity development program were typical of an older patient population with a history of a prior CVA (including myocardial infarction, CVA/TIA, and pulmonary issues). She notes 6 cases of “epilepsy” and one of “convulsion” among the spasticity SAEs. Dr. Jones notes that CVA can cause seizures. She confirmed that 3 of these 7 cases had a prior history of epilepsy or “epileptic aura” and 1 patient was diagnosed with epilepsy 3 months subsequent to the event; 1 patient had a seizure approximately 4 months after the last dose (and after recent discontinuation of clobazam); 2 patients had no prior history of epilepsy or seizure (1 in which the event occurred approximately 12 weeks after the last dose of NT 201 and 1 that occurred 7 days after the dose in the OLEX). Dr. Jones also reports no cases of epilepsy in CD or in controlled studies for BEB. She considers the epilepsy/seizures as likely not related to NT 201 treatment. I agree that it is difficult to attribute these events to NT 201. I note that the postmarketing section of the Botox label states, “New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established”.

SAEs – anaphylaxis - Dr. Jones notes that there has been 1 post-marketing report of anaphylaxis following Xeomin administration. This occurred within 3 to 5 minutes after injection of Xeomin 50 U for glabellar lines in a patient who had had 5 prior treatments with Botox. The symptoms were characterized by palpitations, faintness, and nausea lasting for 36 hours. There was no further information on treatment of this event.

In summary, the review of SAEs does not demonstrate a particular pattern in any indication or overall.

2.3.3 Dropouts and/or Discontinuations

² In the CD studies, NT 201-treated patients were 18-75 y.o. (mean 53 y.o.).

In the pooled controlled studies in the NT 201 development program, 6/1313 subjects (0.5%) in the NT 201 treatment group discontinued due to a treatment emergent adverse event (TEAE) compared with 1/396 (0.3%) Botox-treated subjects and 1/346 (0.3%) placebo-treated subjects. In the NT 201 group, these events included muscular weakness (2 subjects), dizziness, neck pain, musculoskeletal pain, nausea, and neoplasm (1 subject each) in the CD controlled studies and paraparesis and TIA (1 subject each) in the spasticity controlled studies according to Dr. Jones' review. The event leading to dropout in the placebo group was intracranial hematoma and the event in the Botox-treated patient was ankle fracture. According to Dr. Jones' review, there were no discontinuations due to adverse events in the BEB studies.

In placebo controlled CD study 0408/1 the 3 NT 201-treated subjects that withdrew due to a TEAE included 2 of the 72-treatment naïve subjects (2.8%) and 1 of the 87 pre-treated subjects (1.2%). Two subjects were in the 240 U group (2/81, 2.5%) and 1 was in the 120 U group (1/78, 1.3%).

In addition to the dropouts in the controlled studies for Spasticity, there were 7 NT 201-treated patients that discontinued OLEX study 0410/2 because of a TEAE. Two were due to death and have been previously discussed in this memo; the other 5 were injection site pain, dysphagia, CVA, hypokinesia, and colon cancer. Dr. Jones reviewed the narrative for the dysphagia event, and found it to be lacking in detail. Upon request, the sponsor provided more information on this subject on 6/8/10. The subject had a past medical history significant for ischemic cerebrovascular accident. He received a 310 U dose of NT201 on (b) (6) in the OLEX and experienced an episode of dysphagia 9 days later. The event resolved on an unknown date. On (b) (6), 1 day after the last injection with NT 201 (325 U) the subject developed a second TEAE of dysphagia, and the event resolved on an unspecified date. Study drug was withdrawn consequently.

I agree with Dr. Jones that there does not appear to be a pattern among the patients discontinuing due to adverse events.

No subjects taking NT 201 discontinued for hepatic failure, hepatitis, Stevens Johnson syndrome, toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, pancytopenia, or aplastic anemia, based on a search of the database by Dr Jones.

2.3.4 Significant Adverse Events

Adverse events of special interest identified prior to the submission of the BLA included spread of toxin effect, hyperglycemia, and elevation of alkaline phosphatase. Dr. Jones has reviewed these adverse events of interest. I will summarize her findings here. Please refer to her review for a more detailed discussion.

Spread of Toxin Effect – Events related to spread of toxin effect are referred to as adverse events of special interest (AESI) in Dr. Jones' review. The sponsor was requested to monitor for AESIs according to a list based on such events provided by FDA. In placebo-controlled studies, according to Dr. Jones' review, Merz reported that the overall incidence of AESIs in the NT 201 treatment group was higher than in the placebo group. At the PT level in the pooled indications, the only AESI that occurred with a greater incidence in the NT 201 group compared with placebo with a difference of $\geq 2\%$ was dysphagia (28/701 NT 201 subjects, 4% vs 5/346 placebo subjects, 1.5%).

In the BEB study 0433/1 Main period, 32/74 subjects (43.2%) in the NT 201 group and 9/34 (29.5%) in the placebo group experienced AESIs. In the NT 201 group, the most common were eyelid ptosis (18.9%), dry mouth (16.2%), vision blurred (5.4%), and dyspnea (5.4%). The doses for the cases of dry mouth ranged from 32.5 – 100 U and occurred within 2-4 weeks of administration. I agree with Dr. Jones that the time course of dry mouth suggests a causal association. The dyspnea occurred at doses of 50-90 U. Three occurred within 3 to 6 weeks, and 1 occurred approximately 13 weeks after the dose. In the placebo group the most common AESIs were eyelid ptosis (8.8%), vision blurred, dysphagia, and muscular weakness (each in 5.9%). Dr. Jones notes that the occurrence of eyelid ptosis in the placebo group suggests that this may be due to some extent to the injection or related to patient expectations. Dr. Jones states that with respect to the occurrence of AESIs, similar findings were observed when the OLEX data were combined with the 433/1 data.

In the Main period of 0408/1 in CD, the overall incidence of AESIs was 23.3% for NT 201 treated subjects (37/159) compared to 4.1% in placebo treated subjects (3/74). In pooled controlled CD studies, the results were similar (16% for NT 201 vs 4.1% in placebo treated subjects). For NT 201 treated subjects, the most common of these events were dysphagia (12.3%) and muscular weakness (4.2%). All other AESIs occurred in $< 1\%$ of NT 201 treated subjects. The Sponsor notes that the incidence of AESIs appears to decrease in NT 201 treated subjects with moderate to severe disease at baseline compared to those with mild disease, and hypothesizes that this is due to more hypertrophic muscles and larger tissue mass in the more severe disease, presenting a greater barrier to diffusion. Dr. Jones finds this a reasonable hypothesis, as do I. Of note, the Botox label states that "Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia", supporting this hypothesis. In addition, according to the sponsor, incidence of AESIs with NT 201 was higher in patients who were treatment naïve at baseline (in 0408/1 it was 23% for toxin-naïve patients vs 14% for pretreated patients according to table 3.5.10.2.1.1.1 in the ISS). The sponsor believes that this was most likely due to enrollment bias in that subjects with prior botulinum toxin experience enrolled in the study are those

with no adverse experience in previous treatment. I agree with Dr. Jones that this seems like a reasonable hypothesis.

In Spasticity Study 0410/1 Main period, 1/73 (1.4%) subjects in the NT 201 group reported AESIs (constipation and paraparesis) compared to 1/75 (1.3%) in the placebo group (dysphagia). However, when the controlled studies (0410/1 and 0607) were pooled, 6/257 (2.3%) subjects in the NT 201 treatment group had AESIs. For NT 201-treated subjects, the most common of these events was muscular weakness (3 subjects 1.1%). All other AESIs (dysphagia, constipation, dysarthria, and paraparesis) occurred in only 1 subject. In the 0410/2 OLEX Period, 9 subjects experienced AESIs (muscular weakness, hemiparesis, dysphagia, dry mouth).

The occurrence of dry mouth and dyspnea in the BEB program would appear to be due to spread of toxin effect beyond the immediate area of injection. There appears to be little evidence of spread in the CD program or in the spasticity program. I agree with Dr. Jones' assessment that the lack of a signal for systemic spread in the NT 201 development program should not be interpreted as a confirmation that systemic spread of toxin effect will not occur.

Hyperglycemia – Based on a small increase in glucose noted in the Dysport label, FDA requested that the sponsor perform an analysis of glucose within the NT 201 development program. Dr. Jones has reviewed the Sponsor's data and agrees with the Sponsor that in the pooled data, there was a slight increase of 1.1 (1.38 mmol/L) with NT 201 treatment to primary endpoint assessment in the > 360 U treatment group in Spasticity, but that this did not persist when change from baseline to final visit was analyzed, and that a larger increase was observed in the placebo group. In BEB, Dr. Jones finds that glucose levels over the course of the study and between NT 201 and placebo groups were "essentially equivalent". There were 2 patients who had a high "clinically significant" serum glucose value in 0433/1 Main Period and 0433/2 OLEX period. One patient (2011) who had no previous history of hyperglycemia or diabetes mellitus had glucose values at screening and before the second injection that were within normal limits (68-110 mg/dl), but had elevated levels of > 140 mg/dl before the 3rd and 5th injections and at the final visit. However, as any effect of NT201 would be expected to have worn off prior to the next injection, it does not seem that NT 201 would have contributed. Patient 2129 was noted to have hyperglycemia at screening with a serum glucose value of 126, and levels of 173 and 126 mg/dl before the 2nd injection and last observation visit, respectively. In CD there were no clinically important mean changes or shifts from baseline to final visit in NT 201-treated patients according to Dr. Jones. No clinically meaningful difference was seen when 0 408/1 and 0408/2 were analyzed together. There were 2 treatment-emergent cases of abnormal serum glucose, 1 with a high serum glucose value of 7.5 mmol/L (normal range 3.8 to 6.1 mmol/L) before injection 4, but within normal limits at screening and before the 5th injection, and 1 patient with a low serum glucose at the last study visit. In

Spasticity, 1 subject had an SAE of hyperglycemia 13 weeks after the last dose, as noted under the SAE section, and 6 subjects with normal serum glucose values at the first injection (5 of whom had a pre-existing history of diabetes) experienced abnormalities in serum glucose values while receiving NT 201. Overall, the mean glucose values compared from initial study visit to primary endpoint visit and final visit with the controlled trials for NT 201, placebo, and Botox were similar, according to Dr. Jones' review. Data to support a clear role for Xeomin in causing hyperglycemia is lacking.

Alkaline Phosphatase – The Sponsor was asked to perform a variety of analyses to assess alkaline phosphatase levels in the development program. Dr. Jones has reviewed the data for all indications and finds no trend toward an increase in alkaline phosphatase. However, she notes that testing was performed in the controlled trials at baseline and at the final visit, not at the primary endpoint visit. The analysis is not useful in evaluating effects on alkaline phosphatase.

2.3.5 Common Adverse Events

Overall, in the pooled, placebo controlled trials, 368/701 (52.5%) NT 201 treated patients and 140/346 (40.5%) placebo treated patients experienced treatment emergent adverse events. Among the most common adverse events ($\geq 2\%$ and greater than placebo) in the controlled trials were sinusitis (2% vs 1.5%), headache (10% vs 7%), neck pain (2.5% vs 0.9%), muscular weakness (2% vs 0.9%), dysphagia (4% vs 1.5%), dry mouth (2% vs 0.3%), eyelid ptosis (2% vs 0.9%), and dry eye (2% vs 1%), according to Section 7.4.1.2 of Dr. Jones' review (Sponsor table 5.3.5.3-15). These AEs are common within the botulinum toxin class in general. As Dr. Jones notes, a table of common adverse events is poorly suited to pooling indications because the AEs are indication specific to some extent.

In BEB, 41.4% of NT 201 treated patients, 70.3% of NT 201 treated patients in placebo-controlled studies, and 61.8% of placebo treated patients experienced TEAEs. After the first injection, 66% of patients in study 0433 Main experienced TEAEs. However, in the OLEX period, approximately 39-52% experienced TEAEs, with the largest percentage at Injection 3, and remaining relatively constant from Injection 4 through injection 6. The adverse events occurring in $\geq 3\%$ of NT 201 treated subjects and greater than placebo were eyelid ptosis, dry eye, dry mouth, diarrhea, headache, visual disturbance, dyspnea, nasopharyngitis, respiratory tract infection, vision impaired, asthenia, and asthenia. When compared by dose (placebo vs 10-40 U NT201 vs > 40 U NT 201), several adverse events in 0433/1 appeared to be dose related including eyelid ptosis, visual impairment, and diarrhea. The most common AEs in the open label studies were eyelid ptosis, dry eye, dry mouth, and visual disturbance.

In CD in the placebo controlled studies, the adverse events occurring in $\geq 3\%$ of NT 201 treated subjects and greater than placebo were neck pain, muscular weakness, musculoskeletal pain, and musculoskeletal stiffness, dysphagia,

nausea, and sinusitis. TEAEs in the extension period were similar to those in the MAIN period.

In the Spasticity placebo controlled study, the AEs in the NT 201 group with the largest increase compared to placebo treated patients were headache, epilepsy, and hyperglycemia. The 2 cases of epilepsy had a history of epilepsy prior to entering the study. In the OLEX study, the most frequent adverse events were muscle spasticity, depression, upper respiratory tract infection, and muscular weakness.

2.3.6 Laboratory findings

Chemistry and Hematology – I note that the placebo controlled studies in BEB and CD (0433/1 and 0408/1) did not measure laboratory parameters at the time of the primary endpoint, although the active control trials 0003 and 0013 and the placebo controlled spasticity trial 0410 did. In the pooled controlled studies, 41/131 NT treated subjects (3.1%) and 14/346 subjects (4%) in the placebo group had treatment-emergent, clinically significant (CS) abnormalities of biochemistry parameters. In the NT 201 group these were elevated glucose, total cholesterol, LDL cholesterol, GGT, AST, ALT, urea, bilirubin, alkaline phosphatase, and creatinine, and low HDL, potassium, and sodium. However, there were no clinically meaningful shifts or mean changes from baseline in most biochemistry parameters. For hematology studies fewer patients in the NT 201 group than in the placebo group experienced clinically significant laboratory abnormalities (7/1313 NT 201 subjects (0.5%) and 4/346 placebo subjects (1.2%) in the pooled controlled studies. Abnormalities in the NT 201 group were low hemoglobin, erythrocytes, platelets, hematocrit, relative reticulocytes, and elevated eosinophils. These were all detected at the final visit of the respective study, which in every study occurred weeks after receipt of a single dose.

In the pooled BEB studies, Dr. Jones found that hematology values and clinical chemistry parameters were similar for treatment group and from screening to final visit in Study 0443/1 Main period. However, Dr. Jones notes the small number of patients on which these results are based (73 in the NT 201 group and 34 in the placebo group).

In the pooled CD studies and in the pooled spasticity studies, Dr. Jones agrees with the Sponsor's findings that there were no clinically meaningful shifts or mean changes from baseline in NT 201-treated patients for hematology data or for biochemistry laboratory testing, including glucose. I also agree.

The data that are available do not suggest meaningful changes in laboratory findings.

2.3.7 Vital Signs

Dr. Jones reports that although BEB showed a slight decrease in heart rate from baseline to final visit for NT 201 (mean 71.9 vs 70.2 bpm) that was not seen in

placebo (mean 70.9 vs 71.3 bpm), this was not replicated in other indications. Other vital signs were not different compared to placebo or over time. Vital signs were performed prior to injection during the study visit, and therefore are not likely to represent an effect of the drug.

2.3.8 Electrocardiograms

According to Dr. Jones' review, (b) (4) in human blood had no effect on hERG tail currents. The sponsor has extrapolated the results, at concentrations of (b) (4) that exceed achievable concentrations in humans, to (b) (4). In male Cynomolgus monkeys, a single IM dose of 16 LUD/kg resulted in a decrease in heart rate 2-3 hours after injection and induced an increase in QTcF of less than 20 ms. As noted in Dr. Jones' review, according to Dr. Barbara Wilcox, a dose of 16 LDU/kg represents 4 times the maximum human dose for CD and 9.4X the maximum human dose for BEB.

In the type B Meeting on September 14, 2004, the FDA stated that specific ECG and cardiac evaluations are generally not required for most biologics. In a 6/8/10 submission in response to an information request, the Sponsor states that in the placebo controlled trials in BEB, CD and spasticity, ECGs were assessed at baseline only. Serial ECGs were performed, however, in studies 0003 (BEB) and 0013 (CD). The sponsor has presented a table of ECG parameters at baseline, primary endpoint visit, and final visit for the pooled controlled studies and has found no clinically meaningful changes in the mean parameters. This does not seem valuable in evaluating effects of drug on the ECG for studies with various doses and very different populations.

No clinically significant changes between baseline and post-baseline visits were observed in ECG parameters when serial ECGs were collected. As shown in ISS table 5.3.5.3-27 there was a mean decrease in QTcF of -3 msec for NT201 and of -1.2 msec for Botox from baseline to primary endpoint visit in the BEB study, and a change of 0.6 msec for NT 201 vs a change of -2.7 for Botox in the CD study. The sponsor states that changes of 60 ms were not present for the QTcF interval, based on the assessments of by a cardiologist associated with a CRO. These results were inadvertently not included in the original submission of the BLA but were included in a 6/16/10 response from the sponsor regarding the ECG assessments. I note that according to the response to an additional information request, the sponsor states that ECGs were printed for 10 seconds at 50 mms/s recording speed, and that no supine position was necessary before measurement. Measurement of intervals was to be done from 3 (possibly consecutive) normal heart complexes in Lead II, and in the case of non-measurable lead II tracings, all tracings of a subject were to be measured in an alternative lead (V5). Given the inconsistencies in the measurement of the ECGs (e.g. not necessarily in supine position without the patient at rest, not measuring consecutive beats), it is difficult to know the reliability of any measurements made in these studies. However, based on these results and on the adverse event profile of NT 201, drug-induced ECG changes do not appear to be

associated with NT201, consistent with the adverse event profiles of the other members of this class of drugs.

An additional ECG assessment was performed if an adverse event of the cardiovascular system occurred. This occurred in 1 patient in study 0410 (spasticity) in which the sponsor states in the 6/8/10 submission that a further ECG assessment was performed at final visit after a syncope.

2.3.9 Special Safety Studies/Clinical Trials

Merz conducted several studies to examine systemic diffusion of NT 201. Study 0709 CSR evaluated migration potential of Xeomin (5 U in 0.125 ml) as compared to Vistabel (5 U in 0.125 ml) and Dysport (12.5 U in 0.125 ml) after IM injection into the forehead in healthy female volunteers with the area of anhidrosis the primary endpoint. Study 0113 was a double-blind study to evaluate dose-response profile of NT 201 in human extensor digitorum brevis (EDB) muscles and comparison of systemic diffusion of different Botulinum toxin Type A products in healthy male volunteers. It evaluated surface electroneurography of EDB on the upper surface of the foot, abductor hallucis (AH), and abductor digiti quinti (ADQ) muscles. The study compared dose of 2, 4, 16, or 32 U of NT 201 and the same doses of Botox. . Neither study used clinically relevant doses in clinically relevant locations for the purposes of evaluating potential for spread for the indications of CD or BEB.

2.3.10 Immunogenicity

Dr. Jones reports that during clinical development of NT 201, antibody assessments were performed using an Enzyme-Linked Immunosorbent Assay (ELISA) or Fluorescence ImmunoAssay for antibodies (FIA-AB) for screening, and positive samples were subsequently tested using the mouse ex vivo hemidiaphragm assay (HDA) for neutralizing antibodies. In the completed studies of NT 201, a total of 12 of 1080 subjects (1.1%) who were antibody negative at baseline developed neutralizing antibodies to botulinum toxin during the course of their study. Each of these 12 subjects had been treated with another botulinum toxin prior to exposure to NT 201. Antibodies to botulinum toxin did not develop in treatment naïve subjects after exposure to NT 201. Dr. Jones notes that the development of antibodies was similar in the NT 201 and Botox groups (0.7% vs 0.8%, respectively).

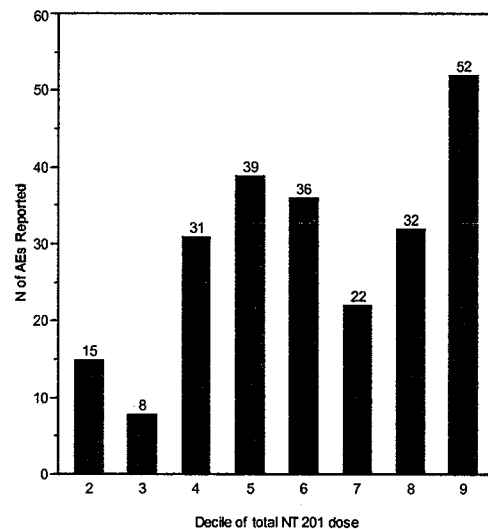
Four NT 201-treated subjects in the BEB studies developed borderline values of antibodies to botulinum toxin. This included 2 subjects in Study 0003 (and in both cases antibodies were not present at the final visit) and 2 subjects in 0433/1 Main period (1 of whom became positive at the final visit and the other who was "borderline" at the final visit) according to Dr. Jones' review. Four subjects in CD study 0408/1 Main period developed antibodies during participation in the study. Four additional subjects in 0408/2 Extension Period developed antibodies to botulinum toxin. One of these subjects had positive FIA at all assessments,

positive HDA before injection 3, and negative HDA at the last study visit. A second subject had positive FIA and negative HDA at baseline, and positive (borderline) at the 6th injection. A third subject had negative FIA and HDA at baseline and positive (borderline) HDA at the 4th injection visit. No patients in the spasticity studies were reported to develop neutralizing antibodies to botulinum toxin. None of the subjects who developed antibodies experienced TEAEs suggestive of immune-mediated events. According to Dr. Jones' review, the sponsor stated that most of the subjects who developed neutralizing antibodies showed a therapeutic response to treatment. I agree with Dr. Jones that a strong signal for immunogenicity has not been demonstrated, (b) (4)

2.3.11 Other Safety Explorations

AE risk by Study Location – Dr. Jones examined the risk of serious and common adverse events in several North American studies and non-north American studies for BEB and for CD (all of the spasticity studies were conducted outside of North America). In BEB, she finds a higher incidence of AEs in North American Study 0433/1 compared to Non-North American Study 0003 and this was true for both NT 201 and for placebo, and particularly for ptosis (19% vs 6% for NT 201 for 0433/1 vs 0003) and upper respiratory tract infection (1.4% vs 0.7% for NT 201 for 04331/vs 0003). However, I note that the dose in Study 0003 was limited to ≤ 35 U per eye. Similarly, for CD, the overall AEs were greater for both NT 201 and for placebo in North American Study 0408/1 that used single doses of 120U or 240 U vs Non-North American Study 0013 that used a single dose of 70-300 U. For muscular weakness for NT 201 this was 6.4% vs 1.7% for 0408/1 vs 0013 and a smaller difference was observed for dysphagia. I agree that this should be considered when writing labeling, although I note that cross study comparisons are difficult to interpret for a variety of reasons including the differences in dose in this case.

Dose Dependency for Adverse Events – Dr. Jones has considered dose and total number of injections with respect to dose dependency. For BEB, Dr. Ken Bergmann has provided the figure at right showing adverse events by dose in the placebo-controlled period of 0433/1. As Dr. Jones notes, the number of events is small, making it difficult to characterize well the dose response relationships. However, ptosis has a pattern suggesting a possible dose response relationship (9% in placebo, 15% for 10-40 U, and 20% for >40 U). I also note that dyspnea was reported in 2.9% for placebo, none for 10-40 U, and 6.6% for > 40 U. For doses > 40 units I have further explored this event that could reflect spread of toxin effect. The 4 cases of dyspnea on NT



201 in that study had doses of 50 Units, 55.5 Units, 80 Units, or 90 Units.

Dry mouth could potentially be considered a distant spread of toxin effect in the case of administration for blepharospasm. There did not appear to be an excess of dry mouth after doses of > 70 U (total in both eyes) compared to lower doses, although the numbers of events were small. Narratives were available from the sponsor for 11 cases. For all but one of those cases, the event occurred within 1 to 6 weeks after the injections. Doses ranged from 32.5 to 100 U. Two of those subjects had a history of dry mouth that worsened after administration. One subject was taking chlorpheniramine concomitantly. It is difficult to know the role of Xeomin in these events. Of note, one of those subjects also had right upper lip droop that began 1 day after administration of Xeomin.

Dr. Jones also assessed common adverse events by number of injections, but does not find a clear trend, noting that when stratified over 6 injections the number of patients in each subgroup is small. Given the limited exposure, as discussed in Section 2.1 of this memo, and a possible dose-response relationship for some adverse events, the appropriate upper limit of dosing should be considered.

For CD, common TEAEs that demonstrated a higher risk in the 240 U group compared to the 120 U group were neck pain (15% vs 7%), muscle weakness (11% vs 7%), and dysphagia (18% vs 13%). In CD, Dr. Jones notes that the risk of adverse events decreases as the number of injections increase. I agree with her hypothesis that this may be due to “survivor bias”. As I have noted in Section 2.1, there is limited exposure for multiple doses of 240 U. The appropriate upper limit of dosing should be considered, depending on whether additional benefit is observed at higher doses.

For spasticity, risk of adverse events generally increase with higher doses, although there were no strong dose response patterns, likely due to small numbers of adverse events.

2.3.12 Drug Interactions

Dr. Jones has reviewed drug-demographic interactions. She reports that there were too few non-Caucasian subjects to analyze adverse event data by race.³ In addition, she reports that due to small numbers of patients in the subgroups, no demographic factor was demonstrated to be a modifier of (adverse) effect. Dr. Jones also does not find a clinically meaningful pattern of adverse events based on disease severity for any indication.

Dr. Jones evaluated the relationship between adverse events with a status of “pre-treated” and “treatment naïve”. Three of the 222 patients in the pooled BEB

³ In BEB, 91.9% in the pooled controlled studies were Caucasian; in 0433/1 78.4% in the NT 201 group and 91.2% in the placebo group were Caucasian. In CD 97.2% in the pooled controlled studies were Caucasian; in 0408/1, 93.1% of NT 201 treated subjects and 87.8% of placebo subjects were Caucasian.

studies were botulinum toxin naïve, and therefore no assessment based on this status could be performed. For CD, Dr. Jones reports that although pre-treated patients in the CD indication seem to be over-represented among patients who experienced adverse events, the number of patients is small and the comparison not controlled for dose or disease severity.

The Sponsor did not perform drug-drug interaction studies.

2.3.13 Human Carcinogenicity

According to the integrated summary of safety, in the pooled, placebo-controlled trials, treatment-emergent adverse events in the "Neoplasms benign, malignant and unspecified" SOC occurred in 5 of 701 subjects (0.7%) in the NT 201 group, compared with 4 of 346 subjects (1.2%) in the placebo group. The events that occurred in the NT 201 group were melanocytic naevus, dysplastic naevus syndrome, haemangioma, lentigo maligna stage unspecified, and skin cancer (1 subject, 0.1%, each). The events in the placebo group were melanocytic naevus (2 subjects, 0.6%), basal cell carcinoma and skin papilloma (1 subject each 0.3%). Dr. Jones notes that the cancers occurring in the placebo controlled trials were primarily skin cancers or precancerous lesions, the most common form of cancer observed in the general population.

2.3.14 Human Reproduction and Pregnancy Data

There were 3 pregnancies in patients taking NT 201 in the database: 1 in CD study 0408/2, 1 in CD study 0013, and 1 in GFL study 0520/2. The subject in study 0013 had an elective abortion "for personal reasons", according to Dr. Jones' review.

The subject in study 0408/2 had a single dose of NT 201 (120 U) in the main period of the study, followed by 3 injections in the Extension study. The last injection was 11/16/07. The patient stopped taking birth control pills between the last week of November and the first week of December, 2007. She had her last menstrual period on (b) (6). On (b) (6) she gave birth at 37 weeks gestation to a healthy boy.

The subject in 0520/2 received the first dose of NT 201 (20 U) in the Main Period on 11/20/06 and the most recent dose on 7/9/07. At visit 10 of the Main Period (8/30/07) her pregnancy test was positive. A healthy baby was born on (b) (6).

I agree with Dr. Jones that the number of pregnancies was too small to make conclusions about the effect of prenatal NT 2201 exposure. (b) (4)

Dr. Jones recommends that patients known to be pregnant be advised not to receive NT 201, given that the indications for NT 201

use are not-life threatening. I agree with that recommendation, unless the consideration between the patient and her physician conclude that the benefits outweigh the potential for this unknown risk.

2.3.15 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the ISS, there is no clinical experience with NT 201 overdose. The Sponsor has included in the proposed label some information about excessive doses of botulinum toxin type A in general. I recommend that the class language from Botox and from Dysport be used in the overdose section (section 10) of the Xeomin label. This should include the language regarding the availability of antitoxin.

With respect to abuse potential, the Sponsor states that there are no reports of drug abuse with Botulinum toxin type A preparations. Dr. Jones agrees with the Sponsor that based on post-marketing results of other botulinum toxins and the apparent lack of similarity between botulinum toxin actions and known abuse mechanisms, there is little evidence of an abuse potential for NT 201. I agree. I also agree with her suggestion that withdrawal seems unlikely.

2.3.16 Postmarketing Experience

I agree with Dr. Jones' assessment that the majority of events observed in the postmarketing experience are those expected with the use of a botulinum toxin product.

2.3.17 Summary of Significant Safety Concerns:

Dr. Jones has evaluated the safety data for Xeomin. She has specifically evaluated safety issues of concern with the botulinum class of products including distant spread of toxin effect, as well as other issues of special interest including changes in glucose and in alkaline phosphatase. She has not identified other safety concerns in this submission that have not been already identified for botulinum toxin products.

2.3.18 Postmarketing Risk Management Plan

Merz submitted a REMS with the original BLA and subsequently submitted a revision. The REMS includes a MedGuide and a Communication plan, as described in Dr. Jones' review, and a timetable for assessments.

2.3.19 Conclusions

I agree with Dr. Jones' assessment that the application for Xeomin (BLA 125360) allowed for an adequate safety review, and no safety concerns that would preclude approval were identified should NT 201 be found to be effective. I recommend considering the maximum dose that should be used for either cervical dystonia or blepharospasm due to limited experience with the highest

doses the Sponsor has proposed for use and because of dose-related adverse events observed in the ISS, particularly in cervical dystonia.

The safety review identified cases of dyspnea and dry mouth in the BEB program that could be due to spread of toxin effect. Other than that, Dr. Jones did not identify any instances of systemic spread of NT 201 effect. This was largely the case for several other previously approved botulinum toxin products in which systemic spread of effect cases were primarily identified following product approval. I agree with her recommendation to include the same Boxed Warning (and class labeling regarding spread of toxin effect) in the Xeomin labeling as required for other approved botulinum toxin products. I also agree that because different formulations of botulinum toxin are not interchangeable, to avoid unintentional overdose the Division should consider some mechanism for alerting clinicians to this issue. This could be in the format of an update to the drug safety information sheet⁴ that was last published in August 2009.

I agree with Dr. Jones' recommendations for the following postmarket evaluations:

1. The sponsor should devise a plan to monitor for systemic spread when NT 201 is used in clinical practice and to forward in an expedited manner any case reports resembling spread of toxin effect.
2. For the ongoing (or future) spasticity studies, the sponsor should be asked to utilize checklists of adverse events related to botulinum toxin to ascertain adverse events.
3. In future studies, the sponsor should be asked to include vital signs at baseline and at specified time periods after NT 201 treatment (for example, at an hour after treatment, at a time point where maximum clinical effect is expected, and at follow-up).

There is limited experience with Xeomin for blepharospasm with doses of greater than 50-75 units, and minimal experience in patients without previous exposure to Botox. I recommend limiting the dose to 50-75 Units and limiting the indication to the population that was studied (patients pretreated with Botox), as there is no information on appropriate dosing for patients who are toxin naive. In addition, a PMC evaluating the appropriate dose as well as safety in that group of patients should be considered.

In addition, as for the other botulinum toxin products, PMRs should include studies of safety assessing distant spread of toxin effects after multiple administrations of Xeomin during a minimum period of 12 months in adult patients with spasticity and in pediatric patients with spasticity. The safety data could come from open-label extension of clinical studies that would be performed as PMCs or from long-term controlled safety and efficacy studies, with doses as

⁴<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm175011.htm>

Safety Team Leader Memo
BLA 125360

least as high as those shown effective in those studies or those doses commonly used to treat spasticity. In addition to spread of toxin effect, evaluation of other safety markers that may be of interest such as vital signs, glucose, alkaline phosphatase, and ECGs, should be performed at a time point when peak clinical effect is expected.

Clinical Review
Anne E. A. Constantino, MD
NDA 125360-1
Botulinum Toxin A, Xeomin@IncobotulinumtoxinA

1

CLINICAL REVIEW

Application Type	NDA
Application Number	125360
Priority or Standard	Standard
Submit Date	July 2009
Received Date	
PDUFA Goal Date	July 31, 2010
Reviewer Name	Anne E. A. Constantino, MD
Review Completion Date	June 2010
Established Name	Incobotulinumtoxin
Proposed Trade Name	Xeomin
Therapeutic Class	Biologic (Botulinum toxin)
Applicant	MERZ
Dosing Regimen	120 units
Indication	Cervical Dystonia
Intended Population	Patients with Cervical Dystonia

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action	8
1.2 Risk Benefit Assessment	8
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	9
1.4 Recommendations for Postmarket Requirements and Commitments	10

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information	10
2.2 Tables of Currently Available Treatments for Proposed Indications.	11
2.3 Availability of Proposed Active Ingredient in the United States.	12
2.4 Important Safety Issues With Consideration to Related Drugs	13
2.5 Summary of Presubmission Regulatory Activity Related to Submission	13
2.6. Request for Waiver of Pediatric Studies	16

3 ETHICS AND GOOD CLINICAL PRACTICE

3.1 Submission Quality and Integrity	17
3.2 Compliance with Good Clinical Practices	18
3.3 Financial Disclosures	18

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls	19
4.2 Clinical Microbiology.	21
4.3 Nonclinical Pharmacology/Toxicology	22
4.4 Clinical Pharmacology	25

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials	27
5.2 Review Strategy.	31
5.3 Discussion of Individual Studies/Clinical Trials.	33
Study Protocol MRZ 60201-408/1	33

6 REVIEW OF EFFICACY

Efficacy Summary	
6.1 Indication	44

Clinical Review
Anne E. A. Constantino, MD
NDA 125360-1
Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

6.1.1 Indications	44
6.1.2 Demographics	44
6.1.3 Subject Disposition	51
6.1.4 Analysis of Primary Endpoint(s)	56
6.1.5 Analysis of Secondary Endpoints(s)	59
6.1.6 Other Endpoints	65
6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations	67
6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects	69
6.1.9 Supporting Studies	
Study Protocol MRZ 60201-408-2	69
Study Protocol MRZ 60201-0013/1	81
7 REVIEW OF SAFETY	
Safety Summary	87
8. STATISTICAL REVIEWER'S CONCLUSIONS	90
9. REVIEWER'S CONCLUSIONS	90
10 POSTMARKET EXPERIENCE	
11 APPENDICES	
9.1 Literature Review/References	93
9.2 Labeling Recommendations	93
9.3 Advisory Committee Meeting	93
9.4 Dataset Requests to Sponsor	93

Tables

Table 1. Other Non FDA Approved Treatments used in Clinical Practice for Cervical Dystonia: (Source: Reviewer's Table)

Table 2. Botulinum toxins available around the world for the treatment of Cervical Dystonia.

Table 3. Sites Involved in Drug Substance Manufacture (Source: Sponsor).

Table 4. Tables of Studies/Clinical Trials (Source: Sponsor's Submission, modified by Reviewer)

Table 5. Other Clinical Trials conducted by the Sponsor in evaluating NT 201 for other indications. (Source: Sponsor's submission)

Table 6. Study schedule of the Main Period (Source: Sponsor's Submission)

Table 7. Demographic data for the ITT population. (Source: Sponsor's submission)

Table 8. Demographic Data for Subgroups of Treatment Naïve and Pre-treated subjects (ITT Population) (Source: Sponsor's submission).

Table 9. Duration since First Diagnosis and Estimated Duration of Cervical Dystonia in Subgroups of Treatment Naïve and Pretreated Subjects in the ITT Population (Source: Sponsor).

Table 10. Concomitant Medication by ATC Class (applying to > 10% of all subjects) and/or Preferred Term (applying to >5% of all Subjects) in the ITT population (Source: Sponsor's submission).

Table 11. Concomitant Medications that may relieve Cervical Dystonia (Source: Reviewer)

Table 12... Most frequent reasons for screening failure. (Source: Reviewer's Table)

Table 13. Major Protocol Deviations (All randomized subjects, N=233; Source: Sponsor's submission)

Table 14. Reasons for minor deviations are listed in the following tables: (Source: Reviewer's table)

Table 15. List of Drugs that may affect symptoms of Cervical Dystonia (Reviewer's Table)

Table 16. TWSTRS scores in the different groups at baseline and after visit 3. (Source: Sponsor's submission)

Table 17: Baseline to Visit 3 TWSTRS Total Scores in subjects who received 240 U vs. Placebo group. (Source: Sponsor submission)

Table 18: Baseline to Visit 3 TWSTRS Total Scores in subjects who received 120 U vs. Placebo group. (Source: Sponsor submission)

Table 19: Baseline to Visit 3 TWSTRS Total Scores in subjects who received 240 U vs. 120 group. (Source: Sponsor submission)

Table 20. Summary of the Influence of Gender on the Treatment Effect in Total ITT population, Treatment naïve and Pre-treated Subjects (Full ANCOVA Model, Missing values replaced by Baseline value or Group Mean Value) (Source: Sponsor)

Table 21. Mean (SD) Baseline Value and Mean (SD) Change from Baseline to Visit 3, Visit 4 and Final Visit in TWSTRS Severity Score (ITT population). (Source: Sponsor's submission)

Table 22. ANCOVA results based on LS Mean changes from Baseline to Visit 3, Visit 4 and Final Visit in TWSTRS subscale (Severity, Disability and Pain) scores (Source: sponsor's submission).

Table 23. ANCOVA results based on LS Mean changes from Baseline to Visit 3, Visit 4 and Final Visit in TWSTRS subscale (Severity, Disability and Pain) scores (Source: sponsor's submission).

Table 24 Mean Changes from Baseline to Visit 3 in TWSTRS Subscores, Treatment naïve and Pre-treated Subjects (ITT Population) (Source: Sponsor's Submission)

Table 25. Patient Evaluation of Global Response (PEGR) at Final Visit (ITT Population) (Source: Sponsor's submission)

Table 26. ANCOVA Results Patient Evaluation of Global Response at the Final Visit in ITT population, Treatment Naïve and Pre-treated Subjects (Source: Sponsor's submission)

Table 27. Mean (SD) Time to Onset of Treatment Effect in ITT population, Treatment naïve and pre-treated subjects (Source: Sponsor's submissions)

Table 28. Mean (SD) Time to Waning of Treatment Effect (weeks) in ITT population, Treatment naïve and pre-treated subjects (Source: Sponsor's submissions)

Table 29. Mean (SD) Time to Duration of Treatment Effect (days) in ITT population, Treatment naïve and pre-treated subjects (Source: Sponsor's submissions)

Table 30. Extent of Exposure in the 240 U Group: Mean (SD) and Range of Units of NT

201 Injected during the MP, according to Side and Muscle Injected, in Total EFS Population, Pre-treated and Treatment-naïve Subjects (Source: Sponsor's submission)

Table 31. Extent of Exposure in the 120 U Group: Mean (SD) and Range of Units of NT 201 Injected during the MP, according to Side and Muscle Injected, in Total EFS Population, Pre-treated and Treatment-naïve Subjects (Source: Sponsor's Submission)

Table 32: Extension Period Schedule (Source: Sponsor's submission)

Table 33. Number of Patients and Doses Received Classified into Naïve (N) and Pre-Treated (P) at Each Visit (Source: Reviewer)

Table 34. Number of Patients and Mean TWSTRS score by visit in Naïve (N) and Pre treated (P) patients. (Source: Reviewer)

Table 35. Mean and Median Duration (days) between IncobotulinumtoxinA injections (Source: Reviewer's Table).

Table 36. Number of Patients with three, four and five injections (including the Main Phase and extending into the Extension Phase) of 240 units. (Source: Reviewer)

Table. 37. Results of TWSTRS Severity Score at Control Visit (TPP, N=420) (Source: Sponsor's submission)

Table 38. TWSTRS Severity Score at Control Visit from Baseline Study 0013 (Source: Sponsor's submission)

Table 39. Results of the TWSTRS Pain Subscore (TPP N=420) (Source: Sponsor's submission)

Table 40. Efficacy Data Visual Analogue Scale Pain: Wilcoxon Test P Values (Source: Sponsor's submission)

Table 41. Studies/Clinical Trials Used to Evaluate Safety (Source: Sponsor's submission)

Figures

Figure 1. Diagram summary of the overall production of (b) (4) drug substance from WCB cryovial to bulk drug substance. (Source: Sponsor's submission)

Figure 2. Mechanism of Action

Figure 3. Subject Disposition of all Enrolled Subjects in the Main Period (Source: Sponsor's submission)

Figure 4. Distribution of patients according to number of days since first injection in Main Phase until the first injection in the Extension Phase. (Source: Reviewer)

Figure 5. The number of Days between injections in the Extension Phase between Visit 6 to Visit 8, Visit 8 to Visit 10, Visit 10 to Visit 12 and Visit 12 to Visit 14. Median, Mean and SD are shown below each figure. (Source: Reviewer)

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

1. The clinical trials data meets the regulatory standard for approval of effectiveness of IncobotulinumtoxinA (Xeomin) for the 120 unit dose for the treatment of cervical dystonia.

(b) (4)

The approved recommended dose of IncobotulinumtoxinA should be 120 units. The data from the pivotal CD efficacy trial (408/1) demonstrated no added benefit of 240 units over 120 units in the treatment of Cervical Dystonia. There has been no data to support injection of doses higher than 240 units.

1.2 Risk Benefit Assessment.

The clinical trials data supports the approval of the 120 (b) (4) unit dose of IncobotulinumtoxinA for following reasons:

- A. IncobotulinumtoxinA has demonstrated efficacy in treating patients with cervical dystonia. In the pivotal study conducted in the United States among 37 centers (408/1), the primary efficacy endpoint of change in TWSTRS total score from baseline to week 4 after injections showed a difference of -9 points in the 240 U group and -7.5 points in the 120 U group. Comparison of each IncobotulinumtoxinA group to placebo was statistically significant at $p < 0.001$. (A more negative score signifies improvement).
- B. The Patient Evaluation of Global Response also showed that 67% and 64% of patients who received 240 units and 120 units respectively documented slight improvement to complete abolishment of all signs and symptoms as opposed to 20% of placebo patients.

The safety data reviewed by Dr. Lisa Jones showed that the overall incidence of TEAE was higher in the treatment group. All adverse events, especially dysphagia occurred at a greater risk when patients were treated with 240 U compared to patients injected with 120 U. Neck pain, muscular weakness and musculoskeletal pain were expected findings based on the drug's mechanism of action and administration. Muscle stiffness was also predominant among patients (3.1% in NT 201 and 1.1% in placebo). Dysphagia is one of the more serious adverse events documented in the study. These side effects are consistent with other approved botulinum toxins and there have been no new or unexpected safety issues documented in the studies. Despite this limitation, the overall risk is therapeutically acceptable and the benefits outweigh the risks.

(b) (4), it is still recommended that patients who require botulinum toxin, whether or not they are treatment naïve, be started on 120 units because of the following reasons:

- There is a dose response effect resulting in greater risks of adverse events in patients who received 240 U.

(b) (4)

(b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.

The following REMS Elements were submitted by the company:

A. **Medication Guide:** This will be dispensed with each vial of IncobotulinumtoxinA in accordance with 21 CFR 208.24. Pursuant to 21 CFR 208.24, the Medication Guide will be available in sufficient numbers i.e. the Medication Guide will be provided with each single vial of IncobotulinumtoxinA. The label of each container or package of IncobotulinumtoxinA will include prominent instructions to authorize dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided.

B. **Communication Plan:** MERZ will implement a communication plan consisting of a Dear Healthcare Professional (DHCP) Letter disseminated at the time of launch. The DHCP letter will be distributed to neurologists, physiatrists and other specialties and healthcare professional staff who might prescribe or inject IncobotulinumtoxinA® or other licensed botulinum toxin products (i.e., physical medical and rehabilitation specialists, dermatologists, ophthalmologists and other specialists who have previously dispensed botulinum toxins).

C. **REMS Assessments** will be submitted to FDA at (b) (4), 3 years and 7 years from the date of initial approval of the REMS. The reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

The FDA submitted their comments and proposed revisions to the REMS document and DHCP letter. The timetable for submission for REMS assessment has been corrected to 18 months, 3

years and 7 years. The Sponsor's claim in their document that IncobotulinumtoxinA is a (b) (4),
[REDACTED]—has been deleted by DRISK.

Additional suggestions to the Med Guide are currently being made by the Safety Reviewer.

1.4 Recommendations for Postmarket Requirements and Commitments.

The Sponsor requested a waiver for pediatric studies in cervical dystonia on January 2, 2009 because there are too few children with this disease to study. PeRC approved the waiver on February 24, 2010.

Because the drug is approved and being used for post stroke upper limb spasticity in Europe, a placebo controlled trial in adults and children with spasticity (initially upper, then lower limb spasticity) should be done in the future. (b) (4)

[REDACTED] (b) (4)

There were still unsettled issues with regard to validation of the integrity of the container closure system. The sponsor has agreed to a post marketing commitment to address this issue.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

IncobotulinumtoxinA (trade name Xeomin®, reviewed and approved by DMEPA on March 25, 2010 and meeting the standards of USAN) is, according to the Sponsor, a formulation of highly purified Botulinum neurotoxin type A [150kDa], which the company distinguishes from the other botulinum toxins in the market as being “free from complexing proteins (b) (4)

[REDACTED] The drug product is supplied as a powder solution for injection (lyophilizate) packed in a (b) (4) glass vial with 50 or 100 LD₅₀ units strength. Its proposed indications upon submission are for the treatment of Cervical Dystonia (Spasmodic Torticollis) and Benign Essential Blepharospasm. The specific indication found in the label submitted for cervical dystonia is [REDACTED] (b) (4)

[REDACTED] Their recommended initial dose is 120 (b) (4) U [REDACTED] (b) (4)

Similar to other botulinum neurotoxin type A, IncobotulinumtoxinA acts selectively on peripheral cholinergic nerve endings, inhibiting the release of neurotransmitter acetylcholine (Ach). It is applied through intramuscular injections as a therapeutic means in dystonia and spasticity which are characterized by pathologically overactive muscles. The company differentiates its drug from other botulinum toxin A by stating that it is “highly purified” (b) (4)

These complexing proteins do not contribute to the paralytic effect of the neurotoxin and their removal, the company surmises, may be relevant for chronic and long term treatment.

IncobotulinumtoxinA is currently available and approved for treatment of cervical dystonia, blepharospasm and upper limb spasticity in Europe, Mexico, and Argentina.. It has also been approved in Canada on February 4, 2010 for treatment of post stroke spasticity and dystonia.

2.2 Tables of Currently Available Treatments for Proposed Indications

Before the advent of botulinum toxins, symptomatic treatments for CD were available. The table below provides a short list of the drugs, surgical treatments and alternatives to medical therapy that have been used in Cervical Dystonia. None of these treatments have been approved by the FDA for the treatment of CD.

Table 1. Other Non FDA Approved Treatments used in Clinical Practice for Cervical Dystonia: (Source: Reviewer's Table)		
Drugs (all unapproved)	Surgical Treatments:	Alternative Medicine Treatment
Anticholinergics: Trihexyphenidyl, Benztropine	Rhizotomy	Acupuncture
Benzodiazepines: Diazepam, Clonazepam, Lorazepam	Myotomy	Physical Therapy
Other Chemodenergating Agents: Phenol, lidocaine	Thalamotomy	
Anti-convulsants: Gabapentin	Deep Brain Stimulation	
Dopamine Agonists: Carbidopa-levodopa		
Anti Spasmodics: Baclofen, Tizanidine		

2.3 Availability of Proposed Active Ingredient in the United States.

IncobotulinumtoxinA (Xeomin®) is approved in Germany. Another botulinum toxin A product, Botox® is produced in the United States.

Table 2. Botulinum toxins available around the world for the treatment of Cervical Dystonia.

	BOTOX® Onabotulinumtoxin	Dysport®/ Reloxin® Abobotulinumtoxin	Myobloc®**/ NeuroBloc® Rimabotulinumtoxin	NT-201/ XEOMIN® IncobotulinumtoxinA
Company	Allergan Inc.	Ipsen Inc./ Medicis Inc.	Solstice Neurosciences Inc.	Merz Pharmaceuticals
Type	Type A-	Type A	Type B	Type A-
Approvals	Used in over 75 countries worldwide, Approved in the USA in 1989 for Strabismus and Blepharospasm; Approved in 2000 for CD	Used in over 65 countries; Approved in Europe in 1991 Approved in the USA on April 2009 for CD and glabellar lines	Used in some European countries, US, Canada Approved in the USA in 2000 for CD	Approved in Europe, Argentina, Canada, Mexico and Uruguay for treatment of Blepharospasm and CD. Also approved for upper limb post stroke spasticity and for focal spasticity strabismus and glabellar frown lines in Argentina.
Active Substance (molecular weight)	Botulinum toxin type A complex (900kD)	Botulinum toxin type A complex (900kD)	Botulinum toxin type B complex (700kD)	Botulinum toxin type A, free from complexing proteins (150kD)
Indications	Blepharospasm; cervical dystonia; glabellar lines; hyperhidrosis	Blepharospasm; cervical dystonia	Cervical dystonia	Blepharospasm; cervical dystonia; glabellar lines in Argentina
Pharmaceutical Form	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Solution	Powder dissolved in solution for injection
Units/vial	100	500	2,500; 5,000; 10,000	100

**Myobloc® is a serotype B toxin that is available in the United States and acts on the outside of the synaptic vesicle, cleaving the vesicle-associated membrane protein (synaptobrevin, VAMP) in contrast to the type A which acts on the inner surface of the postsynaptic membrane (SNAP-25).

2.4 Safety Issues With Common to All Botulinum Toxin Products

Cervical dystonia presents with clonic or tonic muscle contractions resulting in abnormal movements and postures of the head and neck. Successful treatment with intramuscular injection of the botulinum toxin is dependent on the site and dose. Regional or local spread of the toxin's biologic activity to the areas around the neck musculature may lead to dysphagia which is the most commonly reported adverse events in both double blind and open label studies following injection of Onabotulinumtoxin (Botox®) (19%), Rimabotulinumtoxin (Myobloc®) (10-25%) and AbobotulinumtoxinA (Dysport®) (15 to 39%) as reported in the clinical trials section of each drug's label.

More importantly, spread from the initial site of injection may produce systemic side effects which may be due to retrograde axonal transport in the spinal motor neurons (Garner CG, Straube A. Witt TN, et al Mov Disord 1993; 8: 33-37) or spread via the circulatory system. Post marketing reports have documented asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dyspnea, dysarthria, urinary incontinence and breathing difficulties reported from hours to weeks after injection. Swallowing and breathing problems may pose a life threatening risk and there have been reports of death. The risk of symptoms is greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions. These adverse events led to the addition of a "Boxed Warning" included in the label for all botulinum products marketed in the US by August 3, 2009.

Patients with myasthenia gravis, swallowing difficulties and muscle weakness are at increased risk for adverse events especially aspiration. Increased risk for adverse events may occur with normal treatment levels or with a history of previously tolerated treatment from botulinum toxin. There may also be increased systemic or muscle sensitivity to the botulinum toxins in some patients.

The product contains a small amount of human albumin, thus carrying the risk for viral infection transmission. A theoretical concern for Creutzfeldt Jakob disease remains although this has never been reported to date,

2.5 Summary of Presubmission Regulatory Activity Related to Submission.

Pre-Phase 3 Meeting: September 14, 2004:

- FDA advised the sponsor to provide more details on the manufacturing process from cell bank characterization up to purification which should be included in the future IND.
- FDA recommended discussing the assay method of the drug with the Office of Biological Products prior to deciding on antibody testing.
- FDA suggested (in response to the sponsor's proposal to initiate a phase 3 study for CD in the US --after conducting a phase 3 trial in CD and Blepharospasm (BPS) in Europe), that proposed studies should assess efficacy of NT 201 against placebo and should consider two additional studies to establish efficacy, obtain dose ranging data against

placebo and to study Botox-naïve patients. However, FDA explained that one very robust and persuasive dose ranging study in CD and another in BPS could provide sufficient evidence of efficacy for both indications and that both studies could be mutually supportive for both indications.

- FDA recommended using the TWSTRS total (b) (4) as the primary endpoint. The Agency also recommended that the placebo period be extended to 6 to 8 weeks (b) (4) to develop adequate placebo controlled safety data.
- FDA recommended that all adverse events observed during the double blind or open label period should be followed until the event resolves or stabilizes.
- FDA also required submission of evidence that efficacy is sustained over time with re-treatment as well as safety data over time.

(b) (4)

Clinical Hold: June 29, 2006

- The IND was placed on “clinical hold” on May 31, 2006 because their final study reports were not compatible with the electronic document requirements of CDER.
- Clinical trials were placed on Full Clinical Hold because of insufficient information from nonclinical studies that can be used to assess risks of study subjects.
- Other non-clinical hold recommendation sent to Merz include:
 - Submission of a standardized method for eliciting adverse event reports;
 - Providing detailed procedures for administering the Jankovic Rating Scale for Blepharospasm,
 - Inclusion of patient reported outcome measures and responder analysis that are familiar to patients.
- The company responded to these deficiencies and the clinical hold was removed on July 20, 2006.

Facility Review Meeting: March 19, 2007: Merz submitted an information package that detailed the intended design and general operational procedures for a new parenterals facility to be constructed by Merz in Dessau, Germany.

- FDA referred the company to the following guidance: “Guidance for Industry-Sterile Drug Products Produced by Aseptic Process—Current Good Manufacturing Practice (September 2004)” to make sure that the new facility for manufacturing is in compliance with the FDA aseptic processing requirements.
- FDA also clarified that submitted stability data from this new facility will be reviewed by the Agency prior to granting a final decision on stability acceptance.
- FDA confirmed acceptability of environmental monitoring stations within the (b) (4),

(b) (4)

Type C Meeting for Cervical Dystonia and Blepharospasm: June 11, 2007

- FDA recommended that treatment-naïve patients should be enrolled in the efficacy studies for CD and Blepharospasm. Recognizing the difficulty in recruitment of treatment naïve patients posed by the sponsor, the Agency agreed to define treatment naïve as patients who have not been treated with Botulinum toxin products for Blepharospasm or other indications for one year.
- FDA required two phase 3 placebo controlled trials in cervical dystonia or in a different focal dystonia. Merz was told that the ongoing CD trials enrolling pretreated and naïve patients combined with the ongoing Blepharospasm study in pretreated patients appear capable of fulfilling the requirement for two adequate and well controlled trials necessary for a BLA in cervical dystonia.
- FDA agreed that the proposed safety database from a previous study done in Europe would provide sufficient safety information for cervical dystonia.
- FDA also required that additional reproductive toxicity data be submitted.
- FDA informed the sponsor that the measurement of plasma PK may not be necessary if the sponsor would be able to present a scientific rationale to show why this measurement would not be possible.

Type B Pre-BLA December 12, 2008: Discussion of the administrative, quality, preclinical and clinical questions related to the BLA for the proposed indications cervical dystonia (b) (4)

- FDA required and the sponsor agreed to provide at least 6 months of stability data on three drug validation batches and formulation homogeneity.
- FDA emphasized the need to conduct pre- and post-natal development studies and provide written justification if they are unable to provide these studies.

- FDA (CMC) required the Sponsor to provide drug substance specification for aggregates, to tighten the drug product pH specification and provide a lot release protocol for 100 and 50 unit vials.

(b) (4)

- FDA recommended that the long-term safety data which is up to 1 year of exposure must cover a full dose range for each indication (up to 400 units per treatment). The Sponsor agreed to delay filing in order to include data from 60 patients exposed for 1 year at 400 units, 30 patients exposed for 1 year at 300 to 400 units and 30 patients exposed for one year at 200 to 300 units. In addition, 85 patients with cervical dystonia will have been treated for one year at 240 units. It was also agreed upon that the pooling of datasets should be for each indication and across all indications and it should include a subgroup analyses by dose, indication and duration of exposure.

Additional Issues Presented by CMC:

CMC's review noted that Merz did not use a specific anti type A antibody to conduct the General Safety Testing (GST) for the drug product release. Because the GST is a regulatory requirement for the DP lot release, not complying with the Agency's standards may lead to potential CR issues. A meeting with the sponsor to discuss GST procedure was scheduled on May 26, 2010.

2.6 Request for Waiver of Pediatric Studies

The Sponsor requested a waiver for Pediatric Studies in Cervical Dystonia which they included in their submission on July 1, 2009. This waiver was approved by the FDA during the PeRC meeting on February 24, 2010, after careful review of the reasons presented by the Sponsor, stating:

"We are waiving the pediatric study requirement for this application for the indication of cervical dystonia because necessary studies are impossible or highly impracticable because there are too few children with the disease to study."

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

Submission Quality

For the Cervical Dystonia indication, the following issues regarding text and data submission were raised.

- The SAS macros used to calculate the primary endpoint in their (b) (4) CD and Blepharospasm pivotal trials were not readable and the Sponsor was asked to provide the revised macros on July 27, 2009.
- FDA requested the sponsor to provide SAS codes and SAS data (.xpt) for tables and figures reported in the study and summary efficacy reports. The Sponsor was also required to submit a Summary of Clinical Efficacy table which should include all doses used in their studies and the protocol specified covariates.

The company complied with the requests listed above.

(b) (4),
[Redacted]

The review clock was likewise extended to July 31, 2010 because the Sponsor failed to respond to the CMC requirements that were requested on May 26, 2010.

Integrity

For Study 408/1(the CD indication) two domestic sites were selected for inspection by the Division of Scientific Investigation on the basis of having the largest number of enrolled subjects.

1. Alberto Vasquez, MD of Suncoast Neurological Associates, Inc. in St. Petersburg, FL was selected for inspection because he enrolled a high number of subjects in the clinical trial. DSI report “found no evidence of under reporting of adverse events” in this site and both field and headquarters’ classification was “No Action Indicated (NAI)”.
2. Paul Cullis, MD of St. John’s Hospital Medical Center, Detroit, MI was another site inspected because of the high number of enrollments. The inspection covered review of informed consent forms for all 15 subjects and the medical records were reviewed in

depth. There were no deaths and one SAE was reported. The DSI investigation “found no evidence of under reporting of adverse events and both field and headquarters’ classification was “No Action Indicated (NAI)”.

These two sites were chosen by the Quality Assurance GCP contracted by the Sponsor and were given Clinical Investigator Audit Certificates. The choice of audit sites and results of the internal audits conducted by the company was similar to those of the DSI reports.

3.2 Compliance with Good Clinical Practices

- The sponsor attested that all of the clinical trials were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice [GCP] and its applicable regulatory requirements. This supports compliance with 21 CFR 312 Parts 50 and 56, and ICH E6. National and international ethical principles for protection of human subjects in clinical research trials were adhered to. The reviewer did not find evidence of unethical conduct on the part of the sponsor or study site personnel.
- Clinical Investigator Audit Certificates were given to 8 sites (these were the only sites inspected).
- The company certified that it did not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in the implementation of this application.

3.3 Financial Disclosures

Financial Disclosures of the three Principal Investigators on the (b) (4) studies were reviewed. (b) (4) had admitted to being paid by the company more than \$25,000. The details of the payments are as follows:

- (b) (4) was paid \$69,229 and Euro 11,110 for consulting activities from July 2002 to July 2004. She is PI of (b) (4) which enrolled (b) (4) patients with (b) (4) patients receiving NT 201 and (b) (4) patients receiving placebo.
- (b) (4) was paid \$25,062 for consulting and work done as trainer for the TWSTRS. She is Principal Investigator in (b) (4). This site enrolled (b) (4) patients with (b) (4) patients receiving NT 201 and (b) (4) patients receiving placebo.
- (b) (4) was paid \$110,505 for consulting, training video and readability. (b) (4) was the PI and sub PI in (b) (4). This site enrolled (b) (4) patients, with (b) (4) receiving NT 201 and (b) (4) receiving placebo.

Merz claims that this compensation did not impact the results of studies (b) (4)
(b) (4) For the CD indication, the following measures were taken by the Sponsor to avoid bias at the study sites of the physicians mentioned above:

- Verification of protocol compliance in the study conduct achieved by means of site monitoring by Merz CRO partner (b) (4).
- Designing the studies as double blind and placebo controlled to provide intrinsic control and avoid bias by the investigator.

Financial disclosures were also obtained from all the site investigators in the study done in the United States. The clinical reviewer has reviewed each of the statements signed and submitted by the Investigators, Sub-Investigators and Coordinators. There were no conflicts of interest noted.

REVIEWER'S COMMENTS:

- The three highest paid Principal Investigators enrolled a total of 24 patients with 18 patients receiving NT 201. The 18 patients enrolled by these investigators in study NT 201 could not have influenced the study outcome given that the study included 233 subjects overall for the CD indication.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Drug Product: IncobotulinumtoxinA

Drug Substance: Highly purified Botulinum neurotoxin type A (150 kDa), free from complexing proteins

Sponsor Name: Merz Pharmaceuticals GmbH

Company Name: NT 201 for the drug product

Manufacturing Process (overview)

Manufacturing to batch release of the drug are all solely based in Germany and there were no US sites established. Below (Table 3) is a list of the manufacturing sites and their corresponding responsibilities:

Table 3. Sites Involved in Drug Substance Manufacture (Source: Sponsor).	
Name and Address	Responsibility
Merz Group Services GmbH Site Dessau Am Pharmapark 15A D-06861 Dessau-Rosslau Germany	(b) (4) drug substance
Merz Pharmaceuticals GmbH Hermannswerder Haus 15 D-14473 Potsdam Germany	Quality control, release and stability testing with the exception of microbiological testing and the mouse LD ₅₀ assay
(b) (4)	Microbiological testing
(b) (4)	Mouse LD ₅₀ assay
Merz Group Services GmbH Site Dessau Am Pharmapark 15A D-06861 Dessau-Rosslau Germany	Final batch release

The initial stage of manufacturing comprises the (b) (4) of the cell (b) (4) (b) (4) of the Working Cell Bank (WCB). (b) (4)

(b) (4)

(b) (4)

Although the Sponsor attests to have taken careful steps in manufacturing to ensure safety of the product, FDA CMC reviewer has identified problems that include lack of validation of methods used in the determination of aggregates in NT 201. Measures to prevent cross contamination and drug stability problems were also raised. A comprehensive review of the manufacturing process will be provided by the FDA CMC Reviewer.

(b) (4)

The sponsor submitted a substantial amount of new microbiology and manufacturing process data in response to these deficiencies after 6 months into the review cycle, triggering an extension of the review period.

4.2 Clinical Microbiology

According to the sponsor:

- No microbial growth was observed in IncobotulinumtoxinA vials which were challenged artificially with a low bioburden of approximately 50 cfu of eight different test organisms mainly from human skins.

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

- A 72 hour stability study on sterility and presence of endotoxins of microbial parameters was done in reconstituted IncobotulinumtoxinA vials. The drug product remained unaffected over the whole 3 day period at a storage temperature of 2-8°C.

The FDA Microbiology Reviewer commented that contamination issues in the manufacturing process, which have been raised early in the submission of the NDA (October 2009) have not been properly addressed by the sponsor. There is lack of validation of the sterilization procedure of (b) (4) used from bulk to the filling process. A subsequent meeting was held on April 30, 2010 to discuss these issues. FDA also questioned the Sponsor's use of a (b) (4) as opposed to a specific type A antibody in the "abnormal toxicity and safety test". During a teleconference with the Sponsor on May 26, 2010, the Sponsor explained their rationale for choosing this specific antibody. The Sponsor also submitted a justification of this rationale on June 6, 2010, which the agency considered an adequate explanation.

4.3 Nonclinical Pharmacology/Toxicology

Safety Pharmacology:

The sponsor has made the following claims:

- The active pharmaceutical ingredient in NT 201 is (b) (4), biotechnologically derived from *C. botulinum* and purified (b) (4). This ingredient has been used by the sponsor in some of the animal toxicity studies that they have conducted. The extremely high potency of BoNT/A is illustrated by the fact that 1 LDU corresponds to less than 10 pg of (b) (4).
- The intended dose per injection is up to (b) (4) which is a maximum clinical dose of approximately (b) (4); for a 60 kg patient.
- One (1) LDU (abbreviated to Units, U) is the quantity of BoNT/A which kills 50% of male mice by intraperitoneal injection, i.e. the mouse LD₅₀.
- Most of the nonclinical pharmacology and toxicology studies with (b) (4) and NT 201 were conducted in compliance with national GLP regulations and/or OECD guidelines.

REVIEWER'S COMMENTS:

- There have been no data provided on how (b) (4) compares with NT 201 although the Sponsor mentions that NT 201 is the active pharmaceutical ingredient in (b) (4).
- The conclusions below have been obtained from the Sponsor's non-clinical reports of studies done using NT 201 except for hERG channel screening report on cardiovascular effects with which the Sponsor tested concentrations of (b) (4) instead of NT 201.
- **FDA Pharm Tox Reviewer will provide details and comments on the Sponsor's data.**

Single dose toxicity studies

These were done in mouse and Sprague Dawley rats. The LD-50 ranged from 50 Units (given intravenously) to 100,000 Units given orally with the maximum lethal dose causing death within

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

48 hours to 5 days. All animals at 150 LDU/kg died 3 to 8 days after injection and one treated with 50 LDU/kg died on day 5. There was also a decrease in body weight and body weight gain at doses of 50 and 150 LDU/kg. The calculated LD-50 of 41 and 87 LDU/kg was established for male and female mice respectively. The results indicated that 5 LDU/kg can be considered as the NOAEL for a single intramuscular injections of NT 201 in mice, however, there was no LD-50 determined for the IM administration. In male Sprague-Dawley rats, maximum paralysis score was reached by all animals from 48 to 96 hours after treatment at 32 and 64 LDU/kg.

Repeat dose toxicity studies

Repeat dose toxicity studies done in the cynomolgus monkeys who were given doses as high as 12 LDU/kg in 4 weeks for 10 injections resulted in atrophied gastrocnemius muscle fibers. There were no treatment related effects on ophthalmology, cardiovascular function, food consumption, hematology, serum chemistry and urinary parameters. Based on this dose, the NOAEL for systemic toxicity is >4 times higher than the maximal recommended human dose. Doses given above 10 LDU/kg every 2 to 4 weeks caused death when given intramuscularly in the rabbits.

Local tolerance toxicity

Local tolerance of NT 201 has been assessed by histopathological examination of the injection sites in the repeat dose intramuscular study in mice, rabbits and monkeys. No clinically relevant local injection site reactions after repeated intramuscular injection up to 40 LDU/kg (in mice, rabbit and monkeys) or repeated intradermal administration up to 8.34 LDU/kg (in rabbits).

Locomotor activity

The results were dose dependent in mice and the reduction in motility parameters was observed starting at 20 LDU/kg. The NOAEL for motility parameters after a single IV injection is 9 LDU/kg which is approximately 1.3 fold greater than maximum clinical dose in humans (7.24 LDU/kg for 60 kg patient).

CNS Toxicity

Studies in the mouse at repeated doses with an approximate LD₅₀ of 50 LDU/kg showed clinical signs of piloerection, ptosis, lacrimation, mydriasis, reduced motility, muscular tonus, ataxia, hypothermia and dyspnea.

GI toxicity

The NOAEL of a single intramuscular injection of NT 201 for effects on gastro-intestinal motility in rats is 32 LDU/kg which is 4.5 fold greater than the maximum human clinical dose.

Genotoxicity

No mutagenicity studies have been conducted by the sponsor. The sponsor's rationale for not conducting mutagenicity studies is based on the ICH guidance (S6 1996, Module 4, Section 4.3), "The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology derived pharmaceuticals and therefore are not needed."

Carcinogenicity

No carcinogenicity studies have been conducted based on a similar rationale as stated for genotoxicity.

Reproductive and developmental toxicity

The studies which were performed in rabbits and rats did not demonstrate reproductive toxicity up to a dose level that was associated with maternal toxicity. Maternal NOAEL was 30 LDU/kg and embryotoxicity NOAEL was 90 LDU/kg. (b) (4)

(b) (4)

Cardiovascular effects in vivo

Based on studies done by the sponsor, repeated intramuscular administration of dose levels at least two times higher than therapeutically recommended human doses in cynomolgus monkeys, did not show any deleterious effects on atria and intraventricular conduction velocity or ventricular repolarization. The NOAEL for cardiovascular effects in monkeys after four IM injections was 16 LDU/kg. However, a decrease in heart rate and variations in respiratory rate and QT intervals were noted two to three hours after treatment but this was attributed to ketamine hydrochloride anesthesia. Interestingly, one week after treatment, heart rate was markedly higher than during the pre-test period or during the day of treatment and this was associated with an increase in QTc interval duration corrected with Fridericia's formula but no effect was observed on the QTc interval length corrected with Bazett's formula. The sponsor did not consider this as biologically relevant because the increase was less than 20 ms and only visible after correction with Fridericia's formula.

In vitro hERG channel screening: At a concentration of 10,000 LDU/ml, (b) (4) had no effect hERG tail currents at -20mV, which according to the sponsor, this concentration exceeds achievable concentration in human blood concentration. The sponsor further comments that the tested concentration of (b) (4) in the hERG assay exceeds the maximal achievable concentration in human blood by a factor of at least 10,000. Since (b) (4) was used in this particular study, extrapolating results from this study to make conclusions about in vitro hERG channel screening of NT 201 may not be appropriate because of insufficient data comparing the chemical and pharmacologic characteristics between these two preparations.

The Sponsor has made these following comparisons with the other FDA approved botulinum toxins:

- Similar to the diffusion of Botox and Dysport, IncobotulinumtoxinA injection into the mouse tibialis anterior, gastrocnemius or quadriceps muscle was very low.
- Systemic distribution of NT 201 is similar to that of Botox and Dysport based on their effects in single dose comparative intravenous toxicity study in mice.

- NT 201 pharmacokinetics and pharmacodynamics are comparable to Botox based on time course of onset, degree of paralysis and systemic body weight loss induced by intramuscular hindlimb injections in mice.

4.4 Clinical Pharmacology

Mechanism of Action

Pharmacodynamics

Three Phase 1 pharmacodynamics studies were performed by the sponsor in healthy subjects. The sponsor claims, that from these studies, IncobotulinumtoxinA and BOTOX® were similar in terms of time course, degree of muscle paralysis and local diffusion into adjacent muscles. In a sponsor's study on area diffusion, Dysport® produced a greater area of diffusion in the forehead than IncobotulinumtoxinA when given in comparable doses and volume.

The Botulinum toxins inhibit cholinergic transmission at the neuromuscular and autonomic postganglionic synapses reducing excessive muscular activity or glandular secretions.

The mode of action can be divided into extracellular and intracellular components. The heavy chains bind specifically to extracellular structures on cholinergic nerve terminals. Through endocytosis, the light chain of the toxin is then transported across the vesicular membrane into the cytosol. The 4 step sequential process includes:

1. docking to the binding site at the plasma membrane
2. internalization of the BoNT/A molecule
3. translocation into the cytosol of the zinc dependent endopeptidase part of BoNT/A
4. proteolysis of synaptosomal associated protein 25 (SNAP 25), a component of the vesicle fusion machinery, which finally stops exocytosis of acetylcholine.

At the neuromuscular junction, the desired target blockade leads within about a week to retraction of the endplate nerve terminal and compensatory sprouting, with re-innervations and partial recovery of function within a month. Within 2 months, the poisoned terminals begin to exocytose acetylcholine again, leading to true recovery of endplate organization and withdrawal of collaterals. Within 3 months, there is recovery both morphologically and functionally in motor endplate. Clinically, when injected into the target tissue (skeletal muscle or gland), clinical effects are observed in two to five days, reach therapeutic effect at 10 to 14 days and resolve within 16 to 24 weeks. The figure below illustrates the important steps in its mechanism of action at the target organ.

Figure 2. Mechanism of Action of Botulinum Toxin A
Copyright Material

Source: Amon SS, et al. J.Amer.Med. Assoc. 285: 1059, 2001

Pharmacokinetics

Distribution

The high chemical specificity and extreme potency of Botulinum neurotoxin limits PK profile studies in humans.

Absorption

After oral ingestion, the neurotoxin is absorbed in the gastrointestinal tract and taken up by cholinergic terminals leading to the toxic effects seen after ingestion.

Metabolism

After systemic absorption, the neurotoxin is rapidly metabolized to smaller molecular structures. White blood cells play a role in the disposal of circulating toxin type A as shown for other proteins. The neurotoxin is then degraded intracellularly. Like all proteins, Botulinum toxin type A is rapidly metabolized by proteases and molecular components are recycled through normal metabolic pathways.

Drug interactions:

Direct interactions of other drugs with botulinum toxin at the receptor or effector level have not been found. However, botulinum toxin A can potentially interact with any drug which has a peripheral cholinergic mode of action or with drugs that affect neuromuscular transmission like aminoglycosides or curare like compounds.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

The tables below summarize the phase 2 and phase 3 studies of IncobotulinumtoxinA conducted by the applicant. Study 408/1, the pivotal study will be discussed in detail. Supporting studies will include the Randomized Double Blind study, 408/2 and the European efficacy trial, 0013.

Table 4 Tables of Studies/Clinical Trials (Source: Sponsor's Submission, modified by Reviewer)	
Study ID MRZ 60201-0408/1	Safety and Efficacy of two doses of NT 201 compared with placebo in pre-treated and treatment-naïve subjects with Cervical Dystonia
Study Design	Phase 3 Randomized, prospective, double-blind, placebo-controlled, multicenter study (37 study centers in the United States)
Entry Characteristics	Pre-treated and treatment-naïve patients with Cervical Dystonia (predominantly rotational form), TWSTRS total >20, TWSTRS Disability > 3 TWSTRS Severity > 10 TWSTRS Pain >1
Dose	120 U or 240 U NT 201 or placebo in a 1:1:1 ratio
Primary Endpoints	Change from baseline in TWSTRS total score at visit 3 (Week 4)
Secondary Endpoints	TWSTRS Total at all other post baseline visits. Change from baseline in TWSTRS Disability, Severity, and Pain Scores at all post baseline visits. PEGR (Patient Evaluation of Global Response) at Visit 5 (final visit).
Analysis	Planned: 222 subjects (at least 87 subjects treatment naïve; Analyzed: N=233 ITT (Intent to Treat) (90 naïve) N=215 TPP (Treatment Per Protocol) (80 naïve)

Study ID MRZ 60201-0408/2	Extension Phase: To Evaluate the Safety and Efficacy of repeated injections of 2 doses of NT 201 over a one year period
Study Design	Randomized, Double Blind, Parallel Group Multi-center design
Entry Characteristics	Following Visit 4 of the Main Phase, the subject was to be questioned every two weeks, either by phone or at a visit, about the need for a new injection. The interval between two visits was not to exceed 4 weeks. If a subject expressed via phone the need for a new injection, a visit was scheduled immediately. If the physician did not see the need for a new injection (the Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] Total score was <20), the subject was to be seen every 2 weeks from that time. In addition, the subject could return at any time up to Week 20 after the first injection, if he/she felt the need for a new injection session. If the Investigator agreed that a new injection was required (the assessment of the TWSTRS score revealed a TWSTRS-Total score > 20), this represented the end of the MP for this subject and all assessments of the Final Visit (Visit 5) of the MP were performed. The MP for this subject was terminated before any further injections of study medication was administered.
Dose	120 units, 240 units (there were patients who were given less than 120 units; the maximum dose was 240 units)
Duration of Study	68 weeks (Last week of injection at week 48 and 20 weeks of safety evaluation) EP (Extension Phase): up to 5 injection sessions, last injection not later than 48 wks with 20 week safety observation phase.
Primary Endpoints	Change in TWSTRS total score from previous injection
Secondary Endpoints	TWSTRS Disability, Severity and Pain Scores and PEGR

Study ID MRZ 60201-0013	Non-inferiority of NT 201 compared to Botox in terms of Efficacy and Safety in patients with Cervical Dystonia
Study Design	Randomized, double blind, parallel group, active controlled and multicenter design.
Entry Characteristics	Patients with cervical dystonia; previous successful treatment with Botox in two consecutive sessions directly before trial entry
Dose	70-300 u NT 201, 70-300 u Botox intramuscular injection at baseline
Duration of Study	Up to 16 weeks
Primary Endpoints	Change in TWSTRS severity score from baseline to control visit on day 28+/-3 changed into day 28+/-7 after injection of study medication
Secondary Endpoints	TWSTRS Pain subscore, VAS (Visual Analogue Scale), Patient's evaluation of global response at control and final visit, TWSTRS Severity at final visit,
Analysis	Planned: 460 patients randomized including 10% dropouts, 412 TPP; Analyzed: 463 patients ITT, 420 patients TPP Number of patients in analyzed as per submitted data: 466

REVIEWER'S COMMENTS:

- Whereas Study 60201-0013 will be discussed in this review to supplement the safety data and demographics, it cannot be used to compare its efficacy results to the pivotal study 408/1. The primary endpoint in Study 0013 is the TWSTRS Severity subscale score as compared to the TWSTRS Total score (the severity subscale was selected as a secondary endpoint) used in Study 408/1 , which makes it more difficult to compare efficacy data across trials.

The table below summarizes the key features of other clinical trials exploring the effects of NT 201 in other conditions. All these studies have been conducted in Europe where the medication is approved for most of these indications. These are also the studies that have been submitted for the indication of Blepharospasm and Spasticity. A separate review of Blepharospasm has been submitted

(b) (4)

(b) (4)

Table 5. Other Clinical Trials conducted by the Sponsor in evaluating IncobotulinumtoxinA for other indications. (Source: Sponsor's submission)

Study	Title/Design	Dosage and Site of Administration	Number of subjects	Diagnosis	Duration of study
MRZ 60201-410/1	Randomized, double blind placebo controlled parallel group multicenter trial to test superiority of NT 201 compared to Placebo	170 to 400 units IM	ITT = 148 TPP = 140 EFS = 148	Naïve and pretreated post stroke spasticity of the upper limb	Up to 20 weeks
MRZ 60201/410/2	Open label, non controlled multicenter trial to evaluate Efficacy and safety of individually dosed, repeated injections of NT 201 over one year	Up to 400 units, repeated treatments with up to 5 injection sessions	ITT = 145 TPP = 145 EFS = 145	Post stroke spasticity of the upper limb who participated in the placebo controlled study MRZ 60201-410/1	Up to 49 weeks
MRZ 60201/607/1	Prospective, observer blind, randomized multicenter controlled study to evaluate efficacy and safety of two dilutions of NT 201	Up to 400 units (20 or 50 ml dilution)	ITT = 192 TPP = 165 EFS = 192	Pre treated or treatment naïve subjects with spasticity of the upper limb of various etiologies	Up to 20 weeks
MRZ 60201-433/1	Randomized double blind, placebo controlled, multicenter study to	Up to 50 u per eye vs. placebo in a 2:1 ratio	ITT = 109	Pretreated patients with Blepharospasm with previous successful treatment with	Up to 20 weeks

	evaluate safety and efficacy of NT 201			Botox in 2 consecutive sessions before trial entry	
MRZ 60201-003	Randomized double blind, active controlled (Botox) parallel group multicenter trial to test non-inferiority of NT 201 compared to Botox	<35 U per eye of NT 201 <35 U per eye of Botox	ITT = 300 TPP = 256 EFS = 303	Pretreated Blepharospasm patients with previous successful Botox treatment in two consecutive sessions before trial entry	Up to 16 weeks

5.2 Review Strategy

Efficacy review:

The review strategy will focus on the following questions:

1. Is NT 201 (b) (4) doses of 120 units and 240 units) superior to placebo in the treatment of cervical dystonia?

- The review will rely primarily on study 408/1 for the evaluation of effectiveness. The primary source of efficacy data will be TWSTRS Total Score at Week 4 (Visit 3) compared to the TWSTRS Total Score at the Baseline Visit. This 20 week (12-to 16-weeks treatment period) duration pivotal study (408/1) presented by the Sponsor is a randomized, multicenter trial to investigate the efficacy and safety of the 120 and 240 unit doses of NT 201 in the treatment of cervical dystonia. This is the only study that included sites in the United States.
- The FDA agreed to accept data from a single pivotal trial in CD with supporting data coming from the Blepharospasm (another focal dystonia) pivotal trial. The Meeting Discussion from June 11, 2007 clarified this in the meeting minutes:
 - *“The Division agreed that the currently ongoing CD trial in pretreated and treatment naïve patients combined with the currently ongoing Blepharospasm trial in pretreated patients appeared capable of fulfilling the requirement for two adequate and well controlled trials necessary for a BLA in CD”.*
- The sponsor had also submitted efficacy data from Study MRZ 60201-0013 which supported the approval of IncobotulinumtoxinA for the CD indication in Europe. The

trial is designed as a non-inferiority trial comparing NT 201 to Botox. The trial will not be relied upon heavily because of its lack of assay sensitivity (there was no placebo arm) but will be analyzed for safety.

2. Is there an added benefit to treating patients with 240 units instead of the 120 units?

The data from the pivotal study 408/1 and to a lesser degree the extension study 408/2 will be used to analyze data to evaluate the benefits of a 240 units over 120 units.

- What are the significant differences in the TWSTRS scores (if any) of those who had received 240 compared to 120 units of NT 201?
- Are there any subgroups that have benefitted from the 240 units more than 120 units of NT 201?
- What is the effect of duration (from previous dose) and frequency of injections in the dose response, if any, between the two treatment groups?

3. What is the duration of effectiveness of NT 201?

- The data from the Extension Phase of trial (408/2) will provide data regarding duration of treatment effect and sustained benefit.

A separate efficacy review of NT 201 for the indication of Blepharospasm was assigned to Dr. Kenneth Bergman, MD, FAAN.

Safety Review:

This clinical reviewer looked at safety data review from all the clinical trials listed in the following:

- Pivotal trial 408/1
- Extension Phase of Clinical Trial 408/2
- Non inferiority Clinical Trial done in Europe: Clinical Trial 0013

The safety review was assigned to Dr. Lisa Jones, MD, MPH.

5.3 Discussion of Individual Studies/Clinical Trials

Trial: Study Protocol: MRZ 60201-0408/1

This is the sponsor's presentation of the trial design.

Title: Prospective, double-blind, placebo controlled, randomized, multicenter trial with a double blind parallel group extension period (408/2) to investigate the efficacy and safety of different doses of NT 201 in the treatment of cervical dystonia.

Phase 3

Purpose: To investigate the safety and efficacy of 240 units dose and the 120 units dose of NT 201 compared with placebo in subjects with Cervical Dystonia as well as to compare the efficacy and tolerability of the two doses of NT 201.

Trial design: Prospective, multicenter trial, randomized, double blind, placebo controlled parallel group (240 units group and 120 units group), single treatment.

Endpoints:

Primary endpoint:

The primary efficacy variable was the change from Baseline to Week 4 (Visit 3) following injection in the TWSTRS Total Score, in the Intent to Treat (ITT) Population. This was similar to the endpoint used in the studies for approving Dysport®. In contrast, the studies on Botox® used the Cervical Dystonia Severity Scale which was devised for the Botox study combined with Physician Global Assessment Scale.

- TWSTRS Total score is the sum of the TWSTRS Severity, Disability and Pain Score and ranges from 0 to 85 points where higher scores indicate greater impairment.
- The TWSTRS total score was to be carried out at each visit and the change from baseline was to be obtained by computing the difference between the TWSTRS score at baseline and at each visit.

Analysis of Primary Endpoint:

- **Analysis Populations:** All efficacy analyses will be performed on the ITT population and TPP population.
 - Intent to Treat (ITT) Population: all randomized subjects were included in the analyses of each endpoint parameter. This was the primary analysis population.
 - Treatment per Protocol (TPP) Population: Identical to the ITT population but excluding subjects with identifiable protocol

deviations; this population was also used for the sensitivity analyses.

- **Methodology:**
 - First analysis will occur after completion of the Main Phase. The blind was broken in order to proceed to statistical analysis of results after the BDRM (blind data review meeting) and after the database was closed for the Main Phase.
 - Second analysis will occur when 100 subjects will have completed the Extension Phase with an observation period of at least 48 weeks for the 120-day safety update that will be sent to the FDA after the NDA has been filed.
- **Randomization:**
 - Each subject received one intramuscular injection of the investigational product or placebo. Subjects were randomized to the 240 U, 120 U or the placebo group. As the identity of the study medication was not provided, the treatment assignment remained blinded from patients and study site personnel.
 - Depending on the treatment arm, the trial medication for a particular patient consisted of 4 vials with 100 U NT 201 (240 units), 2 vials with 100 units NT 201 and 2 vials with placebo (120 U group or 4 vials with placebo (Placebo group).
 - The same subject number assigned to a patient at V2 (baseline visit) was used for both the Main and Extension phases of the trial. The patients from the Main Phase were re-randomized at the start of the extension phase to 120 or 240 units of IncobotulinumtoxinA in a double-blind fashion. Randomization was performed using RANCODE version 3.6 which ensured blocked randomization by centers. The duplicates of randomization lists were sealed and stored in a safe in the Total Quality Management Department of Merz Pharma. They were not accessible prior to database close of the respective trial period
- **Handling method for missing data include:**
 - Missing value replaced by baseline value
 - Observed Cases
 - Missing value replaced by Group Mean

Primary Efficacy Parameters:

- Primary efficacy parameter is the change from baseline Visit 2 (Day 0) in the TWSTRS total score to control visit 3 (week 4). Confirmatory analysis will be performed for the difference between the treatment groups in the ITT population.
- Confirmatory analysis of the primary efficacy parameter will be based on the comparison of least square means from an analysis of

covariance (ANCOVA) model at Visit 3 (Week 4) between treatment groups. ANCOVA will be used to define the model for the primary efficacy analysis. The dependent variable is the change from baseline of TWSTRS Total score and the independent variables are treatment, baseline TWSTRS Total score, gender, age, pre-treatment of cervical dystonia and pooled center.

- Comparisons between treatment groups will be performed by using a fixed sequence test procedure (step downward) in the ITT Population.
 - The first hypothesis of the first step downward test procedure is the comparison between the NT 201 Regular Effective Dose Group (240 units) and placebo regarding least square means for the change from baseline in the TWSTRS Total score.
 - If the null hypothesis has to be rejected, the second test procedure will be performed to compare the NT 201 MED (minimal effective dose = 120) with placebo.
 - A further test between NT 201 240 U (or regular effective dose) group and NT 201 120 U (or minimal effective dose) group will investigate the difference between the 2 active treatments.
 - Three different models will be presented:
 - Full model with all adjusting variables used for confirmatory testing
 - Final model with all adjusting variables with an influence of $p \leq 0.2$ on the model
 - Simple model including only treatment effect used as sensitivity analysis.
 - All tests of the fixed sequence test procedure will be performed two sided with a type I error of $\alpha = 0.05$.
 - Sensitivity will be performed to assess the influence of the data on the primary efficacy outcome

Secondary Endpoints:

- The secondary efficacy variables were change from baseline in the TWSTRS Total score at all other post baseline visits...
 - Change from baseline in TWSTRS Disability, Severity and Pain Scores were carried out at baseline and at each post baseline visit.
 - TWSTRS severity scale ranges from 0 to 35 points and consists of the following ratings: Maximal Excursion (rotation, lateroanteriorcolls/retrocollis), Duration factor, Effect of sensory tricks, Shoulder elevation, Range of motion and Time factor.
 - TWSTRS Disability scale is an assessment of the degree to which daily activities may be affected by cervical dystonia. Each category is reported on a 6 point scale and total disability scores ranges from 0 to 30 points (higher scores indicate greater impairment. The categories of the questions include work

performance (job or domestic), activities of daily living (feeding, dressing, hygiene), driving, reading, watching TV and leisure activities at home.

- TWSTRS Pain scale was used as part of the inclusion criteria it measures the subject's pain during the week prior to the study visit. The TWSTRS Pain scale ranges from 0 to 20 points and is the sum of a pain severity component, a duration component and assessment of the contributing pain to disability. The pain severity component ranges from 0 to 10 points with "0" meaning no pain and "10" the most excruciating pain imaginable". The subject rates the severity of neck pain experienced during the past week with three different grades: the best, the worst, and the usual pain status. The value of the pain severity component is calculated as:
$$\text{Severity} = [(2 \times \text{usual}) + \text{best} + \text{worst}] / 4$$
 - Pain duration component: Subject rates the duration of neck pain on a 6 point scale
 - Contribution of pain to disability: Subject rates the degree to which pain contributes to disability on a 6 point scale
- Patient Evaluation of Global Response (PEGR) at Visit 5 (final visit)
 - PEGR scale is a descriptive subjective 9 point response scale including the following:
 - Very marked worsening (-4)
 - Marked worsening (-3)
 - Moderate worsening (-2)
 - Slight worsening (-1)
 - Unchanged (0)
 - Marked Improvement (+1)
 - Moderate improvement (+2)
 - Slight improvement (+3)
 - Complete abolishment of signs and symptoms (+4).

Secondary Efficacy Parameters

- For the secondary and tertiary parameters, the sponsor did not adjust for multiplicity nor did they identify a priori any secondary or tertiary endpoints for inclusion in the product label.
- TWSTRS Subscale scores (Disability, Severity and Pain) will be analyzed at Control Visit 3 (week 4) of the Main Period using the same analysis procedures used above in the TWSTRS Total score. All three treatment comparisons will be tested in the ANCOVA models as described for the primary efficacy endpoint above and the evaluations will be conducted for the ITT population...

- Patient Evaluation of Global Response (PEGR) will be analyzed at The Final Visit (Visit 5) of the Main Phase using an ANCOVA procedure in the ITT population. Missing data of this endpoint will be set to 0.

Tertiary Endpoints:

- Duration of Effect Measurement Variables
 - Time to onset of treatment: Time (days) from injection (Day 0) to the subjective estimation of the onset of effect. The subject was asked if he/she felt whether there had been a treatment effect at all telephone contacts/visits until Visit 4 (Week 8). If the subject answered “yes”, he/she was asked at which day after the injection the effect had occurred.
 - Time to waning of treatment effect after injection (subjective): Time (weeks) from injection session (Day 0) to the subjective estimation of the waning of effect. Subjects who reported an onset of treatment effect were asked at each visit and telephone contact, starting on Week 4 at the earliest up to the Final Visit of the Main Period if he/she felt whether there had been a waning of treatment effect. If the subject answered “yes”, he/she was asked at which week after the injection the waning of effect had occurred.
 - Duration of Treatment Effect: The duration of treatment effect is defined as time period from the day of injection until the time point of a new injection.
- Global Assessment of efficacy by investigator: The Investigator performed a global assessment of the efficacy of study treatment at Final Visit of the Main Phase on a 4 point Likert scale, with the following items being available: “very good”, “good”, “moderate” and “poor”

Safety endpoints:

- Adverse Events and baseline complaints
- Standard clinical chemistry and hematology
- Vital signs, body weight

Safety Analysis:

- Interim Safety Analysis will be performed for the first 100 completers of the Extension Period (for the 120-day safety update).
- Evaluable for Safety (EFS) Population, which is all subjects who received any amount of trial medication during the main phase, will be included in the safety analysis.

REVIEWER'S COMMENTS:

- The Agency had recommended use of the total TWSTRS instead of the Severity component. The Severity Component of the TWSTRS was used as the primary endpoint in the study done in Europe. Because the company has a claim for pain in their label, analysis of the TWSTRS Pain scores is important in this study.
- The secondary endpoints of Pain, Disability and Severity are components of the TWSTRS total (primary endpoint) and do not provide any added information to the TWSTRS total score since they are both merely subscales of the TWSTRS.
- The PEGR would have provided more information about patient response correlating it to efficacy of the drug if it was obtained at the primary endpoint visit (Week 4, around the peak of the first injection).
- The duration of treatment effect is an important tertiary endpoint because it tells us when the drug had passed its peak which may provide a rough estimate of when a patient needs injections. It would have been a more effective measure of need for injection if patients were followed up at least every week after they have reported that they need injection up to the time that they are actually injected.
- Because there was no formal statistical plan for the secondary endpoints, and no plan to deal with multiplicity, we regard these endpoints to be exploratory in nature.

Inclusion

- Male/Female age 18 to 75 years
- Clinical Diagnosis of Cervical dystonia of predominantly rotational form
- TWSTRS total score > 20, TWSTRS severity > 10, TWSTRS Disability > 3, TWSTRS Pain > 1
- On a stable dose of other medications (if any) used for focal dystonia treatment (e.g. anticholinergics and benzodiazepines) for at least 3 months prior to and expected throughout the Main Period.
- For pretreated subjects only: There should be documentation of the last two consecutive injection sessions with Botulinum toxin and stable therapeutic response directly prior to trial entry. The subject must have at least 10 weeks duration between the last injection with botulinum toxin for cervical dystonia and baseline visit and most recent injection with botulinum toxin must have been a maximum of 300 units of type A or 12000 units of type B.

Exclusion

- Traumatic torticollis or tardive torticollis
- TWSTRS-Severity score for anterocollis>2 (pure anterocollis)
- TWSTRS Severity score for retrocollis>2 (pure retrocollis)
- Myotomy or denervation surgery in the affected muscles
- Hypersensitivity to human serum albumin, sucrose or Botulinum toxin Type A
- Diagnosis of myasthenia gravis, Lambert Eaton syndrome, amyotrophic lateral sclerosis or any other significant neuromuscular disease which might interfere with the trial
- Current swallowing disorder of any origin (dysphagia scale>3=severe, with swallowing difficulties and requiring a change in diet)
- Marked limitation on passive range of motion that suggests contractures or other structural abnormality, e.g. cervical contractures or cervical spine syndrome
- Treatment with Botulinum toxins for any indication other than cervical dystonia within 4 months prior to Baseline and during the trial
- Known current alcoholism or other drug abuse/dependence
- Severe or uncontrolled systemic disease (cardiac, renal pulmonary, hepatic, gastrointestinal, malignant tumor or know HIV infection)
- Present or pre-existing blood coagulation disorders including therapeutic or prophylactic anticoagulation
- Infection in the area of planned injection points or systemic infection presenting a hazard for local injections into the neck muscles
- Planned elective surgery under general anesthesia during the trial
- Nursing mothers
- Severe impairment of cognition or communication that in the opinion of the Investigator does not enable the subject to understand the Informed Consent and participate in the trial
- Patients who are currently involved or were involved within the past three months in another therapeutic research study.
- Previous participation in this clinical study

REVIEWER'S COMMENTS:

- The inclusion and exclusion criteria stated by the sponsor are appropriate for trial entry and are likely to adequately represent the typical patient that may receive treatment with IncobotulinumtoxinA if it is approved by the FDA. They are the same as the inclusion/exclusion criteria in the European study 0013 except that 408/1 includes naïve patients in the study.

Concomitant Medication

- **Prohibited medications**
 - Botulinum toxin of any serotype in any body region four months prior to trial entry
 - Concomitant treatment with phenol or alcohol injections
 - Treatment with intrathecal baclofen was not allowed within two weeks prior to screening and during the maintenance phase of the trial
 - Parenterally administered drugs that interfere with neuromuscular transmission (tubocurarin, volatile anesthetics, barbiturates)
 - Aminoglycoside antibiotics of any dosage and route of administration (e.g. amikacin, gentamicin, netilmycin, spectinomycin, tobramycin,)
 - Antimycobacterials (streptomycin, dihydrostreptomycin)
 - Other antibiotics like lincosamide, tetracyclines and polymyxin
 - Aminoquinolines (chloroquine and hydroxychloroquine)
 - Anesthetics (including those locally applied in the area anticipated for treatment)
 - Drugs that interfere with neuromuscular transmission: phenothiazine/neuroleptics like chlorpromazine, trifluoperazin, prochlorperazin, verapamil, dantrolin or quinine

- **Permitted Medications**
 - Any concomitant medication that was not related to the treatment of cervical dystonia
 - Non steroid anti inflammatory drugs for pain relief
 - Peripheral muscle relaxants are to be used with caution. Intermediate action agents were to be used in preference to those with longer lasting effects and starting dose was to be reduced.
 - These medications are allowed if doses are stable for at least 3 months prior to entry and during the course of the Main phase. Changes in the doses of these medications were allowed in the Extension Phase
 - Anti depressive medications of any route of administration
 - Opioid analgesics
 - Oral medications for treatment of focal dystonia: anticholinergics like trihexyphenidyl, bntropine, ethopropazine/profenamin, tiapride, procyclidine
 - Benzodiazepines

REVIEWER'S COMMENTS:

- The medications used for the symptomatic treatment (and used off label) have been listed above in the Sponsor's protocol. There has been no mention of other anti-epileptics such as Gabapentin that can reduce pain or somehow cause muscle relaxation. These medications are important because taking these medications at a period following injection may affect the efficacy data by providing relief. If there is an imbalance in the

treatment assignment of patients taking concomitant medications it could bias towards the treatment groups. Analysis of the sponsor's data on concomitant medication use for patients in study 408/1 did not find that there was a significant imbalance in the amount or type of concomitant medication use between patients enrolled in the 3 treatment arms.

Subject Enrollment:

- Planned: 222 subjects (N=74 per treatment group of MP with at least 87 subjects (40%) treatment Naïve
- Analyzed for MP:
 - N=233 (81 in group 240 U, 78 in group 120 U and 74 in placebo group) for safety and ITT population (including 90 naïve subjects)
 - N=215 (77 for 240 U, 70 for 120 U, 68 for placebo) in TPP population with 89 naïve subject

Sample Size Estimation: The sample size was based upon a 2 sided t test at $\alpha = .05$ level. A study with N=49 completing subjects per group has 90% power to detect a treatment difference of 4 points for placebo and of 10 points for 240 U group with a common standard deviation of 9 points for the mean change from baseline in TWSTRS total score. The sample size was increased to 59 subjects per group to increase the database size for safety assessments and to increase the power for demonstrating a difference between 120 units group and placebo. Assuming a 20% dropout rate, a target of 74 subjects per treatment group was required, with a total sample size of 222 subjects.

Protocol Deviations:

- Defined as deviations from the procedure outlined in the protocol.
- Identified for each subject during the respective Blind Data Review Meeting for the MP/EP.
- Assessed as “minor” or “major” depending on its impact on efficacy results.
- Protocol deviations were fully documented prior to unblinding.

Treatments and other ancillary management

The protocol did not prespecify the amount of study medication to be injected per muscle or the number of injections. The protocol described the total volume (4.8 ml) of the study drug to be injected, which was equal for all 3 treatment arms. The instruction was “The Investigator must rely on a careful physical and neurological examination of the patient, as well as previous experience to select the dystonic muscles” for treatment. In addition, a table of muscles frequently involved in stereotypic abnormal head positions was provided to help the investigator determine which muscles to inject with the study drug. The Investigator also determined the number of injection sites and the dose at each site. The maximum volume of IncobotulinumtoxinA that could be administered in a single injection could not exceed 1.0 to 1.2 ml. A table of drug exposure of NT 201 (U) by muscles used in Patients with Cervical Dystonia was provided by the sponsor as a guide. The protocol included a statement that “an injection

with more than 100 U in the sternocleidomastoid (SCM) and a bilateral injection in the sternocleidomastoid muscles should be avoided to decrease the risk of dysphagia. Additionally, an injection in “the upper third of the sternocleidomastoid will minimize the risk of dysphagia”. Most patients received well below 100 units in the SCM during the Main and Extension Phases of the trial.

Study Visits Checklist

Table 6. Study schedule of the Main Period (Source: Sponsor’s Submission)

Text Figure 2: Main Period Schedule of Events

Trial visit	V1 (Screening)	V2 (Baseline)	T1 Telephone Contact	V3 (Visit)	V4 (Visit)	Optional phase: At least fortnightly contacts (visits and telephone calls)*		V5 (Final Visit Main Period)
	Day -7 ± 3 days	Day 0	Week 1 (Day 7± 1 day)	Week 4 (Day 28± 3 days)	Week 8 (± 3 days)	Week 10, 12, 14, 16, 18 or visits on subject’s request		Up to Week 20
Assessment time point and time window						Phone call	Visit	
Informed consent	X							
Med. His. / Conc. Dis. / Conc. Med.	X							
Demographic data	X							
Physical/Neurological examination, body weight	X							X
Inclusion & exclusion criteria	X	X						
TWSTRS-Total score	X	X		X	X		X	X
Dysphagia scale	X	X	X	X	X	X	X	X
Vital signs	X	X		X	X		X	X
ECG	X							
Clinical Chemistry, Hematology	X							X
Antibody titer	X			X				X
Pregnancy test	X (Blood)	X (Urine)						X (Blood)
Patient Evaluation of Global Response***								X
Randomization for Main and Extension Period		X						
Injection session		X			Ask for need	Ask for need	Ask for need	Ask for need
Adverse events	X**	X**	X	X	X	X	X	X
Changes in Conc. medication /Conc. Diseases		X	X	X	X	X	X	X
Global assessment of efficacy/tolerability								X
Onset (O) / Waning (W) of effect			X (O)	X (O/W)	X (O/W)	X (W)	X (W)	X (W)
Documentation of termination of Main Period								X

Subgroup Analysis:

Demographic and Baseline Characteristics: Data will be compared among the three treatment groups with descriptive statistics and frequency tables.

Naïve vs. Pre-treated Subjects: Subgroups analysis of treatment naïve and pretreated patients will be performed for all efficacy and safety analyses in both the main and extension phase.

- **Treatment naïve subjects:** All randomized subjects who did not receive any prior treatment with botulinum toxin of any serotype.
- **Pre-treated subjects:** All subjects of the EFS population who received prior treatment with Botulinum Toxin of any serotype.

Protocol Amendments

The following Amendments were dated March 24, 2006:

1. Start date changed from March 2006 to July 2006.
2. Enrolment of 222 patients with at least 87 patients (40%) as treatment naïve. The previous protocol only reported enrolling 198 treatment naïve and pretreated patients and there was no mention of how many patients will be treatment naïve.
3. An amendment allowed dose reduction in case of essential safety concerns in the Extension Period.
4. All analysis will be performed on the ITT as well as TPP population and all safety analyses of the Main Period will be performed on the subgroups of treatment naïve and pre-treated patients.
5. In the case in the EP that 240 U of NT 201 would represent an essential safety concerns, the volume of 4.8 ml can be reduced.
6. Patients counted as treatment naïve in the Extension Period were all treatment naïve patients who participated in the Main Period and who were randomized to the placebo group. These patients will be handled as treatment naïve in the extension in the Extension Period until they receive the 2nd injection during Extension Period.
7. All efficacy analyses will be performed in the subgroups, the ITT and TPP population.
8. Safety analysis will be performed for the whole sample as well as for treatment naïve and pre-treated patients separately for Main Period and Extension Period.

The following amendments were made on April 18, 2007

1. The trial will be performed in approximately 40 centers (as opposed to 35 centers).
2. Treatment periods with any type of Botulinum toxins prior to screening should be recorded. Certain previous medications or treatment, if applied within the time frame in the exclusion criteria, will prevent a patient's enrollment in the study.

6 REVIEW OF EFFICACY

Efficacy Summary

6.1 Indication

In the proposed label submitted by the sponsor, the drug **Xeomin® is indicated** (b) (4)

i. This study investigated the efficacy, safety and tolerability of two doses of NT 201 (240 U and 120 U doses) compared to placebo in subjects with Cervical Dystonia. The study involved 37 centers in the United States, enrolling 233 patients from July 24, 2006 to March 19, 2008. Its Extension Phase (408/2) is ongoing with 24 blinded patients. The indications written in the label for both Botox A® and Dysport® are similar to the indications proposed by Xeomin®.

This is a randomized, double blind, placebo controlled, single treatment study which measured the TWSTRS total score, the primary efficacy parameter, at week 4 (visit 3) after baseline injection. Secondary efficacy variables obtained are the subscores of the TWSTRS total which include Disability, Severity and Pain. A Patient Evaluation of Global Response at the Final Visit of the Main Phase was done. Tertiary efficacy parameters include duration of effect, time to onset and time to waning of treatment after injection. The choice of measuring the efficacy parameter at the 4th week coincides with the peak of effect of the dose as seen in studies for the other botulinum toxins. The Sponsor also lists relief of pain in the desired indication and the TWSTRS Pain subscore was the only data used to support this claim. The result from these subscore was not replicated with another validated rating scale for pain such as the VAS. Although the tertiary treatment efficacy parameters rely on subjective reporting, including these parameters in the Sponsor's protocol will provide a rough estimate on the frequency of administration of the drug. Each of the primary and secondary efficacy parameters were evaluated in different subgroups (gender, pre-treated and naïve patient).

6.1.2 Demographics

The two tables below present the sponsor's summary of the Demographic data of each randomized group and more specifically, classifying into each subgroup. Generally, the groups are identical in age and race distribution.

Table 7. Demographic data for the ITT population. (Source: Sponsor's submission)

Parameter	240 U group N = 81 n (%)	120 U group N = 78 n (%)	Placebo group N = 74 n (%)	Total N = 233 n (%)
Gender				
Male	27 (33.3%)	27 (34.6%)	25 (33.8%)	79 (33.9%)
Female	54 (66.7%)	51 (65.4%)	49 (66.2%)	154 (66.1%)
Race				
American Indian or Alaskan Native	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.4%)
Asian	0 (0.0%)	0 (0.0%)	3 (4.1%)	3 (1.3%)
Black or African American	2 (2.5%)	0 (0.0%)	4 (5.4%)	6 (2.6%)
Hispanic or Latino	5 (6.2%)	3 (3.8%)	2 (2.7%)	10 (4.3%)
White	74 (91.4%)	74 (94.9%)	65 (87.8%)	213 (91.4%)
Smoking				
Non-smoker	39 (48.1%)	36 (46.2%)	38 (51.4%)	113 (48.5%)
Smoker	22 (27.2%)	19 (24.4%)	11 (14.9%)	52 (22.3%)
Ex-smoker	20 (24.7%)	23 (29.5%)	25 (33.8%)	68 (29.2%)
Age (years)				
Mean (SD)	53.2 (12.17)	52.8 (11.53)	52.4 (10.75)	52.8 (11.47)
Median	53.0	54.0	52.0	54.0
Height (in)				
Mean (SD)	65.9 (3.44)	66.8 (3.67)	66.56 (3.33)	66.4 (3.49)
Median	66.0	66.4	66.0	66.0
Weight (lb)				
Mean (SD)	160.8 (35.46)	178.6 (36.26)	170.1 (35.52)	169.7 (36.35)
Median	160.0	179.0	165.0	165.0
Body Mass Index [a]				
Mean (SD)	25.9 (5.19)	28.1 (5.63)	26.9 (4.49)	27.0 (5.20)
Median	24.4	27.7	26.9	26.4

Source: Table 14.1.3.1.1
 [a] BMI was calculated according to the formula: BMI = (Weight(lb) / Height(in)²) x 703.
 SD=Standard Deviation, U=Units

REVIEWER'S COMMENTS

- In clinical trial 408/1, the mean age was 52.8 years (17% or 39 patients were 65 years old and above). This is consistent with the age of occurrence of cervical dystonia. There is a predominance of females (66%) enrolled in the study compared to males, which is consistent with the data from previous epidemiologic studies (Nutt, JG, et al. Mov Disord 1988; 3:188-194) in Cervical dystonia reporting a 2:1 female predominance over males.
- Two hundred thirteen patients were Caucasians and 20 were non Caucasians (Asians, African American, Hispanic or Latino and American Indian). This difference is not expected to affect the safety or efficacy outcome of the study as incidence of Cervical dystonia has been reportedly higher in white individuals (1.23/100,000) than other races (0.15/100,000) (Tanner CM, et al Neurology. 2007, 69:676-680).

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

- The median weight was slightly higher by 19 lbs in the 120 U group (179 lbs) than in the 240 U group (160) and placebo group (165 lbs). This is not explained by the gender distribution of the groups as there are equal number of males and females in each treatment arm. The BMI (affected by weight) is also higher in the 120 U group.
- There were a total of 39 patients who were 65 years or older. The oldest patient enrolled in the study is 79 years old. Only 25 patients over the age of 65 were treated with IncobotulinumtoxinA (14 patients received 240 U and 11 patients received 120 U). There were too few patients age 65 or older enrolled in the study to make any inference regarding tolerability and safety of IncobotulinumtoxinA in this patient population.

The table below is a summary of the demographic data which further divides these subgroups mainly according to gender and pre-treated and naïve patients.

Table 8. Demographic Data for Subgroups of Treatment Naïve and Pre-treated subjects (ITT Population) (Source: Sponsor's submission).

Parameter	240 U group		120 U group		Placebo group	
	Treatment-Naïve N=31	Pre-treated N=50	Treatment-Naïve N=31	Pre-treated N=47	Treatment-Naïve N=28	Pre-treated N=46
Gender						
Male	8 (25.8%)	19 (38.0%)	10 (32.3%)	17 (36.2%)	11 (39.3%)	14 (30.4%)
Female	23 (74.2%)	31 (62.0%)	21 (67.7%)	30 (63.8%)	17 (60.7%)	32 (69.6%)
Race						
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.5%)
Black or African American	1 (3.2%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	2 (7.1%)	2 (4.3%)
Hispanic or Latino	2 (6.5%)	3 (6.0%)	0 (0.0%)	3 (6.4%)	2 (7.1%)	0 (0.0%)
White	28 (90.3%)	46 (92.0%)	31 (100.0%)	43 (91.5%)	24 (85.7%)	41 (89.1%)
Smoking						
Non-smoker	15 (48.4%)	24 (48.0%)	17 (54.8%)	19 (40.4%)	16 (57.1%)	22 (47.8%)
Smoker	9 (29.0%)	13 (26.0%)	6 (19.4%)	13 (27.7%)	6 (21.4%)	5 (10.9%)
Ex-smoker	7 (22.6%)	13 (26.0%)	8 (25.8%)	15 (31.9%)	6 (21.4%)	19 (41.3%)
Age (years)						
Mean (SD)	50.9 (12.07)	54.7 (12.13)	50.9 (11.89)	54.0 (11.23)	51.5 (10.51)	53.0 (10.97)
Median	51.0	55.5	53.0	57.0	53.0	52.0
Height (in)						
Mean (SD)	65.4 (3.13)	66.2 (3.61)	67.2 (3.39)	66.6 (3.86)	66.9 (3.09)	66.4 (3.48)
Median	65.0	66.0	66.8	66.0	66.0	66.5
Weight (lb)						
Mean (SD)	161.2 (39.96)	160.5 (32.67)	164.9 (30.67)	187.6 (37.10)	173.9 (37.97)	167.9 (34.28)
Median	158.1	161.0	161.9	191.0	165.0	164.0
Body Mass Index [a]						
Mean (SD)	26.5 (6.43)	25.6 (4.25)	25.7 (4.58)	29.7 (5.72)	27.1 (4.45)	26.7 (4.56)
Median	24.7	24.3	24.7	28.7	27.4	26.8

Source: Table 14.1.3.1.1

[a] BMI was calculated according to the formula: $BMI = (Weight(lb) / Height(in)^2) \times 703$.

SD=Standard Deviation, U=Units

REVIEWER’S COMMENTS

- The gender, race distribution and age in years are similar in the subgroups of pre-treated and naïve patients and are not different from those seen in the general population. Patients in the 120 U, pre-treated group have a higher BMI compared to all the groups. This group may need higher doses of botulinum toxin to attain benefit and to arrive at a significant change in TWSTRS score from baseline to week 3.

Medical History:

A. Duration of Disease

The reported medical history of the subjects in the study showed the following:

- The prevalence of musculoskeletal and neurologic disorders that can affect cervical dystonia were similar in the 240 U, 120 U and placebo groups.
- All patients, as required in the inclusion criteria, had the rotational form of cervical dystonia.

The table below reveals differences between duration since first diagnosis and estimated duration of cervical dystonia in naïve vs. pre-treated patients. The shorter disease duration for naïve patients in all 3 treatment arms is expected although the 120 U group had CD for 1 year (median) longer compared to patients in the 240 and placebo groups. This difference in disease duration is not likely to affect drug effectiveness.

Table 9. Duration since First Diagnosis and Estimated Duration of Cervical Dystonia in Subgroups of Treatment Naïve and Pretreated Subjects in the ITT Population (Source: Sponsor).

Parameter	240 U group		120 U group		Placebo group	
	Treatment-Naïve N=31	Pre-treated N=50	Treatment-Naïve N=31	Pre-treated N=47	Treatment-Naïve N=28	Pre-treated N=46
Duration Since First Diagnosis (months)						
Mean (SD)	8.7 (18.85)	84.9 (73.97)	25.3 (59.40)	73.5 (64.73)	5.4 (16.69)	93.0 (76.04)
Median	2.1	62.0	1.1	53.8	0.8	62.8
Estimated Duration of CD (months)						
Mean (SD)	88.5 (108.62)	134.1 (103.89)	113.6 (118.03)	109.4 (88.83)	106.8 (116.34)	143.7 (100.88)
Median	60.0	102.0	72.0	92.0	60.0	122.5

REVIEWER’S COMMENT:

- Duration of Cervical dystonia is based on when the patient first experienced the symptoms. Pre-treated patients in both the placebo and 240 U group had longer disease duration. The treatment naïve patients were diagnosed more recently than the pre-treated patients in all treatment groups which is expected.

B. Concomitant Medications

The table of concomitant medications (below) taken by the patient at the time of enrolment into study 408/1 and 408/2 is important because some of the medications might alleviate the symptoms of CD and this effect may be attributed to IncobotulinumtoxinA. Important medication classes in this table are the anti-inflammatory, analgesics, psychoanaleptics, antiepileptics, psycholeptics and muscle relaxants. These treatments have been used (although not FDA approved) to relieve some of the symptoms of cervical dystonia (including pain). The protocol required that the patients be maintained on stable dosages of these medications prior to trial entry to prevent the effect of these drugs in influencing the efficacy endpoints for IncobotulinumtoxinA.

Table 10. Concomitant Medication by ATC Class (applying to > 10% of all subjects) and/or Preferred Term (applying to >5% of all Subjects) in the ITT population (Source: Sponsor's submission).

ATC2 Preferred Term [a]	240 U group N=81 n (%)	120 U group N=78 n (%)	Placebo group N=74 n (%)	Total N=233 n (%)
Subjects with concomitant medication	80 (98.8)	77 (98.7)	70 (94.6)	227 (97.4)
Antiinflammatory and antirheumatic products	41 (50.6)	29 (37.2)	32 (43.2)	102 (43.8)
Ibuprofen	24 (29.6)	18 (23.1)	18 (24.3)	60 (25.8)
Naproxen sodium	9 (11.1)	4 (5.1)	3 (4.1)	16 (6.9)
Vitamins	36 (44.4)	28 (35.9)	23 (31.1)	87 (37.3)
Multivitamin	22 (27.2)	13 (16.7)	11 (14.9)	46 (19.7)
Tocopherol	5 (6.2)	5 (6.4)	7 (9.5)	17 (7.3)
Ascorbic acid	7 (8.6)	6 (7.7)	3 (4.1)	16 (6.9)
Lipid modifying agents	27 (33.3)	29 (37.2)	23 (31.1)	79 (33.9)
Atorvastatin calcium	5 (6.2)	7 (9.0)	4 (5.4)	16 (6.9)
Inegy	3 (3.7)	5 (6.4)	6 (8.1)	14 (6.0)
Simvastatin	4 (4.9)	7 (9.0)	3 (4.1)	14 (6.0)
Fish oil	7 (8.6)	3 (3.8)	3 (4.1)	13 (5.6)
Analgesics	25 (30.9)	29 (37.2)	23 (31.1)	77 (33.0)
Paracetamol	5 (6.2)	11 (14.1)	7 (9.5)	23 (9.9)
Vicodin	5 (6.2)	1 (1.3)	6 (8.1)	12 (5.2)
Psychoanaleptics	28 (34.6)	25 (32.1)	21 (28.4)	74 (31.8)
Escitalopram oxalate	4 (4.9)	5 (6.4)	4 (5.4)	13 (5.6)
Antiepileptics	27 (33.3)	23 (29.5)	21 (28.4)	71 (30.5)
Clonazepam	14 (17.3)	15 (19.2)	12 (16.2)	41 (17.6)
Psycholeptics	25 (30.9)	15 (19.2)	22 (29.7)	62 (26.6)
Diazepam	6 (7.4)	5 (6.4)	5 (6.8)	16 (6.9)
Lorazepam	6 (7.4)	3 (3.8)	6 (8.1)	15 (6.4)
Muscle relaxants	21 (25.9)	15 (19.2)	13 (17.6)	49 (21.0)
Baclofen	6 (7.4)	7 (9.0)	6 (8.1)	19 (8.2)
Mineral supplements	23 (28.4)	14 (17.9)	10 (13.5)	47 (20.2)
Calcium	17 (21.0)	9 (11.5)	3 (4.1)	29 (12.4)
Drugs for acid related disorders	16 (19.8)	18 (23.1)	10 (13.5)	44 (18.9)
Beta blocking agents	11 (13.6)	20 (25.6)	10 (13.5)	41 (17.6)
Propranolol	5 (6.2)	7 (9.0)	2 (2.7)	14 (6.0)
Atenolol	3 (3.7)	6 (7.7)	4 (5.4)	13 (5.6)
Antithrombotic Agents	13 (16.0)	14 (17.9)	11 (14.9)	38 (16.3)
Acetylsalicylic acid	11 (13.6)	14 (17.9)	11 (14.9)	36 (15.5)
Sex hormones and modulators of the genital system	18 (22.2)	11 (14.1)	9 (12.2)	38 (16.3)
Agents acting on the renin-angiotensin system	11 (13.6)	15 (19.2)	7 (9.5)	33 (14.2)
Antihistamines for systemic use	12 (14.8)	10 (12.8)	7 (9.5)	29 (12.4)
Antibacterials for systemic use	10 (12.3)	9 (11.5)	5 (6.8)	24 (10.3)
Nasal preparations	7 (8.6)	7 (9.0)	10 (13.5)	24 (10.3)
Diuretics	5 (6.2)	10 (12.8)	8 (10.8)	23 (9.9)
Hydrochlorothiazide	3 (3.7)	7 (9.0)	3 (4.1)	13 (5.6)
Thyroid therapy	10 (12.3)	7 (9.0)	5 (6.8)	22 (9.4)
Levothyroxine sodium	9 (11.1)	5 (6.4)	5 (6.8)	19 (8.2)

The table 11 (below) summarizes the table above as it includes only classes of drugs that may relieve Cervical Dystonia.

Table 11. Concomitant Medications that may relieve Cervical Dystonia				
Drugs that may relieve Cervical Dystonia	240 units	120 units	Placebo	Total
Anti-inflammatory: Ibuprofen, Naproxen	33	22	21	76
Analgesics: Paracetamol, Vicodin	10	12	13	35
Muscle Relaxants: Clonazepam, Diazepam, Lorazepam, Baclofen	32	30	29	91
Total	75	64	63	202

REVIEWER'S COMMENT:

The table above shows that:

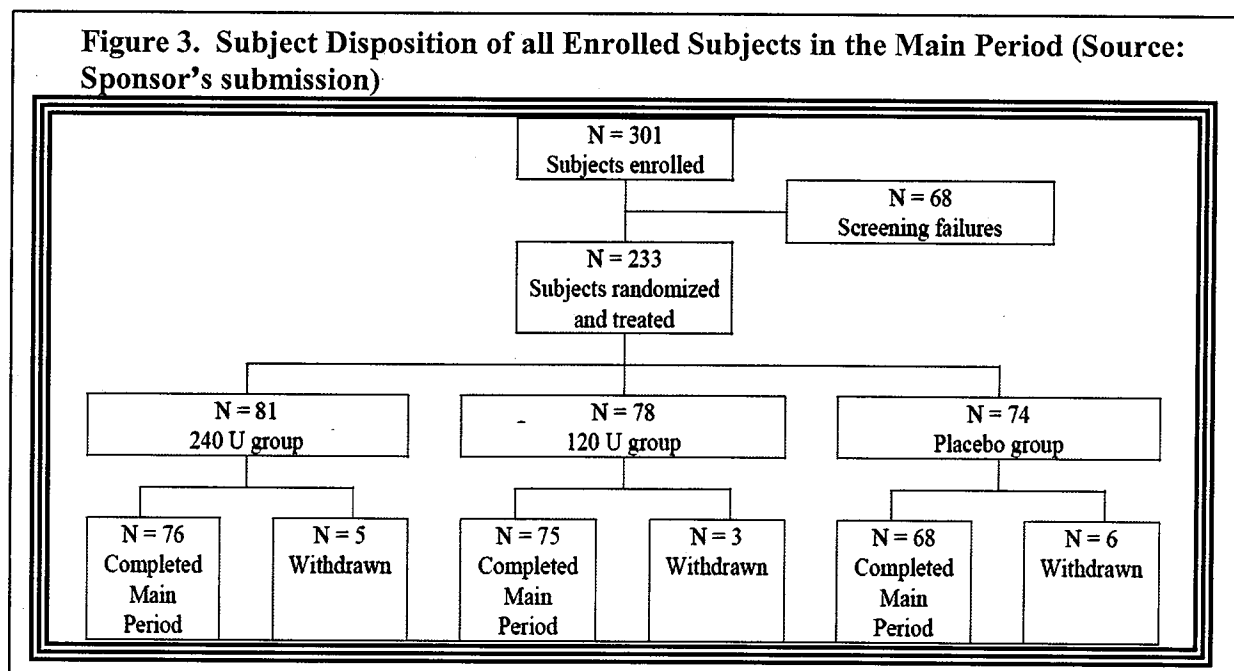
- There are a few more patients in the 240 U group who had used concomitant medications that may alleviate symptoms of cervical dystonia. The small number of patients contributing to the slight imbalance in the number of patients taking potentially “symptomatic relief of CD” medications are unlikely to influence the efficacy outcomes in the main or Extension Phases of the study. .
- Anti-cholinergic medications which have been used to alleviate symptoms of cervical dystonia are not included in this table submitted by the sponsor perhaps because it is not under the ATC or preferred term classification—which was what the sponsor used.

6.1.3 Subject Disposition

There were three hundred one subjects (301) enrolled from 37 centers in the United States. Sixty eight patients were excluded for screen failures (most common reasons are listed in the table below). Only 233 (77%) of patients were randomized and treated and 219 (94% of randomized patients) completed the Main Period of the study. Site 1017 was the highest enroller (31 subjects) and also had the highest number of screen failures.

TWSTRS severity score < 10	15 subjects
TWSTRS Total Score < 20	11 subjects
TWSTRS Disability score < 3	9 subjects
No clinical diagnosis of cervical dystonia	8 subjects
No source documentation of the last two consecutive injections with Botulinum toxin or no stable therapeutic response	8 subjects

The diagram below shows subject disposition, including the number of patients who had withdrawn from each randomized group.



REVIEWER'S COMMENTS:

- The sponsor analyzed all efficacy variables using the ITT population consisting of 233 subjects (81 in the 240 U group, 78 subjects in the 120 U group and 74 subjects in the Placebo group). Of these subjects, 219 (94%) completed the MP of the study and 14 (6%) withdrew from the study: Three subjects in the treatment group had adverse events: musculoskeletal pain, neck pain/muscle weakness and nausea and dizziness. Three (3) subjects in the placebo group withdrew due to insufficient efficacy, which was expected from the group. There were three patients who were lost to follow up (one in each treatment group) and 3 others who “withdrew consent”—and the reasons were not further explored by the Sponsor. The total number of patients who withdrew from the study was a small number and was equally distributed in the three treatment arms. The reviewer believes that these withdrawals did not affect the efficacy results nor did it contribute to any bias in one particular group.

Protocol Violations:

The table below lists all the major protocol deviations. The major protocol deviations are not mutually exclusive as subjects may have had more than one deviation. A total of 18 subjects in the ITT population were excluded from the TPP analysis due to major protocol violations. The TPP analysis included 215 (92% of the ITT population) subjects (77 in the 240 U group, 70 in the 120 U group and 68 in the placebo groups). The most number of major protocol deviations (7 of 18 or 3%) occurred because of errors in the “administration of the study medication” in which subjects were injected with an incorrect amount (number of units or volume) of the drug or the drug was injected into the wrong muscle. Five patients (2.1%) had raters who were different in each visit or were untrained raters. There were 3 patients who were in the category “early termination”.

Table 13. Major Protocol Deviations (All randomized subjects, N=233; Source: Sponsor's submission)

Major Protocol Deviation [a]	240 U group	120 U group	Placebo group	Total
	N = 81 n (%)	N = 78 n (%)	N = 74 n (%)	N = 233 n (%)
Total subjects with at least one deviation	4 (4.9)	8 (10.3)	6 (8.1)	18 (7.7)
Administration of study medication				
Different rater	1 (1.2)	4 (5.1)	2 (2.7)	7 (3.0)
Trained rater	1 (1.2)	3 (3.8)	1 (1.4)	5 (2.1)
Early termination	1 (1.2)	1 (1.3)	1 (1.4)	3 (1.3)
Exclusion criterion #14 (#9) not met at Screening (Baseline)	1 (1.2)	0	1 (1.4)	2 (0.9)
Inclusion criterion #1 not met at Baseline	0	1 (1.3)	0	1 (0.4)
Inclusion criterion #4 (#3) not met at Screening (Baseline)	0	1 (1.3)	0	1 (0.4)
Too early re-injection	0	0	1 (1.4)	1 (0.4)

REVIEWER'S COMMENTS:

- There were 14 patients who withdrew from the study with 219 (out of 233) patients completing the Main Phase. Eighteen major protocol deviations were documented in the TPP population of 233 patients. It was not explained clearly why there were still 215 patients left in the TPP population unless patients who withdrew also were the same one's who had protocol deviations. Nevertheless, despite this unexplained discrepancy, the major protocol deviations were still a small number that was distributed among the treatment groups and may not have affected the study outcome.

There were a total of 229 (98.3%) of the 233 randomized subjects with minor protocol deviations which did not lead to exclusion from the TPP. The most common were missing study procedures (79%) and non adherence to time schedule (63.9%). The reviewer tabulated the reasons for minor deviations in the table below.

Table.14. Reasons for minor deviations are listed in the following tables: (Source: Reviewer's table)

	NT 201 120 (N=78)	NT201 240 (N=81)	Placebo (N=74)
Inclusion 1 (exceeds upper age limit): age 18 to 75 years			1
Inclusion 2 (not rotational dystonia)			1
Inclusion 7:	16	17	10
Inclusion 8	5	5	4
Less than 10 weeks between most recent injection	3	1	1
Inclusion 10	3		5
Inclusion 11 (had Dysport)	3	2	1
Exclusion 1 (traumatic neck injury)	1		
Exclusion 3 Severity for retrocollis > 2	4	1	5
Exclusion 4 myotomy		4	
Exclusion 9 treatment with botulinum toxin for other dystonias			1
Exclusion 11: Severe or uncontrolled systemic disease	2	3	
Exclusion 14: Non authorized concomitant treatments (these are medications that were not allowed during the study, details of which are not available)	30	35	22
Randomization deviation	3	3	4
Time schedule deviation	32	30	32
Study not according to GCP	21	21	14
Early termination	3	4 Minor 1 Major	5 Minor 1 Major
Missing visit	32	29	14
Missing assessment	6 (1 with no visit 3)	2 (no visit 3)	8 (2 no visit 3)
Missing study procedure	65	66	58
ECG Protocol Deviation	30	31	31
Too early re injection	3	5	5
Different rater	4	6	2
Trained rater	0 (1 major)	1 (1 major)	0 (2 major)
Efficacy measure deviation	25	31	20

REVIEWER'S COMMENTS:

- There were minor deviations that were considered as major deviations by some centers. For example, "early termination" and "trained rater" were reported as minor protocol deviations in some centers while others have listed these as major protocol deviations leading to withdrawal of study subject. It is unclear from the data submitted why these types of violations were classified differently. These inconsistencies in the classification of major/minor protocol violations may have been overlooked by the Sponsor.
- The number of missing visits, assessments and study procedures, when combined, were the most common minor deviations. The number of minor deviations was roughly

distributed among the three treatment groups. The number of missing assessments is too small to have affected the efficacy analysis

- One minor deviation that was listed by the Sponsor is “non-authorized concomitant treatment”. In this category, 33 (14%) patients in the 120 U group and 35 (15%) patients in the 240 U group compared to 25 (11%) patients in the placebo group have been found to use a non-authorized concomitant treatment. Relief from such medications may improve CD symptoms and confound the TWSTRS score.

The drugs listed in the table below have been reported (case reports or anecdotally) to alleviate or contribute to the alleviation of symptoms of Cervical Dystonia. These are not FDA approved for the treatment of CD and were used by patients in the study. (The Sponsor has provided a list of pain medications only and the reviewer supplemented this list with other medications used in clinical practice for “treatment” of CD), Although the percentage difference is not too large, the fact that these medications were seen more in the treatment groups (29%) than in the placebo seems to be favorable to the treatment groups.

Table 15. List of Drugs that may affect symptoms of Cervical Dystonia (Reviewer’s Table).

Drugs used	NT 201 120	NT 201 240	Placebo
	N=78	N=81	N=74
Anti depressants: Duloxetine, Escitalopram Venlafaxine, Zolpidem, Sertraline, Fluoxetine	5 (5%)	7 (8.6%)	4 (5.4%)
Anticholinergics: Amitryptiline, Diphenhydramine, Trihexyphenidyl, Fexofenadine Loratadine	4 (5.1%)	3 (3.7%)	2 (2.7%)
Antiepileptics/Muscle Relaxants Oxazepam, Clonazepam, Gabapentin Lorazepam, Primidone, Topiramate Pregabalin, Diazepam	2 (2.6%)	7 (8.6%)	2 (2.7%)
Other Hypnotics		1 (1.2%)	
Sinemet		2 (2.5%)	
Percocet	1 (1.3%)		
Ropinirole	1 (1.3%)		
Escopiclone	1 (1.3%)		1(1.4%)
Procyclidine			1 (1.4%)
Total	15 (19.2%)	20 (24.5%)	10 (13.5%)

REVIEWER'S COMMENT:

- There were more patients in the treatment groups, 20 (24.5%) in the 240 U and 15 (19.2%) in the 120 U and only 10 (13.5%) in the placebo group who were treated with medications that might have relieved the symptoms of cervical dystonia.

6.1.4 Analysis of Primary Endpoint(s)

General Analysis

- All efficacy variables were analyzed for the ITT population and for the TPP population. Confirmatory efficacy analysis was based on the ITT population. The sponsor presented analyses for the ITT population and TPP population was discussed only if different from the ITT population
- The primary efficacy variable was the change from Baseline (Visit 2, Day 0) in the TWSTRS Total score to Visit 3 (Week 4) following injection of the study medication.

The table presented below is a summary of the TWSTRS scores for each treatment group at baseline and at visit 3. This shows the efficacy results of treatment by 120 U and 240 U compared to placebo.

Table 16. TWSTRS scores in the different groups at baseline and after visit 3. (Source: Sponsor's submission)

	NT 240	NT 120	Placebo
Total TWSTRS at baseline	42.1	42.6	41.8
Total TWSTRS at Visit 3	31.2	32.7	39.5
Mean (SD) Change in TWSTRS score from baseline to visit 3	-10.9 (11.7)	-9,9 (10.4)	-2.2 (7.3)
Mean difference of 120 U and 240 U groups with Placebo	-9,0 (p<.0.001)	-7.5 (p<0.001)	
Mean difference bet. 240 U and 120 U	1.3 (p=0.447)		

REVIEWER’S COMMENTS

- The change from baseline to Visit 3 (week 4) in the TWSTRS Total score was significantly higher in the 240 units and 120 units group than in placebo.
- Patients who received 240 units had a numerically higher change in TWSTRS score than those who received 120 units (8.7 vs. 7.7)
- There was a statistically non-significant difference in the total TWSTRS score for patients who received 240 units compared to those who received 120 units.

The three tables below presents the Change from Baseline to Visit 3 (Week 4) showing the results on Missing Data Handling Method: Missing Data Replaced by Baseline Value and Observed Cases, using the Full Model.

Table 17: Baseline to Visit 3 TWSTRS Total Scores in subjects who received 120 U vs. Placebo group. (Source: Sponsor)

	P value	Treatment Difference		
		LS Mean (SE) (95% CI)		LS Mean difference (95% CI)
Missing Data Handling Method		240 U Group	Placebo Group	
Missing Data Replaced by Baseline Value	<0.001	-10.8 (2.11) (-15.0; 6.6)	-3.3 (2.20) (-7.6; 1.1)	-7.5 (-10.4; 4.6)
Observed Cases	<0.001	-10.7 (2.13) (-15.0; -6.5)	-3.2 (2.22) (-7.5; 1.2)	-7.6 (-10.5; -4.6)

Table 18: Baseline to Visit 3 TWSTRS Total Scores in subjects who received 240 U vs. Placebo group. (Source: Sponsor)

	P value	Treatment Difference		
		LS Mean (SE) (95% CI)		LS Mean difference (95% CI)
Missing Data Handling Method		240 U Group	Placebo Group	
Missing Data Replaced by Baseline Value	<0.001	-7.3 (2.18) (-11.6; -3.0)	1.6 (2.28) (-2.9; 6.2)	-9.0(-12.0; -5.9)
Observed Cases	<0.001	-7.4 (2.19) (-11.8; -3.10)	1.71 (2.29) (-2.8; 6.2)	-9.1 (-12.2; -6)

Table 19: Baseline to Visit 3 TWSTRS Total Scores in subjects who received 240 U vs. 120 group. (Source: Sponsor)

	P value	Treatment Difference		LS Mean difference (95% CI)
		LS Mean (SE) (95% CI)		
Missing Data Handling Method		240 U Group	Placebo Group	
Missing Data Replaced by Baseline Value	<0.447	-9.2 (2.27) (-13.7; -4.7)	-10.5 (2.25) (-14.9; -6.0)	1.3 (-2.1; 4.6)
Observed Cases	<0.425	-9.93 (2.28) (-13.8; -4.8)	-10.7 (2.27) (-15.2; -6.2)	1.4 (-2; 4.8)

The table below provides additional data on the effects of Gender (Subpopulation) on the Treatment Effect.

Table 20. Summary of the Influence of Gender on the Treatment Effect in Total ITT population, Treatment naïve and Pre-treated Subjects (Full ANCOVA Model, Missing values replaced by Baseline value or Group Mean Value) (Source: Sponsor)

(Sub)Group	Treatment Group	Total ITT Population	Treatment-Naïve Subjects	Pre-Treated Subjects
Gender				
Descriptive statistics				
Male	240 U group	-7.5	-8.4	-7.1
	120 U group	-9.4	-13.3	-7.1
	Placebo group	-0.8	-1.1	-0.6
Female	240 U group	-12.6	-10.6	-14.1
	120 U group	-10.1	-11.3	-9.3
	Placebo group	-2.9	-2.5	-3.1
ANCOVA full model (missing values replaced by baseline value /group mean value)	240 U vs. Placebo	p=0.043/p=0.027	p=0.805/p=0.805	p=0.01/p=0.007
	120 U vs. Placebo	p=0.449/p=0.353	p=0.958/p=0.958	p=0.163/p=0.099
	240 U vs. 120 U	p=0.128/p=0.095	p=0.755/p=0.755	p=0.036/p=0.025
Source: Tables 14.2.1.1.6.1, 14.2.1.2.1.1				
U=Units				

REVIEWER'S COMMENTS:

- Using the full model, there is a treatment difference in the primary efficacy variable, which is the change from baseline (Visit 2, Day 0) in the TWSTRS Total Score to Control Visit 3 (Week 4) as shown in the tables 18, 19 and 20 (above). Regardless of the imputation method for handling missing data, the mean difference in TWSTRS total score in the 240 U group and the Placebo group ranged from -9 to -9.1 (p value <0.001).
- Similarly, the change from baseline to visit 3 in the TWSTRS Total Score in the 120 U group and the placebo group ranged from -7.5 to 7.
- There was a slight mean difference of 1.3 to 1.4 units in the TWSTRS total score, between the 240 U group and 120 U group, favoring the 240 units but this did not reach statistical significance (0.425 to 0.447) even with different imputation methods for handling missing data.
- In the study, the sponsors presented detailed results using other sensitivity analyses employing different methods for handling missing data and different models that yielded very similar results. Consistently, treatment groups showed a statistically significant benefit over placebo and a non statistically significant small numerical difference between treatment groups, favoring the 240 U group.
- Additional information on Gender and baseline TWSTRS Total scores demonstrated that the mean improvement in TWSTRS score was generally higher in females especially those pre treated with botulinum toxin and who received 240 U. Although the “female gender advantage” is seen in the 240U group over placebo (with a p=0.01), the change in TWSTRS score between the two treatment groups is not as robust. Using gender as a covariate should not have been allowed in the study method mainly because the ANCOVA analysis pre-specified a high p-value (0.2) for covariates that included gender. Besides, there is no plausible biological reason to expect a significant difference in response to IncobotulinumtoxinA in women compared to men. The difference in pre-treated women is more likely explained by the larger number of women enrolled into the trial.

6.1.5 Analysis of Secondary Endpoints(s)

The subscales of the TWSTRS (Severity, Disability and Pain) were analyzed at Visit 3 (Week 4) of the Main Phase. The evaluations were conducted for the ITT population.

Table 21 (below) shows the mean baseline value and change from baseline to visit 3 (week 4) and visit 4 (week 8) and also the final visit. This table demonstrates that the highest difference in TWSTRS severity score is during Visit 3, with the largest difference seen in the 240 units group (-5.5). Difference from baseline to visit 3 was also seen in the 120 U group (-3.9) and in the placebo group (-1.9) but the change is greatest with the treatment groups. Although the treatment effect may last up to 12 weeks, this effect wanes with time. There is almost no noticeable difference seen in the placebo group by the 12th week. This shows that the active treatment reaches a maximum effect at week 3 and wanes over time.

Table 21. Mean (SD) Baseline Value and Mean (SD) Change from Baseline to Visit 3, Visit 4 and Final Visit in TWSTRS Severity Score (ITT population). (Source: Sponsor's submission)

	240 U group N = 81	120 U group N = 78	Placebo group N = 74
Baseline	18.6 (4.05)	18.0 (4.38)	18.9 (3.47)
Visit 3 - Baseline	-5.5 (5.99)	-3.9 (4.34)	-1.9 (3.36)
Visit 4 - Baseline	-3.5 (5.39)	-3.1 (4.39)	-0.9 (3.57)
Final Visit - Baseline	-1.9 (3.83)	-1.1 (3.18)	-0.2 (3.07)

Table 22 shows the Mean Baseline Value (and Change) from Baseline to Visit 3 (Week 4), Visit 4 (Week 8) and at the Final Visit in the subscale scores of TWSTRS Disability and Pain. A claim for reduced pain is included in the proposed indication.

Table 22. Mean (SD) Baseline Value and Mean (SD) Change from Baseline to Visit 3, Visit 4 and Final Visit in TWSTRS Disability and Pain Scores (ITT population). (Source: Sponsor's submission)

	TWSTRS-Disability Score			TWSTRS-Pain Score		
	240 U group N = 81	120 U group N = 78	Placebo group N = 74	240 U group N = 81	120 U group N = 78	Placebo group N = 74
Baseline	12.5 (4.62)	13.1 (4.44)	11.8 (3.94)	11.0 (3.97)	11.5 (4.02)	11.1 (3.77)
Visit 3 - Baseline	-3.0 (4.35)	-3.3 (4.72)	0.0 (3.41)	-2.4 (4.36)	-2.7 (4.55)	-0.3 (2.97)
Visit 4 - Baseline	-2.4 (3.98)	-2.1 (4.86)	0.8 (3.27)	-2.3 (4.32)	-1.8 (4.15)	0.6 (2.82)
Final Visit - Baseline	-1.3 (3.13)	-1.4 (3.82)	1.0 (3.32)	-1.3 (3.40)	-1.1 (3.96)	0.9 (2.56)

REVIEWER'S COMMENT:

- The TWSTRS disability and pain scores improved at visit 3 (week 4) after baseline injections and continued to demonstrate a small benefit until the final visit.

The table below shows the ANCOVA results based on mean changes in the TWSTRS subscale scores of severity, disability and pain in the ITT population. At Week 4 (Visit 3), both treatment groups show a highly significant ($p=0.001$) difference in pain, severity and disability scores in comparison to placebo but there is no statistically significant advantage of the 240 unit group compared to patients who received 120 units. During subsequent visits (Visit 4 and Final Visit), the treatment difference between the treatment groups over placebo persisted. Although there was a slight numerical difference in the TWSTRS subscale scores between those who received 240 U and 120 U, the treatment difference was not statistically significant.

Table 23. ANCOVA results based on LS Mean changes from Baseline to Visit 3, Visit 4 and Final Visit in TWSTRS subscale (Severity, Disability and Pain) scores (Source: sponsor's submission).

Comparison	Visit	TWSTRS Severity score		TWSTRS Disability score		TWSTRS Pain score	
		LS mean treatment difference [95% CI]	p-value [a]	LS mean treatment difference [95% CI]	p-value [a]	LS mean treatment difference [95% CI]	p-value [a]
240 U vs. Placebo	Visit 3	-3.9 [-5.5;-2.3]	< 0.001	-2.8 [-4.1;-1.6]	< 0.001	-2.2 [-3.4;-1.1]	< 0.001
120 U vs. Placebo		-2.1 [-3.4;-0.7]	0.003	-2.9 [-4.2;-1.6]	< 0.001	-2.2 [-3.5;-1.0]	< 0.001
240 U vs. 120 U		1.6 [0.0;3.2]	0.049	-0.2 [-1.6;1.2]	0.817	0.0 [-1.4;1.3]	0.961
240 U vs. Placebo	Visit 4	-2.7 [-4.2;-1.3]	< 0.001	-3.0 [-4.1;-1.8]	< 0.001	-2.9 [-4.1;-1.8]	< 0.001
120 U vs. Placebo		-2.2 [-3.5;-1.0]	0.001	-2.4 [-3.7;-1.1]	< 0.001	-2.3 [-3.4;-1.1]	< 0.001
240 U vs. 120 U		0.2 [-1.2;1.7]	0.756	0.5 [-1.9;1.8]	0.489	0.8 [-0.5;2.0]	0.233
240 U vs. Placebo	Final Visit	-1.9 [-3.0;-0.8]	0.001	-2.2 [-3.2;-1.2]	< 0.001	-2.3 [-3.3;-1.4]	< 0.001
120 U vs. Placebo		-1.2 [-2.1;-0.2]	0.020	-2.0 [-3.1;-0.9]	0.001	-1.9 [-2.9;-0.8]	< 0.001
240 U vs. 120 U		0.6 [-0.4;1.6]	0.256	0.1 [-0.9;1.2]	0.787	0.5 [-0.5 ;1.6]	0.312

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

The table below (Table 24) looks into mean change in TWSTRS subscores between the pre-treated and treatment naïve groups. Both subgroups who had received treatments had generally a statistically significant change in mean TWSTRS subscale score compared to the placebo group. The treatment difference in the mean TWSTRS subscale scores between the 240 U and the 120 U group is not statistically significant. The 240 U pre-treated group had a statistically significant mean change from baseline in the mean TWSTRS Severity and Pain Scores but this was not reflected in TWSTRS disability score. Treatment naïve subjects who received 120 U had a statistically significant difference in mean TWSTRS disability and pain subscale scores but not for the severity subscale.

Table 24 Mean Changes from Baseline to Visit 3 in TWSTRS Subscores, Treatment naïve and Pre-treated Subjects (ITT Population) (Source: Sponsor's Submission)

Comparison	Subgroup	LS mean treatment difference [95% CI]	p-value "Treatment" (Full model)
TWSTRS-Severity score			
240 U vs. Placebo	Treatment-naïve Subjects	-3.4 [-6.0;-0.8]	0.011
	Pre-treated Subjects	-4.4 [-6.4;-2.4]	<0.001
120 U vs. Placebo	Treatment-naïve Subjects	-2.0 [-4.2;0.2]	0.075
	Pre-treated Subjects	-1.7 [-3.4;0.0]	0.051
240 U vs. 120 U	Treatment-naïve Subjects	1.2 [-1.3;3.7]	0.349
	Pre-treated Subjects	2.0 [-0.2;4.1]	0.071
TWSTRS-Disability score			
240 U vs. Placebo	Treatment-naïve Subjects	-3.1 [-5.0;-1.3]	0.001
	Pre-treated Subjects	-2.7 [-4.3;-1.1]	0.001
120 U vs. Placebo	Treatment-naïve Subjects	-4.7 [-7.0;-2.5]	<0.001
	Pre-treated Subjects	-1.9 [-3.3;-0.4]	0.015
240 U vs. 120 U	Treatment-naïve Subjects	-1.6 [-4.0;0.8]	0.183
	Pre-treated Subjects	0.7 [-1.0;2.3]	0.424
TWSTRS-Pain score			
240 U vs. Placebo	Treatment-naïve Subjects	-1.3 [-3.3;0.6]	0.185
	Pre-treated Subjects	-3.0 [-4.4;-1.5]	<0.001
120 U vs. Placebo	Treatment-naïve Subjects	-2.7 [-4.6;-0.8]	0.006
	Pre-treated Subjects	-1.8 [-3.5;-0.1]	0.035
240 U vs. 120 U	Treatment-naïve Subjects	-1.3 [-3.4;0.8]	0.215
	Pre-treated Subjects	0.8 [-1.0;2.6]	0.397

REVIEWER'S COMMENT:

- Although the 240 U may prove to be more effective than the 120 U in certain subgroups (pre-treated patients, females), the results are inconsistent. There is no rational explanation why the higher dose can relieve both severity and pain but not disability.

The table below displays the Patient Evaluation of Global Response (PEGR) during the final visit. The results of the PEGR at the Final Visit (Visit 5) of the Main Period were analyzed in the ITT population using an ANCOVA procedure.

Table 25. Patient Evaluation of Global Response (PEGR) at Final Visit (ITT Population) (Source: Sponsor’s submission)

Evaluation Category	240 U group N = 81	120 U group N = 78	Placebo group N = 74
Complete abolishment of all signs and symptoms	2 (2.5)	7 (9.0)	0
Marked improvement	29 (35.8)	19 (24.4)	3 (4.1)
Moderate improvement	12 (14.8)	12 (15.4)	5 (6.8)
Slight improvement	11 (13.6)	12 (15.4)	7 (9.5)
Unchanged	17 (21.0)	15 (19.2)	33 (44.6)
Slight worsening	2 (2.5)	5 (6.4)	8 (10.8)
Moderate worsening	2 (2.5)	4 (5.1)	11 (14.9)
Marked worsening	4 (4.9)	0	3 (4.1)
Very marked worsening	1 (1.2)	1 (1.3)	0

REVIEWER’S COMMENTS:

- Fifty four (67%) patients in the 240 U group and 50 (64%) patients in the 120 units reported slight improvement to complete abolishment of all signs and symptoms compared to 15 (20%) patients in the placebo group. There were more patients who received the 120 units group who reported complete abolishment of all signs and symptoms. Marked improvement was predominant in those who received 240 units. Although the number of patients who had experienced worsening was equal in both the 240 units and 120 units group, 4.9% reported marked worsening in the 240 units and none in the 120 units (perhaps because of adverse effects). Narrowing down the table above to those who had “moderate improvement to complete abolishment of symptoms” show a predominance of patients in the 240 U group compared to the 120 U group (53% in the 240 U group, 47% in the 120 U group compared to 11% in the placebo group) who reported at least a moderate degree of improvement.
- The Sponsor did not obtain the PEGR at Week 4 (Visit 3) at the time when the peak drug effect was expected and when the primary endpoint was measured. The PEGR ratings may have been influenced in the patients who experience peak dose adverse effects. At the last visit, dose dependent adverse effects may have resolved weeks earlier and may not have been recalled when patients rated the PEGR at the last visit.

Table 26 (below) illustrates that the treatment effect measured on the PEGR was statistically significant compared to placebo, however the 240 U group was not statistically superior to the 120 U group in a direct comparison. The trial results did not demonstrate a meaningful (reported by patients on the total TWSTRS Score or the PEGR) advantage of the 240 U treated group compared to the 120 U group.

Table 26. ANCOVA Results Patient Evaluation of Global Response at the Final Visit in ITT population, Treatment Naïve and Pre-treated Subjects (Source: Sponsor's submission)

Comparison	(Sub)Group	LS mean treatment difference [95% CI]	p-value
240 U vs. Placebo group	All Subjects	1.5 [1.0;2.1]	< 0.001
	Treatment-naïve Subjects	1.1 [0.3;1.9]	0.009
	Pre-Treated Subjects	1.8 [1.1;2.5]	< 0.001
120 U vs. Placebo group	All Subjects	1.5 [1.0;2.0]	< 0.001
	Treatment-naïve Subjects	1.7 [1.0;2.4]	< 0.001
	Pre-Treated Subjects	1.2 [0.6;1.9]	< 0.001
240 U vs. 120 U group	All Subjects	0.0 [-0.6;0.5]	0.930
	Treatment-naïve Subjects	0.7 [-0.1;1.5]	0.101
	Pre-Treated Subjects	-0.5 [-1.2;0.3]	0.228

6.1.6 Other Endpoints

The Sponsor provided data on the following tertiary endpoints summarized in the subsequent three tables below.

Onset of Treatment Effect: This will be defined as time (days) from injection session until the time point when the subject subjectively assessed there was an onset of effect.

Table 27. Mean (SD) Time to Onset of Treatment Effect in ITT population, Treatment naïve and pre-treated subjects (Source: Sponsor’s submissions)

Statistic	All Subjects			Pre-treated Subjects			Treatment-naïve subjects		
	240 U group N=81	120 U group N=78	Placebo group N=74	240 U group N=50	120 U group N=47	Placebo group N=46	240 U group N=31	120 U group N=31	Placebo group N=28
N _{obs}	59	53	25	36	31	17	23	22	8
Mean (days)	7.1	6.0	6.2	7.2	7.5	4.4	7.1	4.0	9.9
SD	9.14	7.59	6.16	10.85	9.33	2.03	5.73	3.26	9.86

From the table above, the mean time to onset of effect for the 240 U and 120 U groups in days ranged from 4 to 7.5 days and 4.4 to 9.9 days in the placebo group. It appears that treatment naïve subjects who received 120 units had a faster onset (4 to 7.5) than pre-treated subjects (7.1 to 7.2 days). This may be explained by a greater expectation of relief among pre-treated patients.

Table 28. Mean (SD) Time to Waning of Treatment Effect (weeks) in ITT population, Treatment naïve and pre-treated subjects (Source: Sponsor’s submissions)

Statistic	All Subjects			Pre-treated Subjects			Treatment-naïve Subjects		
	240 U group N=81	120 U group N=78	Placebo Group N=74	240 U group N=50	120 U group N=47	Placebo Group N=46	240 U group N=31	120 U group N=31	Placebo Group N=28
N _{obs}	55	50	20	33	27	14	22	23	6
Mean (weeks)	7.6	7.3	4.0	7.8	7.4	3.6	7.3	7.1	4.7
SD	3.60	3.39	1.85	4.14	3.49	1.55	2.64	3.34	2.42

Waning of Treatment Effect: Defined as time in weeks from the injection session until patients subjectively assessed that there was waning of the effect of treatment with blinded study drug. The table above shows that the waning of effect ranged from 7.3 weeks (120 U group) to 7.6 weeks (240 U group) and 4 weeks in those on placebo.

Duration of Treatment Effect: The duration of treatment effect is defined as time period from the day of injection until the until patients believed they needed a repeat injection and their TWSTRS total score was ≥ 20 . The mean time to duration of treatment effect (as shown in Table 29) is about 80 days for the treatment group and 72 days for the placebo group (in all subjects). Mean duration of treatment effect is almost similar among pre-treated and naïve subjects. For those who did not experience a treatment effect, duration of effect will be set to zero

Table 29. Mean (SD) Time to Duration of Treatment Effect (days) in ITT population, Treatment naïve and pre-treated subjects (Source: Sponsor's submissions)

Statistic	All Subjects			Pre-treated Subjects			Treatment-naïve Subjects		
	240 U group N=81	120 U group N=78	Placebo group N=74	240 U group N=50	120 U group N=47	Placebo group N=46	240 U group N=31	120 U group N=31	Placebo group N=28
N _{obs}	52	47	24	33	27	17	19	20	7
Mean (Days)	79.9	79.6	72.4	77.0	79.2	69.3	84.9	80.1	80.0
SD	22.14	21.49	24.77	21.32	23.72	21.48	23.22	18.66	32.04

REVIEWER'S COMMENTS:

- The onset, waning and duration of treatment tertiary variables may provide supporting information regarding the mean duration of treatment effect
- Generalizations about duration of effect, frequency of treatment, safety and efficacy of such treatment can only be made after patients receive repeated injections in the Extension Phase. While the mean duration of treatment is about 78.1 to 79.4 days, review of records show that the first injection in the Main Phase till the first repeat injection in the Extension phase ranged from as early as 42 days and up to 269 days (mean = 72.09 and median 58). Part of this can be explained by the Sponsor's protocol allowing injections as early as 6 weeks since the first injection and up to 48 weeks. This may explain the large range of variability in the treatment duration. More information about duration of treatment will be discussed in the Extension Phase (408/2).

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

1. Both 240 U and 120 U are superior to placebo for the treatment of cervical dystonia demonstrating a statistically significant difference between the treatment and the placebo groups from the baseline TWSTRS total score to the evaluation four weeks after baseline injection (-9 and -7.5 point difference for the treatment group, 240 U and 120 U respectively). The treatment difference was maximum at week 4. There was also a statistically significant treatment effect of IncobotulinumtoxinA compared to placebo reported for TWSTRS severity, disability and pain subscales at week 4 and in the Patient Effective Global Response where slight to complete resolution of symptoms was reported by the patients at the Final Visit.
2. While both 240 units and 120 units groups were superior to placebo at the Week 4 visit compared to baseline for the TWSTRS total and subscale scores, there is no significant benefit associated with the 240 U over 120 U in the over-all population and even among the subgroups.
3. The muscle groups that were injected were not specified in the protocol. A guide was provided to the Investigators regarding muscles that are activated in cervical dystonia. The muscles that were injected, the dose given and the number of injections were decided upon by the investigators.
4. The treatment groups received NT 201 in a volume of 4.8 ml. The dosing regimen was indicated in the protocol and there were a few dosing errors documented in the study report but none that were associated with a SAE.

With regard to drug administration, the protocol did not pre-specify the muscles to be injected or the dose to be injected in each muscle group. The study did not explore which dose ranges were the most efficacious and safest. Tables 30 and 31 below summarizes the extent of exposure to toxin per muscle in the 240U and 120U group and illustrate that there is a very wide range of doses injected in each muscle in this particular study. This collection of data cannot be used as an injection guide in clinical practice. In the study as in clinical practice, the dose to be injected is dependent on the muscle group, the bulk and action of the muscle, the patient's previous exposure to neurotoxins and the Investigator's experience in treating patients with CD

Table 30. Extent of Exposure in the 240 U Group: Mean (SD) and Range of Units of NT 201 Injected during the MP, according to Side and Muscle Injected, in Total EFS Population, Pre-treated and Treatment-naïve Subjects

		N	Total	N	Pre-Treated	N	Naive
Total	Splenius capitis/Semispinalis	79	97.5 (35.76) 40.0-200.0	48	100.1 (34.85) 40.0-200.0	31	93.6 (37.35) 40.0-180.0
	Trapezius	57	62.2 (39.69) 10.0-200.0	34	56.8 (33.28) 10.0-160.0	23	70.2 (47.28) 15.0-200.0
	Sternocleidomastoid	70	52.1 (24.44) 10.0-120.0	44	48.9 (21.56) 10.0-120.0	26	57.5 (28.29) 20.0-120.0
	Levator scapulae	48	44.4 (16.30) 20.0-95.0	31	46.1 (17.40) 20.0-95.0	17	41.2 (13.98) 20.0-70.0
	Scalene	29	48.1 (28.58) 20.0-120.0	19	44.0 (26.38) 20.0-120.0	10	56.0 (32.30) 20.0-100.0
	Other - Spinal or Semispinal Muscles	19	45.3 (23.36) 20.0-120.0	11	52.3 (25.04) 30.0-120.0	8	35.6 (18.02) 20.0-60.0
	Other - Suboccipital Triangle	7	25.0 (5.77) 15.0-30.0	5	26.0 (4.18) 20.0-30.0	2	22.5 (10.61) 15.0-30.0
	Other - Platysma/Other	2	37.5 (17.68) 25.0-50.0	2	37.5 (17.68) 25.0-50.0		-
Total		81	241.11 (18.51) 210.0-400.0	50	238.6 (6.06) 210.0-240.0	31	245.2 (28.74) 240.0-400.0

Source: Table 14.3.1.2

Table 31. Extent of Exposure in the 120 U Group: Mean (SD) and Range of Units of NT 201 Injected during the MP, according to Side and Muscle Injected, in Total EFS Population, Pre-treated and Treatment-naïve Subjects (Source: Sponsor's Submission).

		N	Total	N	Pre-Treated	N	Naive
Total	Splenius capitis/Semispinalis	78	50.5 (25.78) 5.0-125.0	47	50.1 (25.57) 5.0-125.0	31	51.3 (26.50) 25.0-120.0
	Trapezius	55	28.5 (14.20) 5.0-60.0	31	31.0 (14.80) 7.5-60.0	24	25.3 (12.99) 5.0-50.0
	Sternocleidomastoid	63	27.6 (11.04) 7.5-60.0	41	29.6 (10.69) 12.5-60.0	22	23.9 (10.96) 7.5-60.0
	Levator scapulae	49	21.1 (7.13) 7.5-37.5	30	21.8 (7.31) 10.0-37.5	19	20.0 (6.87) 7.5-30.0
	Scalene	27	21.3 (11.30) 5.0-50.0	13	22.7 (12.14) 5.0-45.0	14	20.0 (10.74) 7.5-50.0
	Other - Spinal or Semispinal Muscles	19	19.6 (8.34) 5.0-40.0	8	16.3 (7.07) 5.0-25.0	11	22.1 (8.65) 10.0-40.0
	Other - Suboccipital Triangle	6	16.7 (6.06) 10.0-25.0	3	13.3 (5.77) 10.0-20.0	3	20.0 (5.00) 15.0-25.0
	Total	78	119.6 (5.41) 87.5-150.0	47	120.1 (5.12) 105.0-150.0	31	118.9 (5.84) 87.5-120.0

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The mean time of onset based on the data presented is 4 to 8 days and the mean duration of treatment is 77 to 84.9 days which is close to 11 weeks. For Botox, the onset of action is about one to two weeks (Jankovic and Schwartz, 1990b) and maximum effect is 6 weeks post injection. Duration of effect is 3 months. Dysport peak response is documented at 2 to 4 weeks with peak symptomatic relief within two to 4 weeks after injection.

The discussion of the subsequent Extension Phase study 408/2 will include additional information of the persistence of efficacy and/or tolerance effects of NT 201.

6.1.9. Other Supporting Studies

Study Protocol: MRZ 60201-0408/2

Objective:

To investigate the safety and efficacy of repeated injections of the two different doses of NT 201 in subjects with cervical dystonia over one year period.

Methodology:

Randomized, double blind, parallel group (240 units group, 120 units group, repeated treatment).

REVIEWER'S COMMENT:

- The patients were re-randomized into 240 U group or 120 U group following participating in the Main Phase. There were no adjustment in the doses made during subsequent visits and patients and physicians were blinded into the treatment group. Doses between 120 U to 240 U were not evaluated.

Duration of Treatment:

Up to 5 injection sessions; dosing interval depending on duration of treatment effect, but not shorter than 6 weeks and the last injection could not be given later than 48 weeks after start of EP. Follow up assessments were required at a maximum of up to 20 week safety observation phase without treatment but could occur earlier if reinjection was required..

Efficacy variables:

The Extension Phase will include TWSTRS Total Score and the Patient Evaluation of Global Response.

Safety Variables:

Clinical Chemistry, Hematology
Antibody titer
Pregnancy test
Adverse events
Changes in concomitant medication/diseases

Safety Monitoring:

On going AE's at the trial termination visit will be followed until AE has resolved or has stabilized or until a new injection with Botulinum Toxin of any serotype other than study medication (documentation either by phone or personal contact).

Inclusion

- Completed the double blind portion of the main trial
- Negative Pregnancy test before injection

Exclusion

- Received another botulinum toxin

Extension Period Procedure:

- The Extension Period consists of a 48 (+1 week) double blind treatment period and a safety observation period of up to 20 weeks (+/- 3 days) after the last injection with NT 201.
- Patients immediately enter the Extension Period after completion of Visit 5 of the Main Period (Week 8 to Week 20).
- If patient requires a new injection and the Investigator agrees this is necessary, the patient can be treated immediately with NT 201.
- If patient does not still require a new injection, the first Extension Period visit will be scheduled no later than 48 weeks (+1) after the Final Visit of the Main Period.
- Mandatory telephone contact will be made on Day 7+/-1 after each injection and control visits will take place 4 weeks after each injection.
- During the 48 week extended treatment period, all patients will receive multiple injections as required.
- Minimum interval between two injections must always be at least six weeks.
- Trial Termination Visit will be at 20 weeks (+/-3 days after the last injection of the Extension Period or at the time point when the patient receives a new injection of Botulinum Toxin of any serotype other than study medication which are allowed after patient has finished the extended treatment period.

- Study staff will determine reason for non attendance if patient does not attend for a new injection for a period of 20 weeks (+/-3 days) following last injection.

Dose

The subjects were re-randomized into receiving 120 units and 240 units. However, the sponsor submitted a protocol amendment for allowing individual dose adjustment reduction if the Investigator believed a dose reduction was needed because of safety concerns. The Extension Phase of the study is ongoing and approximately 1/3 of the randomized subjects remain blinded (at the 120-day update). This reviewer is unable to determine how many patients in each dose group required dose adjustments.

Best Available Copy

Schedule of Events for the Extension Period:

Table 32: Extension Period Schedule (Source: Sponsor’s submission)

SCHEDULE OF EVENTS DURING EXTENSION PERIOD				
Trial visit	Treatment intervals (maximal 5)*			Safety Period
	V6, V8, V10, V12, V14 (Injection)	T2, T3, T4, T5, T6 (Telephone Contact)**	V7, V9, V11, V13, V15 (Control)**	V16 (Trial Termination Visit)
Assessment time point and time window	Day 0 of treatment interval, any day of EP V14 is at the latest 48 weeks (+ 1 week) after start of EP	Day 7 ± 1 day after V6, V8, V10, V12, V14	Day 28 ± 3 days after V6, V8, V10, V12, V14	up to Week 20 ± 3 days after V14 (V14 = last injection visit)
Physical/Neurological examination, body weight	X (only before 3 rd injection during EP)			X
TWSTRS – Total score	X		X	X
Patient Evaluation of Global Response**** (except V6)	X			X
Dysphagia scale	X	X	X	X
Vital signs	X		X	X
Clinical Chemistry, Hematology	X			X
Antibody titer	X			X
Pregnancy test	X*** (Urine)			X (Blood)
Injection session	Only if indicated			
Adverse events	X	X	X	X
Changes in Concomitant medication /Concomitant diseases	X	X	X	X
Global assessment of efficacy/tolerability (except V6)	X			X
Documentation of trial termination				X

REVIEWER’S COMMENTS:

- While the study blind was maintained throughout the extension phase, the intervals between injections were varied and could be as early as 42 days (or 6 weeks) from the last injection but not later than 48 weeks (end of trial).

- Extent of exposure, Safety data and information regarding the maintenance of treatment effect can only be examined after the study is complete and the full data set is unblinded and analyzed. Questions raised while the study is ongoing:
 1. Did the patients who were randomized into the placebo and 120 U groups in the Main Phase develop more side effects when they were re-randomized to the 240 U in the extension phase? A positive answer to this would supplement the dose response adverse effects already seen in the preliminary analysis.
 2. Did the patients who were initially randomized to 240 units in the Main Phase and were switched to 120 U in the EP report a loss of efficacy? If there were no complaints of lack of efficacy or a significant worsening in the TWSTRS scores, then this would support the conclusion drawn from the placebo controlled MP data that the 240 U dose not provided an advantage over the 120 U..

Study Results:

Patient Disposition:

The total number of patients from the Main Phase was 233 patients. Up to the present when these summary data were requested, there were still 24 blinded patients. Eighteen patients (7%) did not receive any injections after the baseline visit. Majority of these patients (N=12 or 66% were assigned to IncobotulinumtoxinA. The following analysis is provided for the 154 patients who have been unblinded.

The table below provides a summary of the number of patients who received injections at each visit including the patients who are still blinded. There were more patients who received 240 U than 120 U especially towards visit 14. There were also more pre-treated than naïve patients (expected as there have been more pre-treated subjects enrolled in the study). As the study progressed, fewer patients needed injections. At the start of the Extension Phase (V6), there were a total of 214 patients who received one injection (other than baseline). A total of 90 patients received five injections by Visit 14.

Table 33. Number of Patients and Doses Received Classified into Naïve (N) and Pre-Treated (P) at Each Visit. (Source: Reviewer's table)

	V6 N=214		V8 N=191		V10 N=168		V12 N=139		V14 N=90	
	N	P	N	P	N	P	N	P	N	P
<120 U	2	1	0	2	1	1	0	0	0	0
120 U	24	50	20	45	15	42	8	35	6	23
>120u to < 240 U	0	1	0	1	0	1	0	1	0	0
240 U	23	47	24	42	18	38	16	34	12	25
> 240 U	0	0	0	0	0	0	0	0	0	0
Still Blinded	23	33	25	32	22	30	17	23	6	18
Total N	82	132	69	122	56	112	41	98	24	66

N= Naïve; P=Pre-treated; Total N=Total Number of Patients

Clinical Trial Results

The duration between injections was determined by patient need in conjunction with the investigator rating and judgment. This will be an important part of the analysis of the Extension Phase Study.

The table presented below was provided by the Sponsor two months before the PDUFA date. The reviewer was interested in the number of patients who had received 120 U and 240 U and further subdivided into Naïve and Pre-treated patients at each injection visit and the corresponding TWSTRS scores.

Table 34. Number of Patients and Mean TWSTRS score by visit in Naïve (N) and Pre-treated (P) patients

Visit 6						
	Naïve N = 82			Pretreated N=82		
	120U	240U	Still Blinded	120U	240U	Still Blinded
Total No. of Patients (N)	25	29	28	50	49	33
Mean Total TWSTRS Score	38.69	39.13	36.66	42.58	41.12	42.98
Visit 8						
	Naïve N=69			Pretreated N=122		
	120U	240U	Still Blinded	120U	240U	Still Blinded
Total No. of Patients (N)	19	25	25	46	44	32
Mean Total TWSTRS Score	37.62	39.01	36.29	38.90	38.45	41.18

Visit 10						
	Naïve N=56			Pretreated N=112		
	120U	240U	Still Blinded	120U	240U	Still Blinded
Total No. of Patients (N)	15	19	22	43	39	30
Mean Total TWSTRS Score	37.88	37.86	35.82	37.92	36.71	37.53
Visit 12						
	Naïve N=41			Pretreated N=98		
	120U	240U	Still Blinded	120U	240U	Still Blinded
Total No. of Patients (N)	7	17	17	35	35	28
Mean Total TWSTRS Score	34.5	37.88	36.62	40.10	36.59	37.50
Visit 14						
	Naïve N=24			Pretreated N=66		
	120U	240U	Still Blinded	120U	240U	Still Blinded
Total No. of Patients (N)	6	12	6	23	25	18
Mean Total TWSTRS Score	33.75	38.13	35.29	39.70	30.32	40.97

REVIEWER'S COMMENTS:

- The table above demonstrates the following:
 1. Out of the 214 patients who had continued into the Extension Phase, only 168 (79%) patients (58 in the 240 U group and 58 in the 120 U group, 52 still blinded) had 4 consecutive injections; 90 patients (42%) had 6 injections, with a total of 37 patients receiving 240 units. Because the trial is still ongoing and the blind for the remaining 52 patients is not yet broken, the reviewer is unaware of the total number of patients in the “still blinded” group who got 120 U or 240 U.
 2. The mean TWSTRS scores of patients in these tables are the TWSTRS scores when they needed the injection at that visit (their worse TWSTRS scores). The mean TWSTRS scores do not vary much based on whether they received 240 U or 120 U except towards the last two visits (Visits 12 and 14) where the patients who had received 120 U had lower mean TWSTRS total scores at the time when they “needed” an injection.
 3. Unfortunately, as previously mentioned this review would be unable to determine who among the patients in the Extension Phase received higher or lower doses than what they have received in the Main Phase and how this change in dose contributes to the efficacy of the drug.

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

The reviewer also looked into the number of days in between injections. This will be important in determining the frequency of when injections should be given to optimize efficacy and to assure and maintain safety. This will be part of the labeling instructions. The subsequent table shows the duration in days between injections.

Visits	V6		V8		V10		V12		V14	
Units received	240U	120U	240U	120U	240U	120U	240U	120U	240U	120U
N	78	75	69	63	69	57	52	43	52	29
Mean	67.65	75.19	89.15	89.56	87.81	99.68	83.96	83.91	70	77.34
Median	58	57	84	82	88	90	87	84	68	77

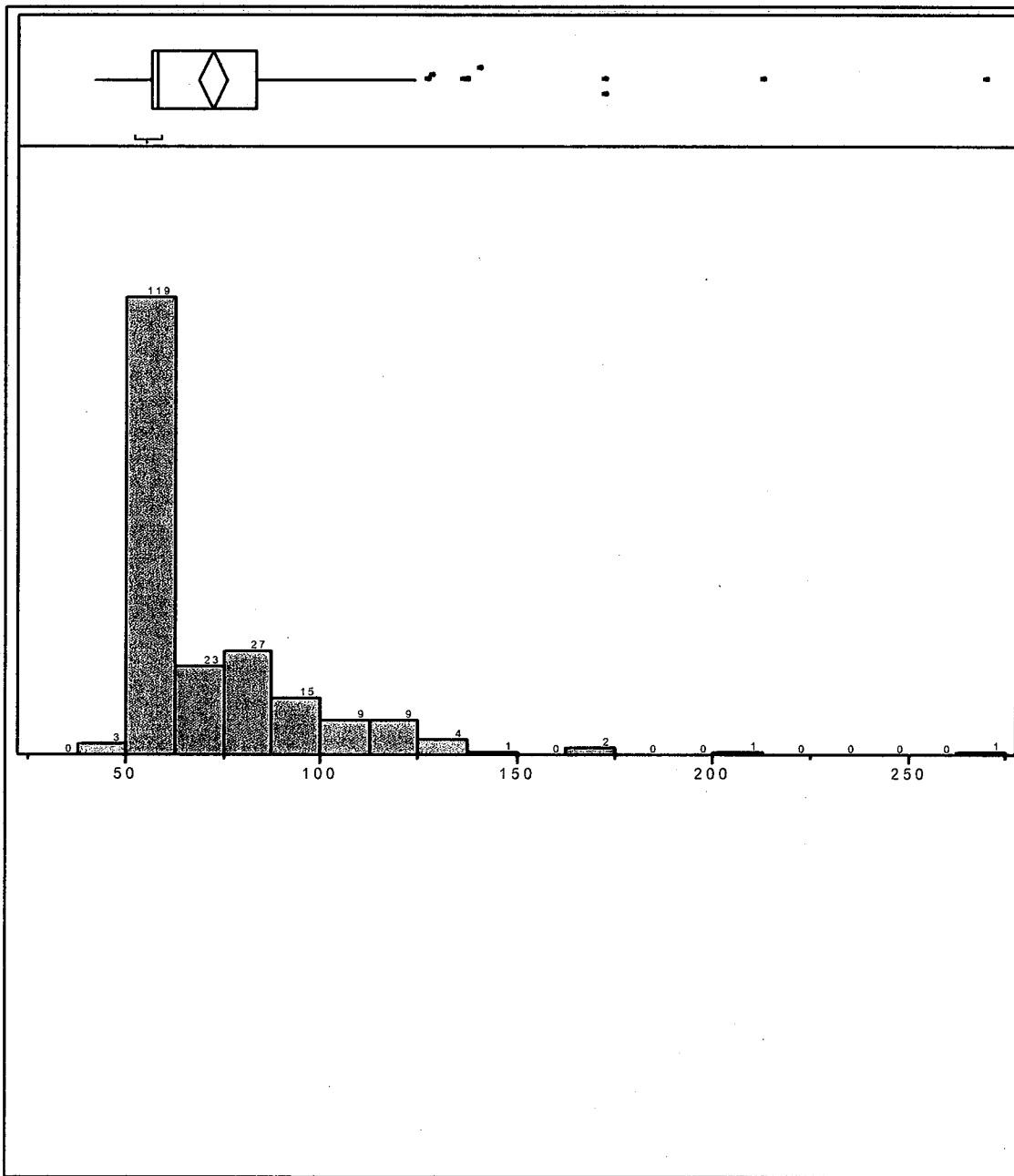
*Still blinded: N=61; Mean 73.96, Median 62

REVIEWER'S COMMENT:

- There is a wide range of variability between the need for injections. The earliest need for injection was at 42 days after baseline treatment and the longest was 269 days from baseline injection. The need for earlier injection among pre-treated patients suggests increased tolerability of the medication.
- There is not much difference in the number of days between injections among patients who had received 120 U compared to those who received 240 U. Higher doses of other botulinum toxin products have been reported to be associated with a longer duration of effect and more frequent peak dose adverse effects. The 240 U dose of Xeomin (NT 201) is not associated with a significantly longer duration of between injections suggesting the duration of action of the 240 U dose is not longer.

The figures below provides a closer look into the Extension Phase Data with regard to number of days between injections.

Figure 5. Distribution of patients according to number of days since first injection in Main Phase until the first injection in the Extension Phase. (Source: Reviewer)



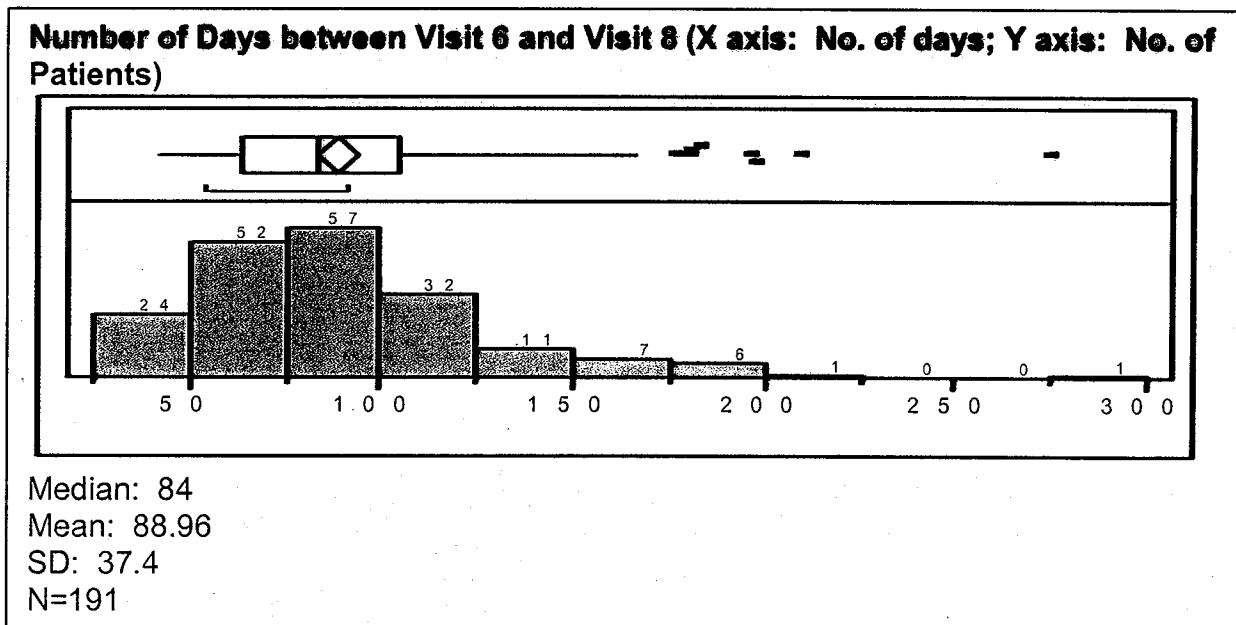
Median: 58
Mean: 72.09
SD: 28.21

REVIEWER'S COMMENTS:

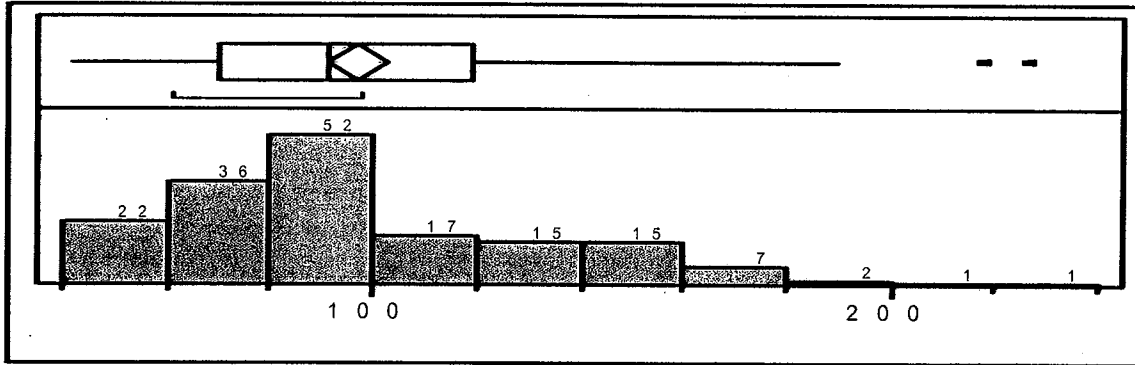
- From figure 5 (above), the median number of days when patients need to be re-injected was 58 days after their first injection in the Main Phase. The mean number of days was 72 but there were a number of outliers (N=4) who had injections more than 250 days later influencing the mean value.

We have also computed the mean and median number of days from the most recent injection in the Extension Phase to the subsequent injection. V6, V8, V10, V12 and V14 were the injection periods and the number of days between V6 to V8, V8 to V10, V10 to V12 and V12 to V14 were computed. The figures and tables below summarize these data. The figures also show the outliers that might be driving the mean.

Figure 6. The number of Days between injections in the Extension Phase between Visit 6 to Visit 8, Visit 8 to Visit 10, Visit 10 to Visit 12 and Visit 12 to Visit 14. Median, Mean and SD are shown below each figure. (Source: Reviewer)

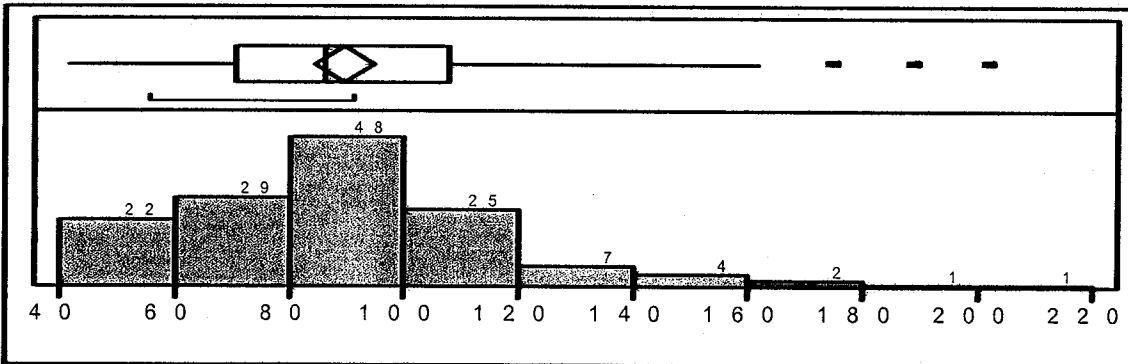


Number of Days between Visit 8 to Visit 10 (X axis: No. of days; Y axis: No. of Patients)



Median: 91
 Mean: 97.14
 SD: 36.66
 N=168

Number of Days between Visit 10 to Visit 12 (X axis: No. of days; Y axis: No. of Patients)



Median: 86
 Mean: 89.56
 SD: 29.69
 N=139

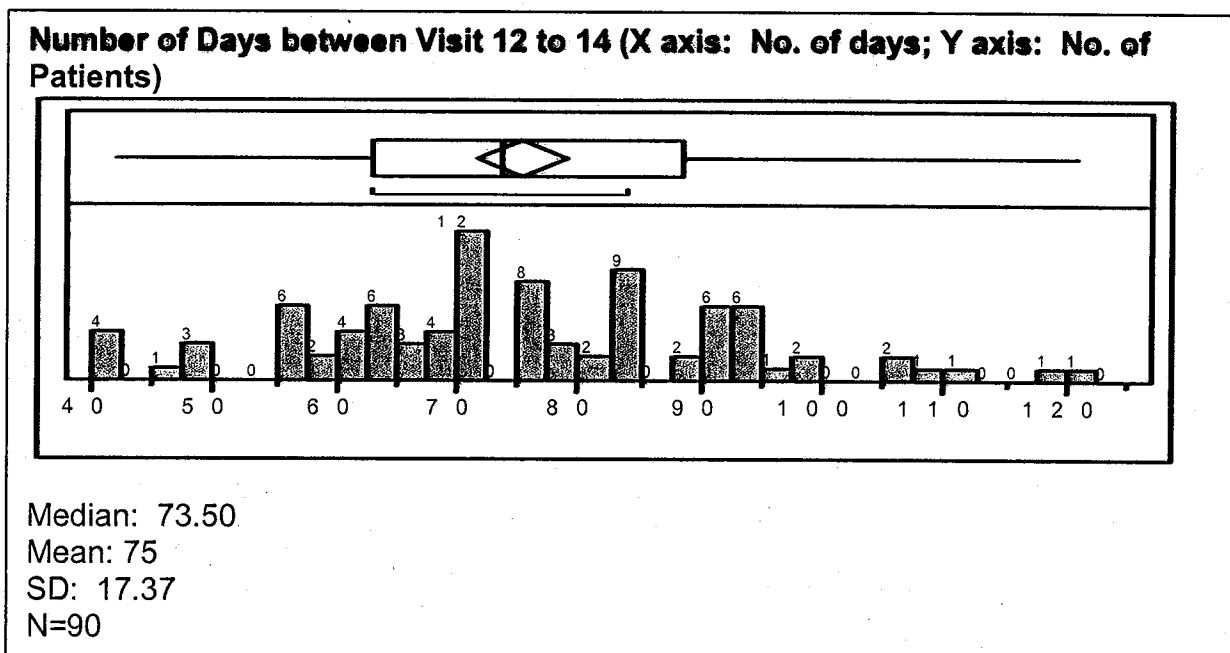


Table 36 (below) presents the number of patients who had three, four and five consecutive injections receiving 240 units. This is important for the safety analysis because it could provide information on the adverse reaction and side effect profile among patients who had received more injections as compared to those who had less injections.

	Three Injections	Four Injections	Five Injections
Number of Patients	69	58	52
Mean Duration between Doses	89 days	87 days	83.96 days
Median Duration Between Doses	84 days	88 days	87 days
Standard Deviations	45	29.79	25.48

REVIEWER'S COMMENT

- Based on the figures above, the median number of days in between doses range from 58 to 91 days. The range of days between injections narrows with the 3rd, 4th and 5th injections where the median number of days is 84 to 89 days. The reviewer also looked into the 75th quartile of each visit and the number of days between injections ranged from 81 to 91 days. Based on all these data, it may be reasonable to recommend frequency of injections at 81 days or between 11 and 12 weeks.

The detailed safety data from the Extension Phase will be discussed by Dr. Lisa Jones, MD, MPH. Additional safety comments are provided below.

Safety

REVIEWER'S COMMENTS:

- The study has not yet been completed and has reports a total of 58 patients received 4 consecutive injections for the entire year and from 37 patients who have received at least 6 subsequent injections for the duration of a year in the 240 U group. Because of this limitation, further comments about safety with frequent dosing at higher doses cannot be made. The FDA may have to require the sponsor to submit PMC to account for more patients receiving higher doses of NT 201 with increasing dosing frequencies. Cervical dystonia, being a chronic disease, requires repeated injection and effects of repeated toxin exposure are important to assess safety of the drug.

MRZ 60201-0013/1:

The study has been included in this review because it provides additional safety data (as they have enrolled a larger number of subjects) and on the effect of IncobotulinumtoxinA on pain. Pain is a secondary efficacy parameter in this study and its results can support the data obtained from 408/1, although the sponsor did not identify Pain as a key secondary outcome and there was no correction for comparisons.. It cannot be used though as a pivotal or supporting study primarily because its primary endpoint (TWSTRS Severity) is different from that in 408/1 (TWSTRS total). As it is designed as a non-inferiority (NI) study between IncobotulinumtoxinA and Botox, it does not have a placebo group comparison and lacks uncontrolled data for safety and assay sensitivity for effectiveness. It is also not adequately powered for non-inferiority. The sponsor did not seek advise from the agency regarding the design of this study or agreement on the NI margins.

Title: Safety and efficacy of NT 201 compared to BOTOX® in cervical dystonia.

Investigators and Sites: 51 main study investigators in 51 centers in 11 European countries

Study Period: March 2001 to April 2002 (Date of last completion)

Phase of Development: Phase 3

Objective: Safety and efficacy of NT 201 compared to BOTOX® in predominantly rotational cervical dystonia.

Methodology:

Randomized, double blind active controlled parallel group, multicenter trial on non inferiority. The drugs were administered by intramuscular injection in a 1:1 ratio, one unit NT 201 is regarded as being equal to one unit Botox.

- Dose Selection: As specified in the protocol submission, “prior to trial, the patient was to have received two successful BOTOX® treatments following the same injection scheme. “ Successful treatment should have been demonstrated and the injected muscles, volume, number of injections and sites had to be recorded. At the baseline visit, patients were treated in a randomized double blind order with NT 201 or BOTOX® following the two consecutive treatments with BOTOX® prior to trial entry with a range of treatment ranging from 70 to 300 units of BOTOX®.

Number of Patients:

- Planned: 460 patients randomized including 10% dropouts, 412 patients treated per protocol
- Analyzed: 463 patients ITT, 420 patients TPP and 463 patients EFS

Diagnosis and main criteria for inclusion:

- Patients with cervical dystonia (rotational form) who needed injection
- Male/Female outpatients <75 years old with last injection session with BOTOX® at least 10 weeks prior to randomization and willingness to participate as documented by written informal consent
- TWSTRS severity score > 10, for rotation > 2,
- Stable therapeutic response to BOTOX® in the last 2 injection sessions prior to trial entry receiving a dose of 70 to 300 units
- Stable dose of other focal dystonia therapy for three months prior to trial entry
- Negative pregnancy test and reliable means of contraception at trial entry for childbearing females

REVIEWER'S COMMENTS

- The inclusion criteria allowed patients enter if their last injection with BOTOX® was at least 10 weeks prior to randomization. This is less than the recommended duration of injection specified in the BOTOX® label (3 months) when patients should return for pre-treatment. The shorter interval since their last Botox dose may make either drug seem more efficacious.

Primary Efficacy Endpoint:

- Change in TWSTRS Severity score from baseline to control visit on day 28+/-3 after the injection of study medication

Secondary Efficacy Endpoint:

- TWSTRS Pain subscore, VAS pain and patient's evaluation of global response at control and final visit.
- Effect duration defined as interval between time of injection and final visit when TWSTRS severity score has reached at least 80% of baseline value or at the latest 112 days after injection
- Responder Analysis defined as an improvement of > 20% from baseline in the TWSTRS Severity Score at the control visit
- Time to onset and time to waning of treatment effect after injection
- Investigator's global assessment efficacy

Safety:

- Dysphagia score, standard labs, vital signs, ECG, pregnancy test, adverse events, general physical and neuro exam, ELISA and HAD tests on BoNT/A antibodies

Statistical methods:

- Primary variable is the non-inferiority of efficacy of NT 201 compared to BOTOX®: based on change in Baseline TWSTRS severity using ANCOVA and 95% confidence

interval method in TPP. In the full model of the confirmatory analysis, the dependent variable was the change from baseline in the TWSTRS severity score and independent variables were treatment, baseline TWSTRS total score, gender, age, pretreatment of cervical dystonia and pooled center.

- Method of Imputation: No missing data was imputed.
- In the analysis of all efficacy variables, descriptive statistics were used for continuous variables and frequency tables for categorical data
- Kaplan Meier method was used for analyzing tertiary efficacy variables (Investigator's global assessment of efficacy) and log rank tests were used to analyze onset of disease, waning and duration of effect.
- Safety variables were analyzed using descriptive statistics, frequency and shift tables subgroup analysis stratification for age, gender, antibody tests. Kaplan Meier method was used to analyze the data was for adverse drug reactions and serious adverse events.

REVIEWER'S COMMENT:

- Although the non inferiority margin was chosen at $\Delta=1.3$, the rationale and the study that was used as a basis for coming up with this margin has not been specified in their study protocol. There is also no pre-specified M2 in their protocol.

Disposition of Patients:

- 51 centers in 11 countries recruited 466 patients and only 463 were randomized and constituted the ITT population (231 patients in NT 201 Group and 232 patients in the BOTOX® Group). There were 43 major protocol deviations (18 NT 201 and 25 BOTOX®) which resulted in a TPP Population of N=420 (213 patients in NT 201 group and 207 patients in the BOTOX® Group). Five NT 201 patients discontinued therapy with lack of efficacy as the most common cause of discontinuation. A total of 226 NT 201 patients completed the study.
- The most common reason for major protocol deviations includes lack of stable response and unavailable source documentation.

Demographics:

- Patient median in the NT 201 group was 50 years old.
- BMI was 24.8 kg/m²
- Estimated duration of cervical dystonia prior to entry was 9.4 +/- 7.7 in the NT 201 group
- Initial diagnosis prior to baseline visit was 7.5 +/-6.9 years in the NT 201 group.

Efficacy Evaluation Summary:

In both treatment groups, the TWSTRS severity score was significantly reduced by about -6.6 for the IncobotulinumtoxinA group ($p<0.0001$, ANCOVA) and -6.4 for the Botox ($p<0.0001$ ANCOVA) group. These results are reported in the sponsor's tables 37 and 38 (below).

Table 37. Results of TWSTRS Severity Score at Control Visit (TPP, N=420) (Source: Sponsor's submission)

Parameter	score points [mean±SD (median)]			
	NT 201	N	BTXCo	N
TWSTRS - Severity score				
Baseline visit (injection)	17.8±3.5 (18.0)	213	17.7±3.7 (18.0)	207
Control visit (28±7 days)	11.1±4.8 (11.0)	213	11.4±4.8 (11.0)	207
Differ. control - baseline	-6.6±4.1 (-6.0)	213	-6.4±3.9 (-6.0)	207

Table 38. TWSTRS Severity Score at Control Visit from Baseline Study 0013 (Source: Sponsor)

The GLM Procedure
 Least Squares Means
 Adjustment for Multiple Comparisons: Dunnett-Hsu

TREAT	parvalue LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=
			Pr > t	LSMean2 Pr > t
BTXCo	-6.61702957	0.32137313	<.0001	0.3628
NT 201	-6.94804745	0.31470525	<.0001	

The TWSTRS Pain Subscore decreased significantly from baseline to control visit in both groups with a mean decrease of -0.4 score points in NT 201 ($p < 0.0001$) and -0.6 score points in the BOTOX® group ($p < 0.0001$). The change from baseline to final visit decreased 0.1 score points in the NT 201 group ($p = 0.1239$) and -0.2 score points in the BOTOX® group ($p = .0032$). These results are illustrated in Tables 39 and 40 (below).

Table 39. Results of the TWSTRS Pain Subscore (TPP N=420) (Source: Sponsor's submission)

Parameter	Score points [mean±SD (median)]			
	NT 201	N	BTXCo	N
TWSTRS - Pain subscore				
Baseline visit (injection)	1.1±1.1 (1.0)	213	1.3±1.2 (1.0)	207
Control visit (28±7 weeks)	0.7±0.9 (0.0)	213	0.7±1.0 (0.0)	207
Final visit (in the latest 112 days)	1.0±1.1 (1.0)	210	1.1±1.2 (1.0)	205
Differ. control – baseline	-0.4±0.8 (0.0)	213	-0.6±1.0 (0.0)	207
Differ. final – baseline	-0.1±0.9 (0.0)	210	-0.2±1.0 (0.0)	205

Table 40. Efficacy Data TWSTRS Pain Subscale: Wilcoxon Test P values (Source: Sponsor's submission)

14.2 Efficacy Data
 14.2.1 TPP-Population, N=420
 14.2.1.2.12 TWSTRS-Pain Subscale: Wilcoxon Test P-Values *)

Treatment	Variable	Visit	Wilcoxon Test: Two-Sided P-Value
NT 201	Change TWSTRS Pain Subscale	Control	0.00000
		Final	0.12392
	Change TWSTRS Pain Subscale-Missings Replaced by ZERO	Control	0.00000
		Final	0.12392
BTXCo	Change TWSTRS Pain Subscale	Control	0.00000
		Final	0.00322
	Change TWSTRS Pain Subscale-Missings Replaced by ZERO	Control	0.00000
		Final	0.00322
NT 201 vs.BTXCo	Change TWSTRS Pain Subscale	Control	0.40815
		Final	0.09826
	Change TWSTRS Pain Subscale-Missings Replaced by ZERO	Control	0.40815
		Final	0.09639

Results of other Secondary Parameters:

- VAS for pain: The two sample Univariate Wilcoxon test did not show any significant difference between NT 201 and BOTOX® treatment groups in the change from baseline in VAS pain score observed at the control and final visit.
- The global response of patients improved significantly (ANCOVA model) in both groups at control and final visits.

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

- There were no significant differences between groups with regard to the median time until onset of effect (7 days for each treatment group). Two treatment groups were comparable regarding time to onset (7 days after injection) and waning of effect (10 and 11 weeks for NT 201 compared to BOTOX®) and duration of treatment effect (110 days vs. 109.5 days for NT 201 vs. BOTOX®).
- There were no significant relevant differences between groups with regard to the median time until waning of effect (10 weeks for NT 201 and 11 weeks for BOTOX®).
- Duration of effect amounted to 110 days for NT 201 and 109.5 days for BOTOX®. The two treatment groups were comparable regarding duration of effect.

Safety Evaluation

- Overall, 65/231 (28.1%) patients treated with NT 201 reported 110 adverse events compared to 56/232 (24.1%) patients treated with BOTOX® who experienced 87 events.

A detailed Safety Evaluation of this study will be provided in the review of Dr. Lisa Jones, MD, MPH.

REVIEWER'S CONCLUSIONS ON STUDY 0013:

- This is an active comparator study of NT 201 and botulinum toxin (BOTOX®), using 70 to 300 units of NT 201 and botulinum toxin. The study enrolled only pre-treated patients. Enrolling only responders will not provide adequate safety data for toxin naïve patients. The study's primary endpoint is the TWSTRS severity score which is one of the components of the TWSTRS total score (used as primary endpoint in the pivotal study). The trial results of this study cannot be directly compared to the results of study 408/1.
- There were 144 females and 87 males who received NT 201 (ratio: 1:1.6) almost comparable to the gender ratio in the pivotal study. The mean BMI is 25.50.
- For the NT201 group, the mean TWSTRS severity score at baseline is 17.43. This is a little bit less than the TWSTRS severity score obtained in the pivotal trial (which was 18 for the 120 U group and 18.6 for the 240 U group). The mean TWSTRS severity score for IncobotulinumtoxinA group at baseline was 17.74 and the mean in 4 weeks is 15.98. The TWSTRS pain score in this study shows a -0.4 difference from baseline after four weeks, similar to the differences seen in 408/1.
- The results of the study showed non inferiority of NT 201 to BOTOX® but the rationale for the choice of the non-inferiority margin and the absence of a pre-specified M2 has not been provided by the Sponsor. Thus, it is hard to make a conclusion of non-inferiority based on the chosen delta because the quantitative effect of BOTOX is hard to determine. Since this study was done for the European regulatory authorities prior to starting the approval process in the United States, this statistical analysis plan was not presented to the FDA.
- Onset of effect for both drug treatments was 7 days after injection; waning of effect was 10 weeks for NT 201 and 11 weeks for BOTOX® and the duration of treatment effect was 110 days for NT 201 and 109.5 days for BOTOX®. The onset of effect in this study

is longer and the waning effect (subjective) was earlier than that documented in study 408/1.

- The total dose of study medication administered, mean and median, for all muscles in one injection session was 140.4 (120) compared to 138.9 (122.5) for BOTOX®. The NT201 dose range was from 50 U to 300 U. The most frequent dose was 100 U. Only 16 patients received a dose greater than 200 units. The doses given here were comparable to the doses given in the US except that the most frequent dose was 100 units which were 20 units less than those given in the United States and the 100 U still showed some benefit.
- Dysphagia and Pain were the most frequent adverse reactions. There is a slight difference in adverse events with more GI symptoms, especially dysphagia and pain occurring in patients given NT 201.

7. Review of Safety

- A detailed safety analysis will be provided by Dr. Lisa Jones. MD, MPH.

The safety population ranged from 8 to 236 patients (most number of enrollees in those with glabellar frown lines). Up to 300 units were used in cervical dystonia, 400 in spasticity and 100 in Blepharospasm. (b) (4)

Table 41. Studies/Clinical Trials Used to Evaluate Safety in Cervical Dystonia Indication (Source: Sponsor's submission).

Study number/Link to Report Indication Phase Design Status	Treatment(s): # of Subjects (Safety Population)	Site(s) of Administration	Frequency of Dosing, Duration of Exposure in Study	NT 201 Dose Range Studied
0408/1 Main Period Cervical Dystonia Phase 3 Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Trial	NT 201 120 U: 78 NT 201 240 U: 81 Placebo: 74	Splenius capitis/semispinalis; trapezius; sternocleidomastoid; levator scapulae; scalene; other spinal/semispinal muscles; suboccipital triangle; platysma/other	Single dose with 8 to 20 weeks of follow-up	120 or 240 U IM
9801 Cervical Dystonia Phase 2 Open-Label, Randomized, Active-Controlled Trial	NT 201 10/20: 14 NT 201 20/40: 13 NT 201 30/60: 14 BOTOX 30/60: 12	Splenius capitis (SPL); sternocleidomastoid (SCM)	Single dose with 14 days follow-up, re-injection with 106 days of follow-up	10 SCM/20 SPL, 20 SCM/40 SPL, or 30 SCM/60 SPL IM <u>Optional second dose:</u> Up to 60 U in muscles other than the SCM
0013 Cervical Dystonia Phase 3 Double-Blind, Randomized, Active-Controlled Trial	NT 201: 231 BOTOX: 232	Splenius capitis/semispinalis; trapezius; levator scapulae; sternocleidomastoid; scalenus; other muscles in the neck region	Single dose with up to 16 weeks follow-up	70 to 300 U IM

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

Study number/Link to Report ¹ Indication or Population Phase Design Status	Treatment(s): Number of Subjects in ITT Population	Site(s) of Administration	Frequency of Dosing, Duration of Exposure in Study	NT 201 Dose Range Studied	Type of Pooling/ Reason Not Pooled
0408/2 Extension Period Cervical Dystonia Phase 3 Double-blind, Parallel-Group Extension Period Ongoing	NT 201: 217	Splenius capitis/semispinalis; trapezius; sternocleidomastoid; levator scapulae; scalene; other spinal/semispinal muscles; suboccipital triangle; platysma/other	Up to 5 injections at least 6 weeks apart over 48 weeks, with 20 weeks of follow-up	120 or 240 U IM	Extension study, repeated administrations, ongoing (Data from this study were pooled for the 120-day Safety Update)
0605/1 Main Period and 0605/2 OLEX Period Cervical Dystonia Phase 4 Main Period: Open-label, Single-arm Trial; Completed Open-label, Single-arm Extension Period: Ongoing	NT 201: 76	Sternocleidomastoid; levator scapulae; scalenus; splenius capitis; trapezius	Main Period: 1 injection with 4 weeks of follow- up. OLEX Period: Up to 5 additional injections over up to 121 weeks	Up to 300 U IM	Open-label study with short observation period (Main Period); OLEX phase is ongoing and thus is not yet reported

Safety Preliminary Conclusions: (Medical Safety Reviewer)

- There have been no new or unexpected safety signals with both doses of NT 201.
- Overall incidence of Treatment Emergent Adverse events was higher in the treated group, more in the 240 units than in the 120 units group. Neck pain and dysphagia were the most prominent TEAE’s experienced by individuals in the study.
- Time to occurrence of adverse events was shortest (16.5, SD 21.03 days) in those who received 240 units than those who received 120 units (15.3, SD 18.37 days).
- Incidence of dysphagia was higher in those who received 240 units than those who received 120 units.
- In pre-treated subjects in the 240 units, percentage of subjects with mild swallowing difficulties was higher than baseline than those in the 120 units group.
- In treatment naïve subjects, likewise, those who received 240 units had more complaints of dysphagia with persistence of symptoms until the final visit.

Safety Review Comments by Dr. Lisa Jones (Safety Medical Reviewer):

I concur with the following comments of Dr. Lisa Jones:

- “...the overall risk of common adverse event for CD patients is similar across doses: 57% in the 120 U group, 55% in the 240 U group and 42% in placebo. However, when restricted to common adverse events most likely to be caused by the drug (based on the frequency of events, the difference from placebo and past experience with other botulinum toxin products), these events appear to demonstrate a dose-response (For

example dysphagia (13% 120U; 19% 240 U, 3% placebo), neck pain (6% 120 U, 15% 240 U, 4% placebo), muscle weakness (6% 120 U; 11% 240 U, 1% placebo).

I believe that there is a dose-response effect demonstrated within this study, with the 240 U dose having a greater risk of adverse events. I believe the reason that the risk for any non-serious AE are similar for the 120 U and 240 U groups is that the table above includes many incidental adverse events unlikely to be drug related (somnolence, sinusitis, syncope, etc) and these obscure the dose-response in the adverse events that are most likely to be drug related. “

- *The adverse events listed above are more likely to be related to toxin injection, all are associated with a greater frequency in patients who are treated with 240 U compared to 120 or placebo. Of note is the nearly 20% of patients who reported experiencing dysphagia following treatment with 240 U of IncobotulinumtoxinA.”*

Immunogenicity:

Part of the safety review is the relevance of Immunogenicity. (b) (4)

(b) (4)

(b) (4) Immunogenicity becomes relevant because the treatment of focal dystonia require long term treatment requiring repeated injection. If neutralizing antibodies develop, patients may experience a permanent loss of effectiveness to all botulinum toxin type A products. A summary of the Sponsor’s findings show that only four subjects, all pre-treated for cervical dystonia, became newly positive for neutralizing Botulinum toxin antibodies after injection of IncobotulinumtoxinA; however there were no reports of secondary treatment failure in these subjects.

(b) (4)

(b) (4)

(b) (4)

(b) (4) In practice, patients who report loss of benefit from a particular toxin product may not have detectable antibodies and that patients continue to demonstrate toxin responsiveness to a frontalis test. Other factors such as injection technique or dose may play a role in patients who report a loss of clinical effectiveness.

8. Agency's Statistical Reviewer's Conclusions for Study 408/1

I concur with the conclusions of Dr. Ohidul Siddiqui. Here is his conclusion on the study:

Xeomin has demonstrated its efficacy in treating patients with cervical dystonia. In the study 408/1, the primary efficacy endpoint was the change in the TWSTRS total score from baseline to Week 4 post injection. In the ITT population, the difference between the Xeomin 240 U group and the placebo group in the change of the TWSTRS total score from baseline to Week 4 was -9.0 points; the difference between the Xeomin 120 U group and the placebo group in the change of the TWSTRS total score from baseline to Week 4 was -7.5 points. Comparison of each Xeomin group to the placebo group was statistically significant at $p < 0.001$. Subgroup analyses also revealed that the efficacy of the two Xeomin doses was similar in pre-treated subjects (i.e., subjects who had received a Botulinum toxin prior to this study) and in naïve subjects (i.e., subjects who had not received a Botulinum toxin prior to this study). Examination of age and gender subgroups did not identify differences in response to Xeomin among these subgroups. There were a few African-American subjects to adequately assess efficacy in that population.

9. Clinical Reviewer's Conclusions

- IncobotulinumtoxinA is another type of botulinum toxin A that has been approved in Europe and other Latin American countries that seeks approval in the United States for the treatment of Cervical Dystonia. It differentiates itself from the other approved neurotoxins as it is highly purified (b) (4)
(4)
- Clinical trial 408/1 attempted to demonstrated the efficacy and safety of two doses of IncobotulinumtoxinA in the treatment of cervical dystonia in a double blind, randomized study utilizing two preparations (240 units and 120 units) and comparing it to placebo. As confirmed by the Agency's statistical reviewer, the drug has demonstrated its efficacy in treating patients with cervical dystonia with a significant change in its primary efficacy endpoint, which is the Total TWSTRS score, 4 weeks post injection. Both formulations of 240 units group and 120 units group proved better than placebo with a statistically significant p at < 0.001 .
- Subgroup analysis (in pre-treated and naïve subjects) also revealed the efficacy of the two dose formulations over placebo.
- In both treatment groups, the PEGR was better than placebo.

- However, there is no statistically significant difference between the treatment effect of 240 units and 120 units. The majority of the subgroup analyses and TWSTRS subscores favor the 240 units by a very small, non statistically significant margin. It is possible that this small difference may be due to chance mainly because of the following reasons in the randomization that may have been overlooked:
 1. The mean difference of the Weight and BMI of patients in the 240 units group is lower than that of the 120 units group and if these variables were equal in these two groups, a treatment difference would not be seen at all.
 2. More patients in the 240 units were using medications that may affect/relieve the overall symptoms of cervical dystonia and this could contribute to the small treatment effect difference seen in the two treatment groups.

These minor (non-statistically significant) differences between treatment groups are important to consider when looking at the treatment effect size between the two treatment groups.

- Merits of the 240 units over the 120 units in subgroups (women and pre-treated patients) are noted but are not consistent in all the efficacy variables. Likewise, the “gender effect”, where pre-treated women were seen to have benefitted more from the 240 units is not adequately supported because the statistical analysis used to obtain this result pre-specified a high p-value (0.2) for covariates that included gender.
- While 240 units may show more benefits than 120 units by a small numerical margin, there have been more TEAE’s especially of dysphagia (prolonged, even if they were mild) in those who received higher doses. It should also be emphasized that there is a need to provide data for more than 60 patients who had repeated exposures to IncobotulinumtoxinA at its maximum dose of 240 U for a year in order to continuously assess safety.
- Whereas the 240 units dose is more effective than placebo, it is still advised that patients, regardless of whether they are pre-treated or treated, be started on 120 units of IncobotulinumtoxinA because of the dose response TEAE’s seen in the higher doses of NT 201.
- Onset of effect, waning of treatment effect and treatment duration for both treatments groups was longer than placebo but there was no difference in the effects of 240 units over 120 units in any of these tertiary variables. The average number of weeks that can be used for recommendation of frequency of injections is 11 weeks.
- Although muscles injected and the doses given were documented in this study, choices of muscles to inject were dependent on the investigator. This implies that only physicians who have had experience with other botulinum toxins (or who have trained extensively with physicians who had experience with injections of botulinum toxins) should be the only ones administering this drug.
- There have been no studies done converting NT 201 to Dysport® or Myobloc®. Even the non-inferiority trial done in Europe comparing NT 201 and Botox does not have a strong basis for its non inferiority margin and cannot be used to make a decision on

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

whether the two drugs are bioequivalent and interchangeable. Its product label should include the statement that IncobotulinumtoxinA dose should not be used interchangeably with other type A botulinum toxin products.

10. Post Marketing Experience

11. Appendices

11.1 Literature Review/References

Borodic GE, Joseph M., Fay L., Cozzolino D. Ferrante RJ. Botulinum A toxin for the treatment of spasmodic torticollis:dysphagia and regional toxin spread. Head and Neck 2001; 12(5) 392-399.

Defazio G, Abbruzzese G, Livrea P, Berardelli A. Epidemiology of primary dystonia. Lancet Neurol 2004; 3(11): 673-678.

Garner CG, Straube A, Witt TN, Gasser T, Oertel WH. (1993) Time course of distance effects of local injections of botulinum toxin. Mov Disord 1993; 9(1); 33-7

Marras C, Van den Eden SK, Fross RD, Benedict-Albers KS, Klingman J, Leimpeter AD, Nelson LM, Risch N, Karter AJ, Bernstein AL, Tanner CM. Minimum incidence of primary cervical dystonia in a multiethnic health care population. Neurology 2007 Aug 14; 69(7); 676-80.

Stacy, M. (2008) Epidemiology, clinical presentation, and diagnosis of cervical dystonia. Neurologic Clinics May 2008; 26 (1); 23-42

11.2 Labeling Recommendations

1. The reviewer recommends 120 units (b) (4); as a starting dose in both pre-treated and naïve patients. In the clinical trial, patients were injected with up to 240 units but there was no added benefit to the higher dose. There have been no doses that were given in between 120 or 240 units. No studies were done on doses above 240 units in this clinical trial.
2. In the study, the drug was given every 11 weeks and the drug may be given similarly every 12 weeks or 3 months.
3. Conversion from one toxin to another is not allowed as there are no bioequivalence data comparing this drug with other drugs from its class.

11.3. Advisory Committee Meeting

- There has been no Advisory Committee convened for this drug.

11.4. Dataset Requests to Sponsor

- The following analysis data sets pertaining to 408/1 were requested from the sponsor and were submitted accordingly.
- The following result summaries were requested from the sponsor pertaining to 408/2.

Anne E. A. Constantino, MD

NDA 125360-1

Botulinum Toxin A, Xeomin® IncobotulinumtoxinA

- Summary Table Total Dose Per Subject of NT 201 Received Per Visit
- Mean and Median doses of NT 201 received at each visit
- Total Number of Patients and Doses Received Classified into Naïve and Pretreated at Each Visit
- Mean TWSTRS Total by Visit of Naïve and Pretreated Patients

CLINICAL SAFETY REVIEW: NT 201 (XEOMIN ®) BLA

Application Type BLA
Application Number(s) 125360
Priority or Standard Standard

Submit Date(s) July 2, 2009
Received Date(s) July 2, 2009
PDUFA Goal Date May 2, 2010
Division / Office Division of Neurology Products
Office of New Drugs (OND)

Reviewer Name(s) M. Lisa Jones, MD MPH
Review Completion Date June 1, 2010

Established Name NT 201
(Proposed) Trade Name Xeomin ®
Therapeutic Class Botulinum Toxin
Applicant Merz

Formulation(s) Intramuscular Injection
Dosing Regimen Variable
Indication(s) (b) (4) Cervical Dystonia and
Blepharospasm
Intended Population(s) Patients with (b) (4) Cervical
Dystonia and Blepharospasma

Template Version: March 6, 2009

Marion Lisa Jones

6/21/2010

Table of Contents

1. RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT 9

1.1 RECOMMENDATION ON REGULATORY ACTION 9

1.2 RISK BENEFIT ASSESSMENT 9

1.3 RECOMMENDATIONS FOR POSTMARKET RISK EVALUATION AND MITIGATION STRATEGIES 9

1.4 RECOMMENDATIONS FOR POSTMARKET REQUIREMENTS AND COMMITMENTS 10

2 INTRODUCTION AND REGULATORY BACKGROUND..... 11

2.1 PRODUCT INFORMATION..... 11

2.2 TABLES OF CURRENTLY AVAILABLE TREATMENTS FOR PROPOSED INDICATIONS..... 11

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 12

2.4 IMPORTANT SAFETY ISSUES WITH CONSIDERATION TO RELATED DRUGS..... 12

2.5 SUMMARY OF PRE-SUBMISSION REGULATORY ACTIVITY RELATED TO SUBMISSION 13

2.6 OTHER RELEVANT BACKGROUND INFORMATION..... 16

3 ETHICS AND GOOD CLINICAL PRACTICES 16

3.1 SUBMISSION QUALITY AND INTEGRITY 16

 3.1.1 *Quality*..... 16

 3.1.2 *Integrity*..... 17

3.2 COMPLIANCE WITH GOOD CLINICAL PRACTICES..... 17

3.3 FINANCIAL DISCLOSURES..... 17

4 SIGNIFICANT SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES..... 18

4.1 CHEMISTRY MANUFACTURING AND CONTROLS 18

4.2 CLINICAL MICROBIOLOGY..... 18

4.3 PRECLINICAL PHARMACOLOGY/TOXICOLOGY..... 18

4.4 CLINICAL PHARMACOLOGY..... 20

 4.4.1 *Mechanism of Action*..... 20

 4.4.2 *Pharmacodynamics*..... 20

 4.4.3 *Pharmacokinetics*..... 21

 4.4.3.1. Distribution 21

 4.4.3.2. Absorption 22

 4.4.3.3. Metabolism 22

 4.4.3.4. Drug interactions..... 22

5 SOURCES OF CLINICAL DATA 22

5.1 TABLES OF STUDIES/CLINICAL TRIALS..... 22

 5.1.1 *Tables of Studies: BEB*..... 23

 5.1.2 *Table of Studies: CD*..... 24

 5.1.3 *Table of Studies: SP*..... 26

5.2 REVIEW STRATEGY 27

5.3 DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS..... 28

 5.3.1 *Summary of Studies: BEB*..... 28

 5.3.2 *Summary of Studies: CD*..... 29

 5.3.3 *Summary of Studies: SP*..... 31

6 REVIEW OF EFFICACY 33

7 REVIEW OF SAFETY 33

SAFETY SUMMARY 33

7.1 METHODS 36

7.1.1	<i>Studies/Clinical Trials Used to Evaluate Safety</i>	36
7.1.2	<i>Categorization of Adverse Events</i>	39
7.1.2.1	Coding of Verbatim to Preferred Terms	39
7.1.3	<i>Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence</i>	41
7.2	ADEQUACY OF SAFETY ASSESSMENTS	41
7.2.1	<i>Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations</i>	42
7.2.1.1	Exposure and Demographics: Pooled Indications	42
7.2.1.2	Exposure and Demographics: BEB	45
7.2.1.3	Exposure and Demographics: CD	49
7.2.1.4	Exposure and Demographics: SP	50
7.2.2	<i>Explorations for Dose Response</i>	54
7.2.2.1	Dose Response: Deaths	54
7.2.2.2	Dose Response: SAEs	54
7.2.2.3	Dose Response: Common Adverse Events	56
7.2.3	<i>Special Animal and/or In Vitro Testing</i>	63
7.2.4	<i>Routine Clinical Testing</i>	66
7.2.4.1	Routine Clinical Testing: BEB	66
7.2.4.2	Routine Clinical Testing: CD	66
7.2.4.3	Routine Clinical Testing: CD	67
7.2.4.4	Routine Clinical Testing: SP	68
7.2.5	<i>Metabolic, Clearance, and Interaction Workup</i>	68
7.2.6	<i>Evaluation for Potential Adverse Events for Similar Drugs in Drug Class</i>	69
7.3	MAJOR SAFETY RESULTS	69
7.3.1	<i>Deaths</i>	69
7.3.1.1	Death Overview	69
7.3.1.2	Deaths Narratives	71
7.3.1.3	Comparison of Death Rates: Drug Versus Placebo	73
7.3.1.4	Relationship of Death to Dose	73
7.3.1.5	Sponsor Conclusions with Reviewer Discussion	74
7.3.2	<i>Nonfatal Serious Adverse Events</i>	74
7.3.2.1	SAEs: Pooled Indications	74
7.3.2.2	SAEs: BEB	77
7.3.2.3	SAEs: CD	79
7.3.2.4	SAEs: Spasticity	86
7.3.2.5	SAEs: SP – Other Studies	91
7.3.2.6	SAEs: SP – Anaphylaxis	91
7.3.2.7	SAEs: Reviewer Summary	92
7.3.3	<i>Dropouts and/or Discontinuations</i>	93
7.3.3.1	Discontinuations: Pooled Indications	93
7.3.3.2	Discontinuations: BEB	95
7.3.3.3	Discontinuations: CD	96
7.3.3.4	Discontinuations: SP	98
7.3.4	<i>Significant Adverse Events</i>	101
7.3.5	<i>Submission Specific Primary Safety Concerns</i>	101
7.3.5.1	Adverse Events of Special Interest (AESIs)	101
7.3.5.2	Spread of Toxin Effect	104
7.3.5.3	Hyperglycemia	105
7.3.5.4	Alkaline Phosphatase	110
7.4	SUPPORTIVE SAFETY RESULTS	113
7.4.1	<i>Common Adverse Events</i>	113
7.4.1.1	Definition of Common Adverse Events	113
7.4.1.2	Common Adverse Events: Pooled Indications	114
7.4.1.3	Common Adverse Events: BEB	117
7.4.1.4	Common Adverse Events: CD	122
7.4.1.5	Common Adverse Events: Spasticity	125
7.4.2	<i>Laboratory Findings</i>	131
7.4.2.1	Laboratory Values: Pooled Indications	131

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

7.4.2.2	Laboratory Values: BEB.....	138
7.4.2.3	Laboratory Values: CD.....	140
7.4.2.4	Laboratory Values: SP.....	141
7.4.3	<i>Vital Signs</i>	142
7.4.3.1	Pooled Indications.....	142
7.4.3.2	Vital Signs: BEB.....	143
7.4.3.3	Vital Signs: CD.....	145
7.4.3.4	Vital Signs: SP.....	147
7.4.4	<i>Electrocardiograms (ECGs)</i>	147
7.4.4.1	Preclinical hERG Channel Testing.....	147
7.4.4.2	ECGs: Other In Vivo Preclinical Studies.....	148
7.4.4.3	ECGs: Pooled Indications.....	149
7.4.4.4	ECGs: BEB.....	153
7.4.4.5	ECG: CD.....	153
7.4.4.6	ECGs: SP.....	154
7.4.5	<i>Special Safety Studies/Clinical Trials</i>	154
7.4.6	<i>Immunogenicity</i>	154
7.4.6.1	Immunogenicity: Pharmacology.....	154
7.4.6.2	Immunogenicity: Literature Review.....	155
7.4.6.3	Immunogenicity: Pooled Indications.....	156
7.4.6.4	Immunogenicity: Safety – BEB.....	156
7.4.6.5	Immunogenicity: Safety – CD.....	157
7.4.6.6	Immunogenicity: Safety – SP.....	157
7.4.6.7	Immunogenicity: Reviewer Conclusions.....	158
7.5	OTHER SAFETY EXPLORATIONS: AE RISK BY STUDY LOCATION.....	158
7.5.1	<i>Dose-Dependency for Adverse Events</i>	160
7.5.1.1	Dose-Dependency for AEs: Pooled Indications.....	160
7.5.1.2	Dose-Dependency for AEs: BEB.....	160
7.5.1.3	Dose-Dependency for AEs: CD.....	163
7.5.1.4	Dose-Dependency for AEs: SP.....	167
7.5.2	<i>Time Dependency for Adverse Events</i>	168
7.5.2.1	Time Dependency for Adverse Events: Pooled Indications.....	168
7.5.3	<i>Drug-Demographic Interactions</i>	169
7.5.3.1	Drug-Demographic Interactions: Pooled Indications.....	169
7.5.3.2	Drug-Demographics Interactions: BEB.....	169
7.5.3.3	Drug-Demographics Interactions: CD.....	170
7.5.3.4	Drug-Demographic Interactions: SP.....	171
7.5.4	<i>Drug-Disease Interactions</i>	171
7.5.4.1	Drug-Disease Interaction: Pooled Studies.....	171
7.5.4.2	Drug-Disease Interaction: BEB.....	172
7.5.4.3	Drug-Disease Interaction: CD.....	173
7.5.4.4	Drug-Disease Interaction: SP.....	173
7.5.5	<i>Drug-Drug Interactions</i>	174
7.6	ADDITIONAL SAFETY EVALUATIONS: PRE-TREATMENT WITH OTHER BOTULINUM TOXIN PRODUCTS... 174	174
7.6.1	<i>Botulinum Toxin Pre-Treatment</i>	174
7.6.1.1	Botulinum Toxin Pre-Treatment: BEB.....	174
7.6.1.2	Botulinum Toxin Pre-Treatment: CD.....	174
7.6.1.3	Botulinum Toxin Pre-Treatment: SP.....	175
7.6.2	<i>Human Carcinogenicity</i>	176
7.6.3	<i>Human Reproduction and Pregnancy Data</i>	178
7.6.4	<i>Pediatrics and Assessment of Effects on Growth</i>	180
7.6.5	<i>Overdose, Drug Abuse Potential, Withdrawal and Rebound</i>	180
7.6.5.1	Overdose.....	180
7.6.5.2	Abuse.....	181
7.6.5.3	Withdrawal and Rebound.....	181
7.7	ADDITIONAL SUBMISSIONS / SAFETY ISSUES.....	181
7.7.1	<i>NT 201- Botox® Comparison Studies</i>	181

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

8	POSTMARKET EXPERIENCE	182
9	APPENDICES	183
9.1	LITERATURE REVIEW/REFERENCES	183
9.2	LABELING RECOMMENDATIONS.....	183
9.3	ADVISORY COMMITTEE MEETING.....	183
9.4	FDA MEETING MINUTES (FEBRUARY 2, 2009) WITH PRE-BLA EXPOSURE SPECIFICATIONS.....	184
9.5	TABULAR SUMMARY OF ALL SERIOUS ADVERSE EVENTS.....	185
9.6	ANAPHYLAXIS POST-MARKETING REPORT.....	197
		(b) (4)
9.8	FULL NARRATIVES FOR BEB PATIENTS WHO EXPERIENCED DYSPNEA OR DRY MOUTH IN STUDY 0433/1	203

Table of Tables

TABLE 1: BOTULINUM TOXIN PRODUCTS APPROVED FOR USE IN THE UNITED STATES AND THEIR INDICATIONS	11
TABLE 2: SAFETY STUDIES FOR BENIGN ESSENTIAL BLEPHAROSPASM	23
TABLE 3: NT 201 SAFETY STUDIES FOR CERVICAL DYSTONIA.....	24
TABLE 4: NT 201 SAFETY STUDIES FOR SPASTICITY	26
TABLE 5: REPORTING OF ADVERSE EVENTS IN NT 201 STUDIES IN THE BEB, CD AND SP INDICATIONS.....	36
TABLE 6: CODING IRREGULARITIES WITHIN THE XEOMIN BLA.....	40
TABLE 7: SUMMARY OF NT 201- STRATIFIED BY INDICATION, NT 201 DOSE AND FOLLOW-UP TIME	43
TABLE 8: NT 201 EXPOSURE BY DOSE GROUP AND OBSERVATION PERIOD FOR THE POOLED INDICATIONS.....	43
TABLE 9: DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS IN THE POOLED CONTROLLED STUDIES AND IN THE CERVICAL DYSTONIA, BENIGN ESSENTIAL BLEPHAROSPASM AND SPASTICITY STUDIES	44
TABLE 10: NT 201 EXPOSURE WITHIN BEB STUDY 0433/1 AND STUDY 0003.....	46
TABLE 11: NT 201 EXPOSURE IN BEB STUDY 0433/1 (MAIN PERIOD) AND 0/433/2 (OLEX) BY THE NUMBER OF INJECTIONS AND THE TIME THE PATIENT WAS MONITORED IN THE TRIAL	46
TABLE 12: CUMULATIVE NT 201 EXPOSURE FOR BEB AT 24 AND 48 WEEKS.....	48
TABLE 13: DEMOGRAPHICS OF THE BEB SAFETY POPULATION: POOLED AND BY STUDY	48
TABLE 14: NT 201 EXPOSURE WITHIN THE PHASE 3 CD STUDIES	49
TABLE 15: NT 201 DOSE IN STUDY 0410 MAIN AND OLEX PERIODS BY DOSE AND NUMBER OF INJECTIONS.....	50
TABLE 16: NT 201 EXPOSURE IN SP STUDIES 04010/1 (MAIN PERIOD) AND 0410/2 (OLEX) BY WEEKS OF OBSERVATION AND DOSE	51
TABLE 17: NT 201 EXPOSURE IN STUDY 0410/1 MAIN AND 0410/2 OLEX BY WEEKS OF OBSERVATION AND NUMBER OF INJECTIONS	51
TABLE 18: DEMOGRAPHICS OF PATIENTS IN THE NT 201 SP DEVELOPMENT PROGRAM	52
TABLE 19: SOC SAEs BY NT 201 DOSE GROUP	54
TABLE 20: COMMON AND VERY COMMON ADVERSE EVENTS IN NT 201-TREATED PATIENTS WITHIN PLACEBO- CONTROLLED STUDY 0433/1.....	57
TABLE 21: VERY COMMON (OCCURRING IN ≥ 10) AND COMMON ADVERSE EVENTS (OCCURRING IN $\geq 1\%$) WITHIN CD STUDY 0408 MAIN PERIOD	59
TABLE 22: OVERALL SUMMARY OF PATIENTS WITH ADVERSE EVENTS BY DOSE AND NUMBER OF INJECTIONS WITHIN THE CD PLACEBO-CONTROLLED CD TRIAL 0408/1.....	61
TABLE 23: COMMON ADVERSE EVENTS ($>1\%$) IN THE 410/1 MAIN PERIOD.....	62
TABLE 24: SAFETY ASSESSMENTS IN THE NT 201 BEB STUDIES	66
TABLE 25: SAFETY ASSESSMENTS IN THE NT 201 SP STUDIES	66
TABLE 26: SAFETY ASSESSMENTS IN THE NT 201 CD STUDIES.....	67
TABLE 27: SAEs IN THE NT 201 DEVELOPMENT PROGRAM – ALL STUDIES	75
TABLE 28: SAEs BY SOC WITHIN THE POOLED NT 201 DEVELOPMENT PROGRAM	75
TABLE 29: SUMMARY OF SAEs WITHIN THE 0433/2 OLEX PERIOD.....	77
TABLE 30: SAEs IN CD STUDY 0408/1 MAIN	80
TABLE 31: SAEs IN STUDY 0408/2 OLEX PERIOD.....	80
TABLE 32: SUMMARY OF SAEs IN OTHER STUDIES (STUDY 9801, STUDY 0013, THE MAIN PERIOD OF STUDY 0605/1, AND IN THE OLEX PERIOD OF ONGOING STUDY 0605/2) IN THE CD INDICATION.....	83
TABLE 33: SUMMARY OF SAEs IN STUDY 0410/1 MAIN PERIOD.....	86
TABLE 34: SP SAEs IN OLEX STUDY 0410/2	87
TABLE 35: ADVERSE EVENTS LEADING TO DISCONTINUATION IN THE POOLED NT 201 STUDIES	94
TABLE 36: CATEGORIZATION OF DISCONTINUATIONS WITHIN BEB STUDIES 0408/1, 9801 AND 0013	96
TABLE 37: CHANGE IN GLUCOSE FROM BASELINE TO FINAL STUDY VISIT IN THE PLACEBO-CONTROLLED PHASE OF STUDY0433 (BEB), STUDY 0408 (CD) AND STUDY 0410 (SP).....	106
TABLE 38: CHANGE IN ALKALINE PHOSPHATASE FROM BASELINE TO FINAL STUDY VISIT IN THE PLACEBO- CONTROLLED PHASE OF STUDY0433 (BEB), STUDY 0408 (CD) AND STUDY 0410 (SP)	110
TABLE 39: COMMON (≥ 1) AND VERY COMMON ($\geq 10\%$) ADVERSE EVENTS IN THE POOLED PLACEBO-CONTROLLED STUDIES WITHIN THE NT 201 DEVELOPMENT PROGRAM	114
TABLE 40: ADVERSE EVENTS IN THE POOLED IN THE BEB STUDIES, OVERALL AND BY POPULATION	117

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

TABLE 41: COMMON ADVERSE EVENTS (≥1) IN BEB STUDY 0433 MAIN AND EXTENSION PERIOD BY SOC)	117
TABLE 42: COMMON AND VERY COMMON ADVERSE EVENTS IN NT 201-TREATED PATIENTS WITHIN PLACEBO-CONTROLLED STUDY 0433/1	119
TABLE 43: PATIENTS WITH DRY MOUTH OR DYSPNEA WITHIN BEB STUDY 0433/1	121
TABLE 44: COMMON AND VERY COMMON ADVERSE EVENTS OCCURRING IN THE NT 201 TREATMENT GROUP IN STUDY 0408 MAIN PERIOD	123
TABLE 45: COMMON ADVERSE EVENTS IN SP STUDY 0410 MAIN AND OLEX PERIODS	125
TABLE 46: ADVERSE EVENTS WITHIN THE MAIN PORTION OF SP STUDY 0410/1 OCCURRING AT A FREQUENCY OF ≥2 PERCENT	127
TABLE 47: ADVERSE EVENTS IN SP OLEX STUDY 0410/2 OCCURRING IN MORE THAN 2% OF PATIENTS	130
TABLE 48: MEAN CHANGES IN BIOCHEMISTRY PARAMETERS IN THE POOLED, PLACEBO-CONTROLLED STUDIES WITHIN THE NT 201 DEVELOPMENT PROGRAM	132
TABLE 49: HEMATOLOGIC TESTING RESULTS AT SCREENING AND FINAL VISIT WITHIN BEB STUDY 0433/1 BY TREATMENT GROUP	138
TABLE 50: CHEMISTRY TESTING AT SCREENING AND FINAL VISIT IN BEB STUDY 0433/1 BY TREATMENT GROUP	139
TABLE 51: CRITERIA FOR CLASSIFYING VITAL SIGNS AS LOW, NORMAL AND HIGH WITHIN THE NT 201 DEVELOPMENT PROGRAM	144
TABLE 52: VITAL SIGNS BY TREATMENT GROUP AND VISIT WITHIN THE PLACEBO-CONTROLLED 0433/1	144
TABLE 53: VITAL SIGNS BY TREATMENT GROUP AND VISIT WITHIN THE PLACEBO-CONTROLLED 0408/1	146
TABLE 54: ECG PARAMETERS IN THE POOLED, CONTROLLED TRIALS IN THE NT 201 TREATMENT GROUP	149
TABLE 55: QTcF INTERVALS (VALUES AND CHANGES FROM BASELINE) OF SUBJECT S003 OF STUDY 0003 (BEB) ..	152
TABLE 56: COMPARISON OF AEs IN THE BEB AND CD INDICATIONS BY STUDY LOCATION (NORTH AMERICAN AND NON-NORTH AMERICAN)	159
TABLE 57: VERY COMMON AND COMMON ADVERSE EVENTS IN THE BEB DEVELOPMENT PROGRAM BY DOSE CATEGORIES	160
TABLE 58: COMMON ADVERSE EVENTS IN THE BEB INDICATION BY INJECTION NUMBER	162
TABLE 59: COMMON AND VERY COMMON ADVERSE EVENTS IN THE CD STUDY 0408/1 BY DOSE GROUP	163
TABLE 60: COMMON AEs IN STUDY 0408 MAIN AND EXTENSION PERIOD BY SOC AND NUMBER OF INJECTIONS...	164
TABLE 61: COMMON ADVERSE EVENTS BY INJECTION NUMBER IN CD	166
TABLE 62: COMMON ADVERSE EVENTS IN THE NT 201 SP STUDY, 0410/1 BY DOSE GROUP	167
TABLE 63: SAEs IN THE TOTAL POOLED INDICATIONS (INCLUDING NON-NEUROLOGIC INDICATIONS) FOR SOCs BY DISEASE SEVERITY	172
TABLE 64 COMMON AEs BY BOTULINUM-TOXIN PRE-TREATMENT STATUS IN THE SP INDICATION OF THE PROGRAM	175
TABLE 65: NUMBER OF PATIENTS WITH EXPOSURE TIME OF AT LEAST 6 MONTHS AND 1 YEAR RECEIVING AT LEAST 3 INJECTION CYCLES	200
TABLE 66: NUMBER OF PATIENTS WITH EXPOSURE TIME OF AT LEAST 6 MONTHS RECEIVING AT LEAST 2 OR 3 INJECTION CYCLES	201
TABLE 67. DURATION OF INJECTION INTERVALS BY NUMBER OF INJECTION SESSIONS (STUDY 0410, REPEATED DOSE DATA, ALL PATIENTS WITH AN EXPOSURE OF AT LEAST ONE YEAR AND RECEIVING 3 INJECTIONS AT LEAST 360 UNITS	201
ERROR! BOOKMARK NOT DEFINED.	

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin ®, NT 201 (Incobotulinumtoxin A)

1. RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

For the indications of Benign Essential Blepharospasm (BEB), Cervical Dystonia (CD) (b) (4) review of the safety data for NT 201 (Xeomin®) demonstrated an adverse event profile similar to other botulinum toxin products. Due to the small number of adverse events, a full analysis of effect modifiers and less common adverse events was not possible. However, the application allowed for an adequate safety review, and no safety concerns that would preclude approval were identified. Should NT 201 be found to be effective, I would recommend its approval and its addition to the other botulinum toxin products currently marketed in the United States.

1.2 Risk Benefit Assessment

The safety review of the BEB, CD (b) (4) indications of NT 201 did not reveal any significant unexpected safety signals compared to other botulinum toxin products currently approved in the United States. If NT 201 is judged to be efficacious, the risk-benefit profile is acceptable and similar to other members of the drug class.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The following standard REMS Elements were submitted by the sponsor¹:

1. **Medication Guide:** A Medication Guide will be dispensed with each vial of XEOMIN® in accordance with 21 CFR 208.24. Pursuant to 21 CFR 208.24, the Medication Guide will be available in sufficient numbers e.g, the Medication Guide will be provided with each single vial of XEOMIN®. The label of each container or package of XEOMIN will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided.
2. **Communication Plan:** MERZ will implement a communication plan consisting of a Dear Healthcare Professional (DHCP) Letter disseminated at the time of drug approval in the United States. The DHCP letter will be distributed to neurologists, physiatrists and other specialties and healthcare professional staff who prescribe or inject Xeomin® or other licensed botulinum toxin products (i.e., physical medical and rehabilitation specialists, dermatologists, ophthalmologists and other specialists who have previously dispensed botulinum toxins).

¹ The following paragraphs were adapted from the NT 201 Efficacy Review for BEB completed by Dr. Ken Bergman.

3. **REMS Assessments:** Merz will submit REMS Assessments to FDA at (b) (4) 3 years, and 7 years from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Merz will submit each assessment so that it will be received by the FDA on or before the due date.

Reviewer comment: This reviewer would recommend the following additions to product labeling and the Medication Guide:

1. Although the safety review did not identify any instances of systemic spread of NT 201 effect, this was also true in previously approved botulinum toxin products in which systemic spread of toxin effect cases occurred following product approval. Due to this and the fact that some clinicians will likely use doses higher than those used in the clinical trial, the NT 201 labeling should include the same Boxed Warning on systemic spread of toxin effect as other approved botulinum toxin products.
2. Because different formulations of botulinum toxin are not interchangeable, to avoid unintentional overdose the Division should consider some mechanism for alerting clinicians to this issue.

1.4 Recommendations for Postmarket Requirements and Commitments

The following postmarket requirements should be considered:

1. The sponsor should devise a plan to monitor for systemic spread when NT 201 is used in clinical practice. This should include literature searches, regular monitoring of the sponsor's postmarketing safety database and other options as applicable. Any case reports submitted to the sponsor resembling systemic spread should be forwarded to the Division in an expedited manner.
2. For the ongoing and future spasticity studies, the sponsor should be asked to utilize checklists of adverse events related to botulinum toxin to ascertain adverse events. Vital signs within the NT 201 development program were largely measured prior to treatment (see Section 7.4.3.1), and thereafter 12 weeks subsequent to NT 201 administration and at a time when NT 201's effect has waned. The sponsor should be asked to perform a study examining vital signs at specified time periods after NT 201 treatment (including the time of maximum clinical effect). These could be included as part of another PMR/PMC study, if possible.

2 Introduction and Regulatory Background

2.1 Product Information

NT 201 is a purified formulation of Botulinum neurotoxin type A which is stated by the sponsor to be free from complexing proteins. The registered trade name for NT 201 for neurological indications is Xeomin®.

NT 201 is synthesized as a single chain polypeptide with a molecular weight of approximately 150 kDa, made using an (b) (4) strain of the anaerobic bacterium *Clostridium botulinum*. The NT 201 neurotoxin is produced as part of a high molecular weight complex (approximately 900 kDa) consisting of NT 201 and (b) (4) complexing proteins. During the manufacturing process, the toxin is (b) (4) purification (b) (4). The active ingredient represents the pure neurotoxin type A, which the sponsor asserts should be considered a new drug substance (Clinical Summary, pg. 4).

Reviewer comment: As noted elsewhere in the review, I defer to the pharmacology reviewers to assess the sponsor's assertion that NT 201 is "free of complexing proteins."

2.2 Tables of Currently Available Treatments for Proposed Indications

The botulinum toxin preparations currently approved in the United States (US) are Botox®, Dysport® and Myobloc®. Botox is approved in the US for the treatment of CD, BEB, strabismus, hyperhidrosis, and glabellar lines. Myobloc® is approved in the United States for the treatment of CD and Dysport® is approved for cervical dystonia and glabellar frown lines (Clinical Summary, pg. 25). These products and indications are summarized in the table below.

Table 1: Botulinum Toxin Products Approved for use in the United States and their Indications

	Botox®	Myobloc®	Dysport®
Year of Approval in United States	1989	2000	2009
Generic Name	Onabotulinumtoxin A	Rimabotulinumtoxin B	Abobotulinumtoxin A
Indications	Cervical Dystonia Blepharospasm Strabismus Glabellar Frown Lines Primary Axillary Hyperhidrosis	Cervical Dystonia	Cervical Dystonia Glabellar Frown Lines

2.3 Availability of Proposed Active Ingredient in the United States

NT 201 has not been approved, and is not available, in the United States. Although other botulinum toxin products have been approved in the United States (specifically Botox®, Myobloc® and Dysport®), Merz notes that NT 201 differs from other botulinum toxin products in that it is a more purified form of the toxin. Botulinum toxin products have been approved in the US since Botox® was first approved in 1989.

NT 201 has been approved in a number of countries outside of the United States, and these are discussed in Section 8 of this review.

2.4 Important Safety Issues With Consideration to Related Drugs

During the pre-BLA, Merz and the FDA developed a list of Adverse Events of Special Interest (AESI). The list was based upon drug-specific adverse events that had been observed during the pre- and post-marketing period of other botulinum toxin products. The results of the examination of AESIs are discussed in Section 7.2.6 of this review.

The review of Botox®, Dysport®, and Myobloc® revealed several important safety issues specific to these drugs. Primary among these is the concern of systemic spread of toxin effect from the site of local injection. A review of post-marketing cases performed by the FDA's Office of Surveillance and Epidemiology in July 2008, identified cases of severe systemic spread of toxin effect. Subsequent analysis found cases of spread of toxin effect in unapproved uses and in approved indications at doses comparable to those used to treat cervical dystonia and at lower doses. A second AESI of interest with botulinum toxins is the development of blocking antibodies which may reduce efficacy with repeated administration. The immunogenicity of NT 201 is reviewed in Section 7.4.5.

In the Dysport® review for cervical dystonia, the safety reviewer² identified a number of common adverse events. The points below (ordered approximately by descending frequency) provide more detail on these events.

- **Muscular Weakness:** Muscular weakness was thought to result from excess of therapeutic effect involving the muscles of the neck, face and jaw. It was the most common event, reported in 18.2% of Dysport-treated subjects and 4.4% of placebo-treated subjects in double-blind studies (Odds Ratio 5.42, 95% CI 2.42-12.14, p<0.0005) and in 28.9% of all Dysport-treated subjects. A few of these events (1.9% of Dysport-treated double-blind subjects and 3.6% of all Dysport-treated subjects but no placebo treated subjects) reported muscle weakness remote from the injection site. Muscle weakness also appeared to be dose-dependent, occurring in 28% of subjects assigned to 1000 U and 11% and 12% of subjects assigned to 250 U and 500 U, respectively, in the fixed dose study.

² Clinical Safety Review BLA 125274 (Dysport®). Prepared by Dr. Marc Stone. Dated August 19, 2008.

- **Dysphagia:** This was the most common serious event in post-marketing reports for Dysport®, and severe dysphagia was also one of the most common serious events reported in clinical studies. Dysphagia may have been involved in the development of pneumonia and a death. Dysphagia was reported in 17.4% of Dysport®-treated subjects and 3.8% of placebo-treated subjects in double-blind studies (Odds Ratio 5.29, 95% CI 2.29-12.18, p<0.0005) with increasing incidence by dosage in the fixed dose study. Dysphagia was reported by 29.1% of all Dysport-treated subjects in the principal cervical dystonia studies.
- **Dyspnea:** Dyspnea was reported in 5.0% of all Dysport®-treated subjects and respiratory complaints were a common serious complaint among Dysport® post-marketing reports (8.7% of serious adverse reactions involved dyspnea). This event was attributed to a weakening of accessory muscles of respiration in the neck following injections for cervical dystonia, perhaps in conjunction with pre-existing lung disease.
- **Blood Glucose Increased:** Due to limited laboratory testing in the Dysport® development program, elevated blood glucose levels was recognized in only a few patients. Despite the small number of patients, Dysport® was assessed as having a small effect on glucose metabolism for which the impact on patients with diabetes is unknown. The following statement was included in labeling, monitoring for elevated glucose in the post-marketing period was recommended.

“Subjects treated with DYSPORT® exhibited a small increase from baseline (0.23 mol/L) in mean blood glucose relative to placebo-treated subjects. This was not clinically significant among subjects in the development program but could be a factor in patients whose diabetes is difficult to control.”

Injection site adverse events as well as fatigue and flu-like syndromes were relatively common complaints in the Dysport® development program, although Dr. Stone noted that these were relatively evenly distributed among Dysport® and placebo-treated patients.

Reviewer comment: *The adverse events listed were examined closely in the sections of this review addressing adverse events with NT 201.*

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The sponsor submitted NT 201 IND 12,821 for the treatment of cervical dystonia in December 2005, for the treatment of blepharospasm in May 2006 (b) (4).

The DNP met with the sponsor during the pre-submission period to provide feedback and recommendations on safety assessments, the primary of which are summarized below:

1. Pre-Phase 3 Meeting: September 14, 2004

(b) (4)

3. Facility Review Meeting: March 19, 2007: Merz submitted an information package that detailed the intended design and general operational procedures for a new parenterals facility to be constructed by Merz in Dessau, Germany.
4. Type C Meeting for Cervical Dystonia and Blepharospasm: June 11, 2007
5. Type B Pre-BLA December 12, 2008: Discussion of the administrative, quality, preclinical and clinical questions related to the BLA for the proposed indications cervical dystonia (b) (4)

Notable safety-related issues discussed during the pre-BLA period for NT 201 are summarized below:

- Due to a small elevation in blood glucose in drug- versus placebo-treated patients within the Dysport® development program, the FDA requested that the sponsor perform expanded analyses of blood glucose.
- The FDA and the sponsor developed a list of Adverse Events of Special Interest (AESIs) based on adverse events observed with previously developed botulinum toxin products, and these were the focus of additional analyses. These particularly included AEs associated with systemic spread such as dysphagia, speech problems, facial weakness, general body weakness and dyspnea or other respiratory problems.
- (b) (4) the FDA recommended that the long term safety data which is up to 1 year of exposure must cover a full dose range for each indication (up to 400 units per treatment). Merz agreed to delay filing in order to include data from 60 patients exposed for 1 year at 400 units, 30 patients exposed for 1 year at 300 to 400 units and 30 patients exposed for one year at 200 to 300 units. In addition, 85 patients with cervical dystonia will have been treated for one year at 240 units. It was also agreed upon that the pooling of datasets should be for each indication and all across all indications and to include a subgroup analyses by dose, indication and duration of exposure.
- The sponsor had proposed recruiting patients who had previously responded to Botox® for the pivotal and supporting trials. The FDA responded that “Reliance on a select responder population generally does not adequately support a claim of safety and efficacy in a more heterogeneous clinical population of patients.”
- The Division noted the sponsor’s concern regarding limiting the placebo period in order to minimize subject dropouts and allow for early re-injection of patients. The DNP concurred that an extensive placebo period may be problematic for patients. “However, it is highly desirable to develop adequate placebo- controlled safety data for NT-201 (which

is not available from the previous clinical investigations) and to measure the NT-201 duration of effect...For these reasons, the Agency strongly recommends extending the placebo period (b) (4) in the second study synopsis, preferably on the order of 6-8 weeks.”

(b) (4)

The FDA further recommended that Merz discuss their antibody assay with our Office of Biological Products for their input on the best assay method.

- Specific ECG cardiac and pulmonary evaluations were not considered to be required unless particular concerns arose. However, the FDA emphasized that be specific and frequent evaluation for adverse events related to collateral spread of NT201 in these and other areas of adjacent muscles:, and so forth.
- Adverse events were to be followed until they stabilize or resolve, and were to be elicited for up to 4 weeks following the last injection.
- The FDA emphasized the need to conduct pre and post natal development studies and Sponsor should provide written justification if they are unable to provide these studies.

The IND for study of blepharospasm (as well as cervical dystonia) had been put on clinical hold because of a deficit in the non-clinical information needed to support the human clinical trials. This information was submitted and discussed with the Division and the clinical hold ended in June 2006. At the time the hold was lifted, the DNP also requested that methods to elicit AEs among study sites be standardized.

(b) (4)

After the BEB and CD indications were filed, FDA reviewers noted CMC issues that were not adequately addressed by the sponsor. These resulted in a delayed submission of these requirements, which extended the review clock to July 31, 2010.

2.6 Other Relevant Background Information

The DNP's review of Dysport®, approved in 2009, is referenced for comparison in various sections of the review.

For the purpose of the safety review, it is notable that different formulations of botulinum toxin are not interchangeable with respect to dosing.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

3.1.1 Quality

Although the quality and organization of the NT 201 BLA documents was generally compliant with eCTD guidelines and allowed for an adequate safety assessment, the application was lacking in several areas. These included:

1. Information regarding exposure was poorly presented to the point that multiple requests for clarification were required in order to determine whether pre-specified exposure criteria had been met.
2. Some documents, including study reports, were scanned and not able to be searched electronically. Searchable versions of these documents were requested and the sponsor provided these.
3. Datasets that were difficult to utilize and lacking in basic components. The primary reviewers provided the sponsor with guidance on how these datasets should be structured, and the sponsor was generally compliant with these instructions.

The sponsor's proposed labeling was also inadequate, and is discussed further in Section 9.2 of this review.

3.1.2 Integrity

Two domestic sites were inspected by the FDA's Division of Scientific Investigation on the basis of having enrolled the largest number of patients.³

1. Alberto Vasequez, MD of Suncoast Neurological Associates, Inc. in St. Petersburg, FL was inspected as he had a high number of enrollments. DSI found that informed consents were obtained from all subjects prior to screening and entry into the study. DSI report "found no evidence of under reporting of adverse events" in this site.
2. Paul Cullis, MD of St. John's Hospital Medical Center, Detroit, MI was another site inspected because of the high number of enrollments. The inspection covered 100% review of informed consent forms for the total 15 subjects screened at that site and the medical records were reviewed in depth. There were no deaths and one SAE was reported. The DSI investigation "found no evidence of under reporting of adverse events."

These two sites were chosen by the Quality Assurance GCP contracted by the Sponsor and were given Clinical Investigator Audit Certificates. The choice of audit sites and results of the internal audits conducted by the company was similar to those of the DSI reports.

3.2 Compliance with Good Clinical Practices

The sponsor attested that all of the clinical trials were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice [GCP] and the applicable regulatory requirements. This is in compliance with 21 CFR 312 Parts 50 and 56, and ICH E6. Merz asserted that the NT 201 development program adhered to national and international ethical principles for protection of human subjects in clinical research trials.⁴

***Reviewer comment:** During the course of the safety review, this reviewer checked coding, source tables in study reports and case report forms, and did not find any instances in which Good Clinical Practices were violated.*

3.3 Financial Disclosures

BEB Indication: In the BEB indication, Merz provided the required information regarding financial disclosure for the confirmatory blepharospasm trial MRZ 6020 –0433. Form FDA 3455

³ Text in this section adapted from Dr. Anne Constantino's review of the efficacy of cervical dystonia in the NT 201 development program.

⁴ Information in this paragraph adapted from the FDA's Review of Clinical Efficacy for the NT 201 Development Program, prepared by Dr. Ken Bergman.

was reviewed for the investigators from 33 sites (31 of which enrolled patients). Three investigators received payments above the threshold for reporting at sites (b) (4) for duties related to the execution of the trial (administrative and training). These sites enrolled (b) (4) patient(s) respectively. Site (b) (4) was also chosen for inspection by the Office of (4) Compliance, Division of Scientific Investigations and was found to be in compliance with GCP. Merz cited the measures taken to avoid the potential for bias at the affected clinical sites. The numbers of subjects at these sites are insufficient to alter the outcome of the trial.⁵

CD Indication: In the CD indication, the FDA further reviewed financial disclosures for three Principal Investigators in Studies 408/1 and 408/2 studies⁶. Financial disclosures were obtained from all the site investigators in the study done in the United States, and reviewed by Dr. Anne Constantino who did not identify any conflicts of interest noted. The three highest paid Principal Investigators enrolled a total of (b) (4) patients with (b) (4) patients receiving NT 201. This small number of patients was not sufficient to influence either the efficacy or safety results.

(b) (4)

4 Significant Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

NT 201 is supplied as a lyophilized powder for reconstitution for injection, packed (b) (4) in glass vials. NT 201 is administered as an intramuscular injection (Clinical Overview, pg. 13).

4.2 Clinical Microbiology

Merz stated that no microbial growth was observed in NT 201 vials challenged with 50 cfu of eight different test organisms derived from human skins. During a 72-hour stability test on sterility and endotoxins of microbial parameters of reconstituted NT 201 vials, the drug product was unaffected over a three day period at 2-8°C.

4.3 Preclinical Pharmacology/Toxicology

Merz explained that the active ingredient in NT 201 is (b) (4), biotechnologically derived from C. botulinum and purified (b) (4). The sponsor used (b) (4) in a number of animal toxicity studies.

⁵ Information in this paragraph adapted from the FDA's Review of Clinical Efficacy for the NT 201 Development Program, prepared by Dr. Ken Bergman.

⁶ This paragraph adapted from the CD Clinical Review by Dr. Anne Constantino.

Other safety-related aspects of the preclinical pharmacology within the NT 201 development program were:

- A study in mice (Carli et al.)⁷ compared Xeomin® with two other botulinum toxins (Dysport® and Botox®) with regard to diffusion from the injection site. The authors concluded that “the three formulations exhibit a very moderate diffusion in nearby muscles from the injection site and only Dysport® shows a slightly wider mobility than Botox® and Xeomin®.
- Systemic distribution of NT 201 is similar to that of Botox and Dysport based on their effects in single dose comparative intravenous toxicity study in mice (Leuschner 1998).
- NT 201 pharmacodynamics (PD) and pharmacokinetics (PK) are comparable to Botox based on time course of onset, degree of paralysis and systemic body weight loss induced by intramuscular hindlimb injections in mice (Leuschner 1999).
- In four nonclinical pharmacokinetics studies conducted in mice, oral LD 50 was estimated to be about 100,000 LDU/animal, intravenous LD 50 for (b) (4) was estimated to be 50 LDU/kg and intraperitoneal LD 50 is 50 LDU/kg. Oral bioavailability of (b) (4) is 1:100000 or 0.001%.
- The sponsor conducted preclinical hERG channel testing, and found no effect of NT 201 at a concentration of 10,000 LDU/m (in vitro) or on ECGs (in monkeys). The hERG channel studies are discussed in more detail in Section 7.4.4 of this review.

Merz also conducted preclinical studies to examine NT 201 diffusion from the injection site. The studies found that diffusion could be up to 5 cm in a rabbit.⁸ EMGs detected electrophysiological changes in the extensor digitorum brevis (EDB) muscle in the foot of subjects who received BoNT injection in the head/neck region (Garner et al: *Mov Dis* 8(1) 33-37, 1993).

Reviewer comment: Please see Section 7.2.3 of this review (*Special Animal and In Vitro Testing*) for a summary of additional preclinical studies.

In her review, Dr. Anne Constantino raised the following concerns regarding preclinical pharmacology and toxicology testing:

“The sponsor has done multiple single dose toxicology studies with NT 201 on different species. In the 2 intramuscular studies that were done, the LD 50 was not determined. This would have been important because it would mimic the administration of the toxin in humans. No specific animal studies were designed to evaluate the presence of toxin spread. With the other toxins reporting the presence of adverse events from toxin spread, the Sponsor should have looked further into causes of toxin spread. There were studies done on mice that had documented results on (b) (4) and implied results into the effects of NT 201. There has

⁷ Carli L et al. An histological of diffusion of different botulinum neurotoxin type A injection in mice leg. Presented at Toxincon 2008, Volume 51, Supplement 1.

⁸ Borodic, et al: *Head and Neck* 12: 392-398, 1990

been no data provided on how (b) (4) compares with NT 201 although the Sponsor mentions that NT 201 is the active pharmaceutical ingredient in (b) (4).”

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Botulinum toxin type A blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine stored in vesicles within the nerve terminal. This results in neuromuscular paralysis which is manifested as persistent (but not permanent) muscle relaxation. This pharmacological effect is responsible for the therapeutic effect of NT 201 in CD, BEB, and (b) (4). In CD, this local muscle relaxation is manifested as decreased abnormal movement of the head and neck. In BEB, the muscle relaxation is revealed as decreased frequency and forcefulness of eyelid closure. (b) (4) Merz stated that impulse transmission is re-established by the formation of new nerve terminals and motor endplates, or by recovery of the previous ones (Clinical Overview, pg. 4, 13).

The mechanism of action for NT 201 is illustrated in the following figure:

Figure 1: Botulinum Toxin’s Mechanism of Action
(Adapted from FDA Figure 2, Clinical Review prepared by Dr. Ken Bergman, pg. 23)

Figure 1: BoNT Mechanism of Action

Copyright Material



4.4.2 Pharmacodynamics

Merz characterized native Botulinum toxin type A as a high molecular weight complex, which, in addition to the neurotoxin (150 kDa), as well as other proteins such as hemagglutinins and non-hemagglutinins (Clinical Overview, pg. 14). The sponsor has asserted that NT 201 is “free of other complexing proteins.”

Reviewer comment: *I defer to the FDA's pharmacology reviewers to evaluate the validity of the sponsor's statement that NT 201 is "free from complexing proteins."*

In single dose toxicology studies in mice, the LD₅₀ for oral NT 201 was "10,000-fold greater than by the intravenous route,"

Merz stated that Botulinum toxin type A undergoes retrograde axonal transport after intramuscular injection. However, the sponsor stated that "transsynaptic passage of active Botulinum toxin type A into the central nervous system has not been found after intramuscular injection (Clinical Overview, pg. 14)."

Merz stated that receptor-bound Botulinum toxin type A is endocytosed into the nerve terminal prior to reaching its target protein (SNAP 25) and is eventually degraded intracellularly. Free circulating Botulinum toxin type A molecules that have not bound to pre-synaptic cholinergic nerve terminal receptors will be phagocytosed/pinocytosed and degraded like any other free circulating protein. The sponsor noted that in human patients, recovery from paralysis after intramuscular injection normally occurs within three to four months as nerve terminals sprout and reconnect with the muscle endplate (Clinical Overview, pg. 14).

Three Phase 1 pharmacodynamics studies were performed by the sponsor in healthy subjects. Based on these studies, the time course and degree of paralysis between NT 201 and BOTOX® were similar. Dysport® was reported to have shown a significantly greater area of diffusion than NT 201. There were no studies done to compare systemic spread of toxin effects and there was a paucity of reports of adverse events in the NDA submission for Xeomin⁹.

4.4.3 Pharmacokinetics

4.4.3.1. Distribution

The high chemical specificity and extreme potency of Botulinum neurotoxin limits PK profile studies in humans. Animal studies suggest that the radiolabeled neurotoxin complex remains at the intramuscular injection site (DasGupta, et al. 1994). Extent of diffusion is dependent on local anatomy, volume injected and dose. In animal studies, diffusion distance can be up to 5 cm (Borodic, et al. 1990). Systemic effects are inevitable after intramuscular injection because of penetration into the circulation as demonstrated by subclinical electromyographic changes (jitter) in muscles distant from the site of injection (Garner et al 1993)¹⁰.

⁹ This paragraph adapted from the CD Clinical Review by Dr. Anne Constantino.

¹⁰ Information in the Pharmacokinetics section of this review were adapted from the FDA's Review of Clinical Efficacy for the NT 201 Development Program, prepared by Dr. Ken Bergman.

4.4.3.2. Absorption

After oral ingestion, the botulinum neurotoxin is absorbed in the gastrointestinal tract and taken up by cholinergic terminals, thus the toxicologic effects seen after ingestion. Gastrointestinal tract absorption is dependent on the presence of bound non-toxin proteins and hemagglutinins that appear to protect the neurotoxin from proteolytic degradation in the gastrointestinal tract (Fujinaga et al 1997).

Reviewer comment: Although the sponsor repeatedly describes NT 201 as "free of complexing proteins," the sponsor notes that native botulinum toxin contains "hemagglutinins and non-hemagglutinins" (Clinical Overview, pg. 14).

4.4.3.3. Metabolism

After systemic absorption (in other words, toxin that was not bound at the site of intramuscular injection), the neurotoxin is rapidly metabolized to smaller molecular structures. White blood cells play a role in the disposal of circulating toxin type A as shown for other proteins. The neurotoxin is then degraded intracellularly. Like all proteins, Botulinum toxin type A is rapidly metabolized by proteases and molecular components are recycled through normal metabolic pathways.

4.4.3.4. Drug interactions

Both bioavailability and storage ability of BoNT/A are affected by accompanying complex proteins (Schantz and Johnson 1994). Exogenous albumin is typically added to (b) (4) the BoNT/A (b) (4). Pharmacokinetic interactions between proteins and NT 201 after intramuscular injections are not expected.

Reviewer comment: The ability to diffuse up to 5 cm (depending on the volume injected) could explain the occurrence of dysphagia in both the BEB and CD indications.

The sponsor stated that classic kinetic and distribution studies could not be conducted with Botulinum toxin type A because the active substance is applied in such small quantities (picograms per injection), and binds so rapidly and irreversibly to cholinergic nerve terminals that no circulating NT 201 can be detected (Clinical Overview, pg. 14).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The table of studies below is divided by indication.

5.1.1 Tables of Studies: BEB

Studies in the NT 201 development program which contributed data to the safety analysis for the BEB indication are summarized in the table below.

Table 2: Safety Studies for Benign Essential Blepharospasm

(Adapted from Sponsor Table 2.5.2, Clinical Overview, pg. 8)

BENIGN ESSENTIAL BLEPHAROSPAM				
PHASE 2				
Study Name	Treatment Groups	Study Description	Dosing/ Length of Study	Purpose/ Location
0703	NT 201: 8	Phase 2, Open-label, Single-arm Trial	Up to 100 U IM (up to 50 U per eye) for up to 8 injections within 70 weeks	Discontinued “due to slow enrollment”
PHASE 3				
Study Name	Treatment Groups	Study Description	Dosing/ Length of Study	Purpose/ Location
0433/1 Main Period	NT 201: 74 Placebo: 34	Phase 3, prospective, double-blind, randomized, placebo-controlled, multicenter study	One IM injection (up to 50 U per eye) with follow-up for up to 20 weeks.	Efficacy and safety of NT 201 compared with placebo in pre-treated subjects with BEB Location: North America
0433/2 OLEX Period	NT 201: 102	Open-label, Extension Study	Up to 5 IM injections (up to 50 U per eye) at least 6 weeks apart over 48 weeks, with 20 weeks of follow-up	Assessed longer term safety and efficacy Location: North America

0003	NT 201: 148 Botox: 152	Phase 3, double-blind, randomized, active-controlled, multicenter, non-inferiority study comparing NT 201 and Botox®	One IM injection (≤ 35 U per eye NT 201 ≤ 35 U per eye BOTOX®) at baseline with follow-up for up to 16 weeks	Subjects with BEB, successfully pretreated with Botox on a stable dose Location: Multiple European countries and Israel

See Section 5.3 of this review for text summaries of the Phase 3 BEB studies listed in the table above.

5.1.2 Table of Studies: CD

Studies in the NT 201 development program which contributed data to the safety analysis for the CD indication are summarized in the table below.

Table 3: NT 201 Safety Studies for Cervical Dystonia

(Adapted from Sponsor Table 2.5.1, Clinical Overview, pg. 6)

CERVICAL DYSTONIA				
PHASE 2				
Study Name	Treatment Groups	Study Description/ Location	Dosing/ Length of Study	Site of Administration
9801	NT 201 10/20: 14 NT 201 20/40: 13 NT 201 30/60: 14 BOTOX 30/60: 12	Open-Label, Randomized, Active-Controlled Trial in Location: Germany	Single dose with 14 days follow-up, re-injection with 106 days of follow-up Dose range: 10 to 60 U	Splenius capitis (SPL); sternocleidomastoid (SCM)
PHASE 3				
Study Name	Treatment Groups	Study Description	Dosing/ Length of Study	Site of Administration

0408/1 Main Period	NT 201 120 U: 78 NT 201 240 U: 81 Placebo: 74	Phase 3 Double-Blind, Randomized, Placebo- Controlled, Parallel-Group Trial Location: United States	Single dose with 8 to 20 weeks of follow-up Dose range: 120 or 240 U	Splenius capitis/semispinalis; trapezius; sternocleidomastoid; levator scapulae; scalene; other spinal/semispinal muscles; suboccipital triangle; platysma/other
0408/2 Extension Period	NT 201: 217	Phase 3 Open-Label Extension Study Location: United States	Up to 5 injections at least 6 weeks apart over 48 weeks, with 20 weeks of follow- up Dose range: 120 or 240 U	Splenius capitis/semispinalis; trapezius; sternocleidomastoid; levator scapulae; scalene; other spinal/semispinal muscles; suboccipital triangle; platysma/other
0013	NT 201: 231 BOTOX: 232	Phase 3 Double-Blind, Randomized, Active-Controlled Trial Location: Europe and Israel	Single dose with up to 16 weeks follow-up Dose range: 70 to 300 U IM	Splenius capitis/semispinalis; trapezius; levator scapulae; sternocleidomastoid; scalenus; other muscles in the neck region
0605/1 Main Period	NT 201: 76	Phase "4" Main Period: Open- label, Single-arm Trial Location: Germany	Main Period: 1 injection with 4 weeks of follow- up Dose range: Up to 300 U	Sternocleidomastoid; levator scapulae; scalenus; splenius capitis; trapezius
0605/2 OLEX Period	NT 201: 76	Ongoing Extension: Study Location:	OLEX Period: Up to 5 additional injections over up to 121 weeks Dose range:	Sternocleidomastoid; levator scapulae; scalenus; splenius capitis; trapezius

		Germany	Up to 300 U	

Reviewer comment: The sponsor refers to Study 0605/1 Main and OLEX periods as Phase 4 studies, presumably due to marketing in Europe.

See Section 5.3 of this review for text summaries of the Phase 3 CD studies listed in the table above.

5.1.3 Table of Studies: SP

Studies in the NT 201 development program which contributed data to the safety analysis for the SP indication are summarized in the table below.

Table 4: NT 201 Safety Studies for Spasticity

(Adapted from Sponsor Table 2.5.4, Clinical Overview, pg. 11)

SPASTICITY				
PHASE 2				
Study Name	Treatment Groups/ Location	Study Description	Dosing/ Length of Study	Site of Administration
(b) (4)	NT 201: 8 Placebo: 6 Location: Germany	Phase 2 Double-blind, Randomized, Placebo -controlled Pilot Trial. Discontinued	Single injection with 84 day follow-up Dose Range: Up to 400 U IM	Upper limb
(b) (4)	NT 201: 6 Placebo: 4 Location: Germany	Phase 2, placebo-controlled pilot Trial. Discontinued.	Up to 4 injection cycles in 48 weeks Dose Range: Up to 300 U IM	Wrist and elbow flexors
PHASE 3				
Study Name	Treatment Groups	Study Description	Dosing	Site of Administration
0607	NT 201 20 U/mL: 97 NT 201 50 U/mL: 95 Location: Europe	Phase 3, Observer-Blind, Randomized, Active-controlled, Parallel-group Trial	Single dose with 12 to 20 weeks follow-up Dose Range: Up to 400 U, at either 20 U/mL	Upper limb

			or 50 U/mL	
0410/1 Main	NT 201: 73 Placebo: 75 Location: Poland, Hungary Czech. Rep.	Phase 3 Double-Blind, Randomized, Placebo- Controlled, Parallel-Group Trial	Single dose with 12 to 20 weeks of follow-up Dose Range: Up to 400 U	Upper limb
0410/2 OLEX	NT 201: 145 Location: Poland, Hungary, Czech. Rep.	Phase 3 Open-label, Single- arm Extension Period Completed	Up to 5 injs. at least 12 weeks apart over up to 48 weeks, with up to 21 weeks of follow-up Dose Range: 170 to 400 U IM	Upper limb

Reviewer comment: The sponsor stated that Phase 2 Study (b) (4) and (b) (4) was discontinued due to “slow recruitment.” See Section 5.3 of this review for text summaries of the Phase 3 SP studies listed in the table above.

5.2 Review Strategy

This review addresses three indications for NT 201: blepharospasm (BEB), cervical dystonia (CD) and spasticity (SP). Due to variation in administration (both for dose and site) and significant differences in the patient populations, the safety data in this review is generally subdivided by indication within each section. However, due to the relatively small number of adverse events, even among common adverse events, in most sections another sub-section analyzing the pooled data is included as well. The limitations of combining such diverse populations should be kept in mind when examining these pooled data sub-sections. For the indication specific sections, the review is generally further divided into sub-sections addressing the placebo-controlled data and the open-label data.

This review will follow FDA-recommended guidelines for the safety review, with a particular focus on deaths and SAEs (Sections 7.3.1 and 7.3.2). Adverse events of special interest (AESIs) due to their occurrence with other forms of botulinum toxin, especially spread of toxin effect, are closely examined (See Section 7.3.2 and 7.4.1 for examination of adverse events which contained any symptom of spread of toxin). Other FDA-recommended aspects of the safety review included in this document are:

1. Evaluation of dose-response relationships with AEs (Section 7.5.2),
2. Examination of potential effect modifiers such as age or gender (Section 7.5.3)
3. An audit of the appropriateness of AE coding (Section 7.1)

The data within the 120 Day Safety Update were incorporated in this review, and material from the 120 Day Safety Update is referenced as such.

5.3 Discussion of Individual Studies/Clinical Trials

Reviewer comment: *Due to the large number of Phase 1 and 2 studies within the three combined indications, only Phase 3 studies are summarized below. I searched all the Phase 1 and 2 studies for SAEs, and found no notable results.*

5.3.1 Summary of Studies: BEB

The pivotal studies in the BEB development program are summarized below:

1. **Study MRZ 60201-0433/1 (Main Period) and 60201-0433/2 (OLEX):** *Prospective, double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of Blepharospasm (ISS, Section 2.7.6)*

Study 0433/1 and 0433/2 were conducted in 34 study centers in the United States and Canada. This study actively recruited patients previously treated with Botox® (as did Study 003). In the Main period of the study (0433/1), a single injection of up to 50 U of NT 201 was given (dose determined by investigator assessment). Patients were followed for 6 to 20 weeks post-treatment, depending on duration of treatment effect. If a new injection was required, the patient was transitioned to the OLEX period of the study. In the OLEX period, the patient could receive up to 5 injection sessions, with the dosing based upon the patient's stable response to the last two BOTOX® treatment sessions prior to entry into the trial. The dose was approximate due to the lack of interchangeability of botulinum toxin products, and difficulties in calculating the corresponding NT 201 dose. The doses and periorbital injection locations then approximated the patient's prior treatment with BOTOX®. In the open extension trial (0433/2) the patient continued the same regimen from the main period of the study.

2. **Study MRZ 60201-0003:** *Safety and efficacy of NT 201 compared to Botox (purified Botulinum Neurotoxin A-complex) in blepharospasm (ISS, Section 2.7.6)*

The sponsor stated that Study 60201-0003 was conducted to “assess the safety of NT 201 compared to Botox in patients with blepharospasm.” This was a prospective, randomized, double-blind, parallel group, active-controlled, multicenter, multinational study. Recruitment criteria for patients included a diagnosis of BEB and at least two prior treatments with Botox®. A total of 303 patients from 41 centers in Europe and Israel were enrolled. At baseline (day 0), patients received an intramuscular injection of NT 201 or Botox with a maximum dose of 35 units per eye. Patients were monitored for up to 16 weeks following the injection. A control visit took place three weeks after baseline (day 21±1 day) and a final visit between days 109 and 112, or before, at the patient's

request. Optional intermediate visits were carried out only at the request of the patients (ISS Section 2.7.6).

5.3.2 Summary of Studies: CD

1. **Study MRZ 60201-0408/1 (Main Period) 60201-0408/2 (OLEX):** *Prospective, double-blind, placebo-controlled, randomized, multi-center trial with a double-blind parallel-group extension period to investigate the efficacy and safety of different doses of NT 201 in the treatment of cervical dystonia (ISS, Section 2.7.6).*

This Phase 3, double-blind, placebo-controlled study was conducted in 37 study centers in the United States in a total of 233 patients with CD. The study enrolled patients aged 18 to 75 years with a clinical diagnosis of cervical dystonia and a Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS]-Total score >20, TWSTRS-Severity score >10, TWSTRS-Disability score >3, and a TWSTRS-Pain score >1. The study recruited patients with or without a history of treatment with Botox®.

Patients were randomized (1:1:1) to either 120 U NT 201 (N=78), 240 U NT 201 (N=78) or placebo (N=74). In the Main Period of CD Study of 0408 (0408/1) a single injection was given followed by 8 to 20 weeks post-treatment phase, depending on duration of treatment effect. If a new injection was required, the patients were transitioned into the Extension Period (0408/2) for up to 5 injection sessions; dosing interval depending on duration of treatment effect, but not shorter than 6 weeks and with the last injection not later than 48 weeks after start of EP.

In the 0408/2 OLEX period of the study, patients continuing from 0408/1 received up to 5 injections at least 6 weeks apart over 48 weeks, with 20 weeks of follow-up. The doses in the study were 120 U and 240 U.

In the placebo-controlled period, 4.9% of the 240 U patients had SAEs, compared to no SAEs in the 120 U and placebo groups. Total common adverse events were experienced by 55 % of patients receiving 240U, 55% of patients receiving 120U and 41% of patients receiving placebo. The most frequent AEs which exceeded placebo were dysphagia (11.6%), neck pain (8.6%), muscular weakness (6.4%), and injection site pain (6.4%).

Reviewer comment: *See Section of this review for further discussion of the common adverse events with the CD trials. As noted within that section, although overall common AE risk is similar between the dose groups, the risk in the AEs which are most likely to be drug-related (based on past botulinum toxin studies difference from placebo) do show a dose-response pattern.*

2. **Study MRZ 60201-0013 :** *Safety and efficacy of NT 201 (highly purified Botulinum Neurotoxin A) compared to BOTOX® (purified Botulinum Neurotoxin A-complex) in cervical dystonia (ISS, Section 2.7.6)*

Study 60201-0013 was a double-blind, parallel-group study comparing the safety and efficacy of NT 201 to Botox®. It was conducted at sites in 11 countries: Austria, Belgium, Czech Rep, France, Germany, Hungary, Israel, Poland, Russia, Slovakia, and Sweden. Inclusion criteria for patient recruitment were diagnosis of cervical dystonia (and a sufficient score on the TWSTRS testing), last Botox® at least 10 weeks prior, aged 18 to <75 and on a stable dose of any other drugs to treat dystonia for three months prior to enrollment. The NT 201 dose in the study was 70-300 Units and patient follow-up was for a maximum of 16 weeks.

Overall, 110 adverse events occurred in 65/231 (28.1%) patients in the NT 201 group as compared to 87 adverse events in 56/232 (24.1%) pts. in the Botox® group. SAEs were observed in 4/231 (1.7%) patients treated with NT 201 (cerebral concussion, vertigo, hematoma, ovarian tumor, worsening of eczema, metrorrhagia) and in 5/232 (2.2%) patients treated with Botox. The most common AE was dysphagia (10.8% in the NT 201 group and 8.2% in the Botox® group)(Study 0013 Final Report, pg.).

3. **Study MRZ 60201-0605/1 and 0605/2:** Prospective, single-arm, multicenter study to investigate the efficacy and safety of NT 201 (Botulinum neurotoxin type A free of complexing proteins) and the duration of treatment effect after one injection session and in long-term treatment in subjects with cervical dystonia.

The main period of the study enrolled adults 18 to 76 years of age with CD of the predominantly rotational form (i.e., spasmodic torticollis). Botulinum toxin pre-treated and treatment-naïve subjects were eligible for the study. Pre-treated subjects must have had a stable response to the two most recent Botulinum toxin injections, with a maximum dose of 300 U Botox or 1200 U Dysport per injection, and must not have received an injection within 10 weeks of study Baseline. All subjects were required to have minimum scores on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

For the OLEX period, patients who completed the Main Period of the study, had their last treatment with Botulinum toxin ≥ 10 weeks ago, and (for women only) were not pregnant and were using highly effective methods of birth control, were eligible for participation in the OLEX Period.

Treatment in the main period of the study consisted of a single intramuscular (IM) administration of 50 to 300 U of NT 201. The number and sites of the injections were to be determined by the Investigator. A control visit for assessment of the primary efficacy variable took place four weeks following injection. In the main part of the study, subjects were followed for up to a total of four weeks.

During the OLEX period, patients received up to four additional injections of up to 200 U of NT 201 (in exceptional cases up to 300 U), depending on their need for a new injection. The date of the injection sessions, as well as the number and sites the muscles

to be injected, were determined by the Investigator. Injections were required to be at least 10 weeks apart. The follow-up period for the Main and OLEX Periods together was up to 121 weeks.

The most frequently observed TEAEs were dysphagia (9.2%), nasopharyngitis (6.6%), neck pain (5.3%), and headache (3.9%). Two patients experienced SAEs. TEAEs of special interest were observed in 7 subjects, and included dysphagia (7 subjects) and dry mouth (1 subject) (120 Day Safety Update, Appendix Group, pg.4).

5.3.3 Summary of Studies: SP

1. Study MRZ 60201-0410/1: *Safety and efficacy of NT 201 compared to Placebo in Post Stroke Spasticity of the Upper Limb (ISS, Section 2.7.6).*

Study 0410/1 was a prospective, double-blind, placebo-controlled, randomized, multi-center trial to assess the safety and efficacy of NT 201 compared with placebo in the treatment of post-stroke spasticity of the upper limb. It was conducted in the Czech Republic, Poland and Hungary. Naïve and pre-treated patients with post-stroke spasticity of the upper limb were recruited. For the patients with prior botulinum toxin treatment, the sponsor set the following criteria:

- The most recent injection with Botulinum Toxin must have been maximal 50 Units BOTOX® or 200 Units Dysport® or 2000 Units Neurobloc® (type B preparation) per each of these flexors: carpi ulnaris, digitorum superficialis, digitorum profundus.
- The most recent injection with Botulinum Toxin must have been maximal 60 Units BOTOX® or 240 Units Dysport® or 2400 Units Neurobloc (type B preparation) for flexor carpi radialis.

Patients received a single injection between 70 and 400 units of NT 201 and were followed for a minimum of 13 weeks and a maximum of 16 weeks. A total of 303 patients were enrolled. Of these, 300 patients were included in the ITT population and 256 patients in the TPP population.

Merz stated that a similar numbers of patients in each treatment group experienced at least 1 AE (NT 201: N = 21, Placebo: N = 20), slightly more AEs were reported in the NT 201 (43) relative to the placebo group (36). An AE of Special Interest (AESI) occurred in one patient in the NT 201 group (nasopharyngitis).

2. Study MRZ 60201-0410/2: *Prospective, double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the upper limb (ISS, Section 2.7.6)*

Study 0410/2 was a prospective, double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the upper limb. It was conducted in Poland, Hungary and the Czech Republic.

Merz stated that a total of 145 patients proceeded from the Main Period of this study to continued NT 201 treatment during the OLEX Period. The inclusion criteria were the same as in Study 0410/1 above. The Main Period had a minimum duration of 13 weeks and maximum of 21 weeks. The OLEX Period had a minimum duration of 48 weeks and maximum of 69 weeks (± 3 days), depending on the time point of the last injection of trial medication.

During the OLEX Period, a total of 145 patients received up to five injection sessions with the intended dosages of up to 400 U NT 201 each. The mean cumulative dose administered in the OLEX Period was 1197.0 ± 450.8 U NT 201.

For the combined main and open label data, the most frequently occurring AEs by preferred term were muscle spasticity (15 patients [10.3%]); upper respiratory infection and depression (both in 7 patients [4.8%]) gamma-glutamyl transferase increased and hypertension (both in 6 patients [4.1%]); epilepsy and muscular weakness (both in 5 patients [3.4%]); respiratory tract infection, urinary tract infection, and injection site pain (each in 4 patients [2.8%]); influenza, pain in extremity, pyrexia, hyperglycemia, and benign prostatic hyperplasia (each in 3 patients [2.1%]).

***Reviewer comment:** A discussion of hyperglycemia with NT 201 treatment is contained in Section 7.3.4.3 of this review.*

3. **Study MRZ 60201-0607/1:** *Prospective, randomized, observer-blind, parallel-group, multi center trial to assess efficacy and safety of two different dilutions of NT 201 in patients with upper limb spasticity (ISS, Section 2.7.6)*

Study 0607/1 was a prospective, randomized, observer-blind, parallel-group, multi-center trial to assess efficacy and safety of two different dilutions of NT 201 in patients with upper limb spasticity. The study was conducted in multiple European countries, including Austria, France, Germany, Italy, Portugal, Spain, Switzerland and the United Kingdom.

A total of 192 patients were enrolled. Of these, 95 were randomized to the 50 U/mL dilution group and 97 to the 20 U/mL dilution group. A total of 89 subjects in the 50 U/mL dilution group and 91 subjects in the 20 U/mL dilution group completed the study. The inclusion criteria for patients enrolled included:

- Being over 18-years-old

- Having with upper limb spasticity caused by either stroke, brain injury, spinal cord injury, multiple sclerosis or cerebral palsy, who had either been pre-treated or were treatment naïve stable upper limb spasticity for 6 months after stroke, brain injury or spinal cord injury, no relapse of multiple sclerosis within 3 months prior to the screening or cerebral palsy
- Disability Assessment Scale (DAS) ≥ 2 points for primary therapeutic target at both screening and baseline visits
- For pre-treated patients only, source documentation of the most recent injection session with Botulinum toxin and sufficient therapeutic response for flexed wrist or flexed wrist and elbow. The total dose of most recent injection with Botulinum toxin must have been not more than 400 units BOTOX® (1600 units Dysport® or 16,000 units Neurobloc® [type B]) for the affected flexors of wrist or affected flexors of wrist and elbow.

Dosing in the study was determined by the Worldwide Education and Awareness of Movement Disorders [WE MOVE] for the corresponding clinical pattern of spasticity, with a maximum dose of 400 units. The patient received a single injection at baseline and efficacy and safety assessments were conducted over a period of 12 weeks. There was an additional follow-up of 8 weeks. If a new injection of non-trial botulinum toxin was administered between Week 12 and Week 20 the follow-up was performed at the time of administration.

In total, Merz stated 73 patients (38.0%) experienced treatment emergent adverse events (TEAEs), with a slightly higher rate 50 U/mL group (41 subjects [42.7%]) compared with the 20 U/mL group (32 subjects [33.3%]). SAEs occurred in 12 patients (6.3%): 6 patients in the 20 U/L group and 6 patients in the 50 U/L group. Injection hematoma was the most common adverse event.

6 Review of Efficacy

The efficacy of treatment with NT 201 is evaluated in separate reviews by Dr. Ken Bergman (for blepharospasm), and Dr. Anne Constantino (for cervical dystonia). Additional information can be found in the Team Leader Memo prepared by Dr. G. Dave Podskalny.

This document examines NT 201 safety only.

7 Review of Safety

Safety Summary

A summary of the safety review for NT 201 is presented below:

- **Deaths:** There were a total of six deaths in patients within the NT 201 development program for all indications (including the non-neurologic indications): two in patients treated with placebo, one in a patient treated with Botox® and three in patients treated with NT 201. The three deaths in the NT 201-treated patients all occurred within the spasticity (b) (4) studies, and all three were during the OLEX period. The causes of death were described as cardiac arrest, CVA and unknown. However, the deaths described as cardiac arrest and CVA both occurred suddenly so that there were no laboratory or imaging results to support this designation. The determination was apparently based on the patient's medical history.
- **Serious Adverse Events:** The SAEs in the NT 201 development program were generally those expected for the background population of the same age group. There were two SAEs of respiratory failure and dyspnea, but neither fit the clinical presentation of systemic botulinum toxin spread and both cases had clear alternate causes (such as post-surgery blood loss). There were 6 cases of epilepsy and 1 case of convulsion among the SAEs, all within the spasticity (b) (4). Some of these patients were known to have pre-existing epilepsy, but in others there was no history of epilepsy. CVA's may lead to subsequent seizures, and all of the patients in the SP (b) (4) had experienced a prior CVA. There has been a post-marketing report of anaphylaxis.
- **Common Adverse Events:**
 - **BEB:** Adverse events occurring in $\geq 3\%$ of NT 201-treated subjects compared to placebo in Study 0433/1 Main Period were eyelid ptosis (19% vs. 9%), dry eye (16% vs. 12%), dry mouth (16% vs. 3%), diarrhea (8% vs. 0%), headache (7% vs. 3%), visual disturbance (7% vs. 6%), dyspnea (5% vs. 3%) and nasopharyngitis (5% vs. 3%). In the BEB open-label studies, the most common AEs in the repeated dose BEB studies were eyelid ptosis (18.9%), dry eye (16.2%), dry mouth (16.2%), and visual disturbance (6.8%).
 - **CD:** In the placebo-controlled CD studies, the most frequent AEs compared to placebo were neck pain (10.7% NT 201 vs. 4.1% placebo), muscular weakness 14 (8.8% NT 201 vs. 1.4% placebo), musculoskeletal pain 8 (5.0% vs. 1.4%) and musculoskeletal stiffness (3.1% NT 201 vs. 1.4%). In the open-label studies, the most frequent events were dysphagia (34 of 214 subjects, 15.9%), sinus infection (7.5%), "common cold" (6.1%), headache and neck weakness (4.2%, each).
 - **SP:** In the placebo-controlled SP studies, the AEs in the NT 201-treated group with the largest increase compared to placebo-treated patients were: headache (2.7% NT 201 versus 1.3% placebo), epilepsy (2.7% NT 201 versus 1.3% placebo) and hyperglycemia (4.1% NT 201 versus 0% placebo). In the open-label SP studies, the most frequent AEs were muscle spasticity (8.5%), depression (7.0%), upper respiratory tract infection (5.6%) and muscular weakness (4.2%).

- **Discontinuations:** Although the number of discontinuations due to AE is low in the NT 201 development program, it is consistent with that seen in other botulinum toxin development programs. The number of discontinuations due to adverse event was (0.5% (6/1313 patients) in the NT 201 treatment group, 0.3% (1/396 patients) Botox-treated subjects and 0.3% (1/346 patient) among placebo-treated patients. During the course of the safety review, I did not notice a pattern among the patients discontinuing due to adverse events. I audited the narratives of patients who discontinued for reasons other than adverse events (such as withdrawal of consent and loss to follow-up). See also “Evidence of Systemic Spread of Toxin” below.
- **Evidence of Systemic Spread of Toxin Effect:** There were no events containing multiple symptoms (such as respiratory failure, paralysis, the need for intensive inpatient care, etc.) of broad systemic botulinum toxin poisoning within the NT 201 development program for BEB, CD and SP.¹¹ It should be noted, however, that there was also no signal for systemic spread of effect in the development program for Botox® and Dysport®, and cases only emerged during the postmarketing period.

One case that raised concern of systemic spread occurred in an SP patient (Patient 1142) who received NT 201 injection in the upper extremity, who twice experienced dysphagia following NT 201 treatment (310 U and 320 U for the first and second adverse events, respectively). Further, the event appeared temporally related to NT 201 administration, occurring nine days after treatment in the first event and one day after treatment in the second event. Time of resolution of the event was not reported in either case.

This reviewer recommends that the Boxed Warning describing systemic spread contained in the label of other botulinum toxin class members also be included in the NT 201 labeling.

- **Hyperglycemia:** Blood glucose was examined closely due to a small elevation of blood glucose in treated versus placebo patients in the Dysport® development program. The data linking NT 201 to an effect on glucose levels is mixed. There were cases of elevated blood glucose in NT 201-treated patients, including one in the spasticity (b) (4) that was classified as an SAE due to the need for hospitalization. Within the placebo-controlled trials, there were also more clinically significant elevated glucose values in the NT 201 compared to the placebo treated patients, but the overall number of patients with events in each group was small (For example, in the spasticity (b) (4), 3 cases in the NT 201 group compared to none in the placebo group). When mean glucose value was compared from the initial study visit to the primary endpoint visit and the final visit with the placebo-controlled trials, the values for NT 201, placebo and Botox® were similar (both over time and between groups).
- **Vital Signs:** Although one indication (BEB) showed a slight decrease in heart rate from baseline to final visits, this was not replicated in (b) (4) (CD and SP). The

¹¹ There were a number of adverse events relating to muscular weakness and dyspnea, but none fit the pattern of systemic botulinum toxin spread.

potential signal for decreased heart rate observed in the Dysport® development program does not appear to be replicated in the NT 201 development program.

- ***Analysis for Effect Modifiers: Study Location:*** The sponsor performed multiple analyses examining the association of age, gender, baseline disease severity and pre-treatment status with adverse events. Although variations in AE risk were observed for some of these factors, the number of events per subgroup was small and the effects were not replicated across indications.

As observed in other drug development programs, a higher number of reported adverse events were observed in the North American studies compared to those conducted outside North America. In many instances the risk of the common adverse events (overall and for specific indications) was approximately two- to three-fold higher in the North American countries compared to the non-North American countries. Consistent with the pattern seen in other drug development programs, the effect is more pronounced for the common adverse events than for serious adverse events.

7.1 Methods

With the exception of the deaths and SAEs, in which the review is integrated across all indications (including non-neurologic), adverse events will be examined by indication. This is due to the differences in product administration and underlying patient population.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A table of all the studies which contributed safety data to the NT 201 development program is contained in Section 5.1 of this review. A more detailed text summary of the Phase 3 studies in the NT 201 development program is supplied in Section 5.2.

The manner in which adverse events are solicited in the clinical trials (open-ended questions, checklists, etc.) can affect the number of adverse events recorded. The sponsor was therefore requested to prepare a table summarizing the methods used to elicit adverse events in each study. The resulting table is shown below:

Table 5: Reporting of Adverse Events in NT 201 Studies in the BEB, CD and SP Indications (as described in the respective clinical study report) (Adapted from Sponsor Table 1, Amendment 0019, dated February 4, 2010)

Study Number (Indication)	Method for detecting AEs	Wording in Protocol
CD Studies		
MRZ 60201-0408 (Cervical Dystonia)	Spontaneous reporting and direct questioning	Subjects were requested to report all AEs to the Investigator. In addition, it was the obligation of the Investigator to detect AEs by direct questioning of the subject at each telephone contact and visit. All AEs observed during the course of the trial were described and commented on in the CRF.
MRZ 60201-0013 (Cervical Dystonia)	Spontaneous reporting and observation of symptoms	Adverse events (AEs) were recorded at each visit based on a patient's spontaneous description or the investigator's observation of symptoms. All AEs were recorded in the AE page of the CRF...
MRZ 60201-9801 (Cervical Dystonia)	Spontaneous reporting and closed questions	Data pertaining to AEs was collected during each trial visit either based on the patient's spontaneous description or by the investigator's inquiry. The

		investigator was first to ask a general question, e.g. "Has your state of health worsened since you last saw me?" rather than using leading questions. If the answer was "no", no further questions were asked. If the answer was "yes", the investigator was to assess and record any AE in detail on the appropriate 'Adverse Event' page of the CRF...
MRZ 60201-0605 (Cervical Dystonia)	Spontaneous reporting and investigator's inquiry, examination	Data pertaining to AEs were collected during each study visit either based on the subject's spontaneous description or by the investigator's inquiry or discovered during the course of examinations. The investigator assessed and recorded any AE in detail on the 'AE' form of the CRF...

BEB Studies		
MRZ 60201-0433 (Blepharospasm)	Spontaneous reporting and direct questioning. AESIs were elicited by active questioning	Subjects were requested to report all AEs to the Investigator. In addition, the Investigator was obliged to monitor AEs by directly asking the subjects at each telephone contact and visit whether they had experienced any AE and if any changes in concomitant medication / diseases had occurred since the last visit. In addition, subjects were actively asked about the occurrence of AEs of special interest (AESI) assumed as predictive for indication of local and distal toxin spread, in particular: drooping of the eyelid, problems with vision, dry mouth, swallowing difficulties, speech problems, shortness of breath, respiratory infection, local weakness, facial weakness, general body weakness, stomach or bowel disturbances.
MRZ 60201-0003 (Blepharospasm)	Spontaneous reporting and observation of symptoms	AEs were recorded at each visit based on a patient's spontaneous description or the investigator's observation of symptoms. All AEs were recorded in the AE page of the CRF with details on the date and time of onset, description, intensity, duration and outcome, aetiology, causal relationship with the trial medication, and action taken.

SP Studies		
MRZ 60201-0410 (Spasticity)	Spontaneous reporting and investigator's inquiry, examination.	Patients were requested to report all AEs to the Investigator. In addition, it was the obligation of the Investigator to detect AEs by directly questioning the
		patient at each visit and telephone contact. All AEs observed in the course of the trial had to be described and commented upon in the CRF.
MRZ 60201-0607 (Spasticity)	Spontaneous reporting and investigator's inquiry, examination.	Data pertaining to AEs, either based on the subject's spontaneous description or by the investigator's inquiry or discovered during the course of the examinations done during the visit, were collected during each study visit. The investigator assessed and recorded any AE in detail on the 'Adverse Event' form of the CRF...

Reviewer comment: The methods used to elicit adverse events (as described in the table above), are adequate but not ideal. In Study 60201-9801 investigators were instructed to ask patients

“Has your state of health worsened since you last visit?” This method of questioning could miss smaller adverse events if misinterpreted by the patient (For example, a patient may respond “no” to this question if his injection site pain and/or bruising has resolved but he now has a dry mouth, thinking that his state of health has not changed). The majority of studies, with the exception of BEB study 0433, appeared not to have specifically used checklists, to ask about known adverse events associated with botulinum toxin. Universal use of such checklists would have likely increased capture of adverse events (for instance, some patients may not mention certain adverse events associated with botulinum toxin to investigators believing that because this is already a known event it does not need to be tracked further).

7.1.2 Categorization of Adverse Events

Merz stated that treatment-emergent adverse events were defined as events with onset at the time of, or following, the first dose of study treatment. In open-label Study 0410/2 (SP), Merz noted that any untoward medical occurrence appearing beyond 20 weeks following the last injection was not considered a TEAE (ISS, pg. 13).

Sponsor definitions of “common” and “very common” adverse event are contained in Section 7.4.1.1 of this review.

The FDA and Merz developed a list of Adverse Events of Special Interest (AESIs) based on adverse events that were observed in the development programs or postmarketing period of other botulinum toxin products. These are described in more detail in Section 7.2.6 of this review.

An issue related to AE calculations is whether AEs are presented as a risk or a rate. In the BLA, Merz presents adverse events as risks (percent) only, and did not calculate time-adjusted rates. This could be a potential source of bias if NT 201-treated patients discontinued from the study more frequently than placebo patients, as the latter group would have a longer observation period in which AEs may occur. However, as shown in Section 7.3.3 (Drop-outs and/or Discontinuations) the percent of patients in the drug and placebo group were similar, and therefore the use of risk in the safety analysis is acceptable.

7.1.2.1 Coding of Verbatim to Preferred Terms

Reviewer comment: *In assessing the quality of the safety data within the NT 201 BLA, I audited the coding of verbatim terms to preferred terms (PTs) within the Xeomin BLA. I paid particular attention to the coding of adverse events of interest, including dysphagia and muscular paralysis. Due to the relatively small number of SAEs, I was able to review all SAE coding.*

The review of coding highlighted the significant number of adverse events of hypertension. However, a comparison of hypertension in drug-treated and placebo patients showed equivalent values over time, and hypertension is a common event in an older age group such as in this database where the mean age was 50-52 years.

I did not find any systemic problems in the AE coding, although there were some minor issues with the coding of some adverse events. The verbatim term “cold symptoms” or “head cold” was sometimes coded to “flu-like symptoms” although there are more specific, non-influenza preferred terms available. It was unclear if these were due to coding problems or due to poor translation to English. This splitting could obscure a number of similar adverse events, but I do not believe re-coding is necessary as this is a non-critical AE and in the pooled placebo-controlled trials the rates of upper respiratory infection, influenza, etc. were essentially equivalent between the placebo and NT 201 groups.

Table 6: Coding Irregularities within the Xeomin BLA

(Adapted from Sponsor Analysis Dataset 5.3.5.1.25.3.1, File coding.xpt; BTC 60201-9801 for CD)

Verbatim Term/Terms	Preferred Term	Coding Issue
“Cat hair and NI – contact allergy”	“Split”	Unclear preferred term
“Systremia”	“Cramp in Limb”	Unclear verbatim term
“Hysterectomy due to excessive menorrhagia”	“Excessive Menstruation”	Multi-term verbatim issue which ideally should be coded as both “menorrhagia” and “hysterectomy”
“Head cold,” “cold,” “upper respiratory track infection”	“Influenza,” “nasopharyngitis,” “upper respiratory track infection”	Although most of the preferred terms which referred to “head cold” were coded to “nasopharyngitis,” others were coding to a variety of different verbatim terms.

An area of focus for the audit of AE coding was the issue of dry mouth and dysphagia in the Blepharospasm indication. Although dry mouth has been previously reported, and is therefore somewhat expected, with botulinum toxin use for blepharospasm, true dysphagia would not be expected with botulinum toxin administration for blepharospasm, and would be evidence of spread of toxin outside the area of administration. I therefore examined the verbatim terms related to dysphagia, dry mouth, and swallowing difficulties to ascertain whether these events were coded properly. I found no instances in which the preferred term did not adequately characterize the reported verbatim term.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Reviewer comment: *As noted elsewhere in the review, the patient demographic profiles for the NT 201 studies varied considerably by indications. Patients in the spasticity indication were older and were more likely to be male (60%) than in the other indications. The differences in the demographic profiles between studies are discussed in further detail in Section 7.21 of this review.*

Due to these differences in patient population, as well as large differences in dose and site of injection between indications, pooling all NT 201 studies for analysis is problematic. However, to adequately capture all deaths and SAEs, and to generally increase the number of patients for subgroup analyses, this review does include analyses of pooled studies. The limitations previously noted should be considered when interpreting these analyses.

Merz documented the studies which were pooled to create the pooled safety database. For placebo-controlled studies, the six studies included were (ISS, pg. 6).

- Study 0408/1 (CD);
- Study 0410/1 (SP);
- Study 0433/1 (BEB);
- Study 0520/1 (Glabellar Frown Lines, GFL);
- Study 0617 (Crow's Feet, CF);
- Study 0527 (GFL).

For the controlled studies (both placebo and active) the 10 studies pooled were: (ISS, pg. 12)

- The 6 placebo-controlled studies in the list above
- Study 0607 (SP); control: different dilutions of NT 201
- Study 9801 (CD); control: Botox
- Study 0013 (CD); control: Botox
- Study 0003 (BEB); control: Botox

7.2 Adequacy of Safety Assessments

As discussed in more detail in Section 7.2.6 of this review, because other botulinum toxins have been previously marketed in the United States, the NT 201 safety review benefitted from their prior pre- and post-marketing experience through the creation of an Adverse Event of Special Interest (AESI) list. The sponsor monitored for these events in the NT 201 development program, which aided the safety assessment.

Reviewer comment: *To assess the adequacy of the sponsor's safety assessment, I examined the clinical testing and safety monitoring methods within the NT 201 studies. These are discussed in detail in Section 7.2.4 and Section 7.1.2 of this review, respectively.*

An important element of the adequacy of safety assessments is that an adequate number of patients were exposed at the therapeutic dose range in order to be able to detect and interpret adverse events. The exposures in the three indications (BEB, CD and SP) are discussed in Section 7.2.1 of this review.

(b) (4)

(b) (4)

Section 3.1.1 of this review also summarizes some of the deficits in the sponsor's safety analysis. None of these deficits were sufficient to prevent an adequate safety analysis. Other minor deficiencies were addressed through requests for additional information to the sponsor, and are discussed throughout the review.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Reviewer comment: *For chronically administered drugs, ICH guidelines recommend that 1500 patients should be treated overall in a drug development program, 300 to 600 patients be treated for six months, and 100 patients be treated for one year. These exposures should occur at the dose or dose range believed to be efficacious.*

It is notable that none of the three neurologic indications reviewed in this document (BEB, CD, and SP) met these ICH guidelines for adequate exposure. In fact, the NT 201 development program does not meet these guidelines even when all of the indications, including non-neurologic indications, are combined (there are a total of 1313 NT 201-exposed patients in the pooled studies for the NT 201 development program). NT 201 is not chronically administered in the sense that it is an intermittent injection, and so exposure guidelines other than the ICH guidelines for chronically administered drugs may apply. During the pre-BLA period, the FDA discussed appropriate exposure guidelines with Merz. The Division's communication with Merz regarding the FDA's expectations for drug exposure

(b) (4)

7.2.1.1 Exposure and Demographics: Pooled Indications

7.2.1.1.1 Exposure: Pooled Indications

In the pooled studies of NT 201, a total of 1313 subjects received NT 201, 346 subjects received placebo, and 396 subjects received Botox®. In the pooled, placebo-controlled studies, Merz stated that a total of 701 subjects received NT 201 and 346 subjects received placebo (ISS, pg. 23).

The table below shows the number of patients exposed and the mean dose per indication.

Table 7: Summary of NT 201- Stratified by Indication, NT 201 Dose and Follow-Up Time
(Sponsor Table 5.3.5.3-6, ISS, pg. 29)

Table 5.3.5.3 - 6: Summary of NT 201 Exposure (in Units) in the Pooled, Controlled Studies, Overall and by Indication

	Overall N=1313	Cervical Dystonia N=431	Benign Essential Blepharospasm N=222	Spasticity N=265	Glabellar Frown Lines N=312	Crow's Feet N=83
Mean Dose	122	152	49	284	20	24
(SD)	(112.0)	(60.8)	(21.4)	(92.1)	(5.6)	(0)
Median Dose	100	120	50	300	20	24
25 th and 75 th Quartile	24, 200	100, 200	36, 60	210, 360	20, 20	24, 24
Minimum Dose	10	30	15	20	10	24
Maximum Dose	495	400	100	495	30	24

The pooled controlled studies were: 0408/1 (CD) Main Period, 9801 (CD), 0013 (CD), 0410/1 (SP) Main Period, 0607 (SP), 0433/1 (BEB) Main Period, 0003 (BEB), 0520/1 (GFL) Main Period, 0527 (GFL), and 0617 (CF).
The pooled CD studies were: 0408/1 Main Period, 0013 and 9801.
The pooled BEB studies were: 0433/1 Main Period and 0003.
The pooled SP studies were: 0410/1 Main Period and 0607.

A summary of exposure by dose group and weeks of observation period for the pooled NT 201 indications are shown below.

Table 8: NT 201 Exposure by Dose Group and Observation Period for the Pooled Indications
(Adapted from Sponsor Table 1, ISS, pg. 12)

Table 1: Summary of NT 201 Exposure by Observation Period and Total Dose, Studies 0408 (CD), 0410 (SP), and 0433(BEB) Main and OLEX Periods, and Study 0609 (GFL) – 120-Day Safety Update Data

Dose Group	Observation Period									Overall
	<2 weeks	2 to <7 weeks	7 to <13 weeks	13 to <21 weeks	21 to <24 weeks	24 to <48 weeks	48 to <72 weeks	72 to <96 weeks	96 to 120 weeks	
>10 to 40 U	11 (1.3%)	1 (0.1%)	2 (0.2%)	10 (1.2%)	5 (0.6%)	93 (11.4%)	240 (29.3%)	4 (0.5%)	-	366 (44.7%)
>40 to 120 U	-	3 (0.4%)	3 (0.4%)	7 (0.9%)	1 (0.1%)	20 (2.4%)	74 (9.0%)	19 (2.3%)	-	127 (15.5%)
>120 to 240 U	1 (0.1%)	2 (0.2%)	4(0.5%)	9 (1.1%)	2 (0.2%)	21 (2.6%)	65 (7.9%)	23 (2.8%)	1 (0.1%)	128 (15.6%)
>240 to 360 U	-	-	1 (0.1%)	-	-	5 (0.6%)	22 (2.7%)	24 (2.9%)	-	52 (6.3%)
>360 U	-	-	1 (0.1%)	3 (0.4%)	1 (0.1%)	6 (0.7%)	51 (6.2%)	23 (2.8%)	-	85 (10.4%)
Still blinded	-	-	-	-	-	3 (0.4%)	25 (3.1%)	33 (4.0%)	-	61 (7.4%)
Overall	12 (1.5%)	6 (0.7%)	11 (1.3%)	29 (3.5%)	9 (1.1%)	148 (18.1%)	477 (58.2%)	126 (15.4%)	1 (0.1%)	819 (100%)

Data are presented as number of subjects (percent of subjects). The data in the "Still Blinded" row are from subjects in Study 0408/2 who were not included in the First Long-Term Safety Analysis. These subjects received NT 201 at a dose of 120 or 240 U.
BEB: benign essential blepharospasm; CD: cervical dystonia; GFL: glabellar frown lines; OLEX: open-label extension; SD: standard deviation; SP: spasticity; U: Units.
Source: Table 1.5, Section 3.3.5.3, Appendix M.

7.2.1.1.2 Demographics: Pooled Indications

The demographic profile of the patients within the NT 201 development program varied widely between indications. The demographic profiles are therefore presented below divided by indication.

The demographic characteristics of the patients in the pooled controlled studies, and in the pooled CD, BEB and SP populations, are summarized in the table below. Patients in the BEB studies had the highest mean age (63 years). The majority of subjects overall, and in the CD (64%) and BEB (74%) studies, were female. The large majority (90 to 95%) of patients were Caucasians (ISS, pg. 27).

Reviewer comment: As shown in the table below, patients who were randomized to NT 201 tended to have more severe baseline disease than those randomized to placebo.

Table 9: Demographic Characteristics of Subjects in the Pooled Controlled Studies and in the Cervical Dystonia, Benign Essential Blepharospasm and Spasticity Studies

Adapted from Sponsor Table 5.3.5.3-4, ISS, pg. 29)

Table 5.3.5.3 - 4: Demographic Characteristics of Subjects in the Pooled Controlled Studies, and in the Cervical Dystonia, Benign Essential Blepharospasm and Spasticity Studies

Characteristic	Overall		Cervical Dystonia		Blepharospasm		Spasticity	
	NT 201	Placebo	NT 201	Placebo	NT 201	Placebo	NT 201	Placebo
Age (years)	N=1313	N=346	N=431	N=74	N=222	N=34	N=265	N=75
Mean	52.3	50.9	50.8	52.4	63.1	62.6	56.1	53.3
(SD)	(12.76)	(11.52)	(12.01)	(10.75)	(9.95)	(8.70)	(13.31)	(13.33)
Min, Max	18, 87	23, 79	18, 75	30, 79	22, 87	44, 79	18, 82	23, 79
Gender (percent)	N=1313	N=346	N=431	N=74	N=222	N=34	N=265	N=75
Male	32.6	33.2	36.0	33.8	26.1	35.3	58.9	66.7
Female	67.4	66.8	64.0	66.2	73.9	64.7	41.1	33.3
Weight (kilograms)	N=1307	N=343	N=427	N=71	N=222	N=34	N=263	N=75
Mean	72.2	72.6	73.6	77.2	73.9	77.5	74.3	77.3
(SD)	(14.68)	(14.34)	(15.17)	(16.11)	(14.81)	(17.56)	(14.08)	(12.65)
Min, Max	41, 149	41, 117	45, 129	43, 113	41, 149	50, 117	44, 126	41, 115
Body Mass Index (kilograms/meter²)	N=1307	N=342	N=427	N=71	N=222	N=33	N=263	N=75
Mean	25.7	25.4	26.0	26.9	27.4	28.1	26.2	26.3
(SD)	(4.53)	(4.24)	(4.69)	(4.49)	(4.66)	(6.09)	(4.17)	(3.54)
Min, Max	16, 48	15, 48	16, 48	16, 41	17, 43	19, 48	18, 41	15, 38
Race (percent)	N=1279	N=346	N=431	N=74	N=222	N=34	N=231	N=75
Am. Ind./Al. Nat.	0.1	0	0.2	0	0	0	0	0
Asian	2.4	3.2	0.2	4.1	3.6	0	0.4	0
Black/Af. Am.	0.4	1.7	0.5	5.4	0.9	5.9	0.4	0
Hispanic/Latino	1.6	1.2	1.9	2.7	3.6	2.9	0.9	0
Caucasian ¹	95.4	93.9	97.2	87.8	91.9	91.2	98.3	100
Other	0.1	0	0	0	0	0	0	0
Baseline Disease Severity (percent)	N=1313	N=346	N=431	N=74	N=222	N=34	N=265	N=75
Mild	16.3	9.8	25.3	16.2	28.8	23.5	15.5	18.7
Moderate	48.4	42.5	56.1	58.1	51.8	52.9	63.4	64.0
Severe	35.3	47.7	18.3	25.7	19.4	23.5	21.1	17.3
Missing	0.1	0	0.2	0	0	0	0	0

AF Am.: African American; Al. Nat.: Alaskan native; Am. Ind.: American Indian.

¹ Caucasian is used as a synonym for "white" that was used in the output tables in 5.3.5.3.1.

The pooled controlled studies were: 0408/1 (CD) Main Period, 9801 (CD), 0013 (CD), 0410/1 (SP) Main Period, 0607 (SP), 0433/1 (BEB) Main Period, 0003 (BEB), 0520/1 (GFL) Main Period, 0327 (GFL), and 0617 (CF).

The pooled CD studies were: 0408/1 Main Period, 0013 and 9801.

The pooled BEB studies were: 0433/1 Main Period and 0003.

The pooled SP studies were: 0410/1 Main Period and 0607.

Source: Table 2.1.1.1, Table 2.1.2.1.1.1, Table 2.1.2.2.1.1, Table 2.1.2.3.1.1, Table 2.3.1.1, Table 2.3.2.1.1.1, Table 2.3.2.2.1.1, Table 2.3.2.3.1.1, Table 2.4.1.1, Table 2.4.2.1.1.1, Table 2.4.2.2.1.1, Table 2.5.1.1, Table 2.5.2.1.1.1, Table 2.5.2.2.1.1, Table 2.5.2.3.1.1, Table 2.6.1.1, Table 2.6.2.1.1.1, Table 2.6.2.2.1.1, Table 2.6.2.3.1.1, Table 2.7.1.1, Table 2.7.2.1.1.1, Table 2.7.2.2.1.1 and Table 2.7.2.3.1.1, Section 5.3.5.3, Appendix H.

7.2.1.2 Exposure and Demographics: BEB

7.2.1.2.1 Exposure: BEB

In the placebo-controlled Phase 3 trial (Study 0433/1), Merz reported that 74 subjects received NT 201 at a mean dose of approximately 33 U per eye (minimum 10 U, maximum 50 U). Thirty-

four patients were treated with placebo with a similar mean dose as in the NT 201 group (Clinical Overview, pg. 29).

Table 10: NT 201 Exposure within BEB Study 0433/1 and Study 0003

(Adapted from Sponsor Table 5, BEB ISS, pg. 14)

Table 5: Summary of NT 201 Exposure (in Units) in the Pooled Benign Essential Blepharospasm Safety Database, Overall and by Study

	Pooled Blepharospasm Studies N=222	0433/1 Main Period N=74	0003 N=148
Mean Dose (SD)	49.4 (21.41)	66.9 (22.32)	40.7 (14.55)
Median Dose	50	65	40
25 th and 75 th Quartile	36, 60	50, 86	30, 50
Minimum Dose	15	20	15
Maximum Dose	100	100	95

U: units.

Reviewer comment: Merz explained that the mean and median NT 201 doses were higher in the Study 0433/1 Main Period than in Study 0003 due to protocol differences. The maximum allowed dose in the Study 0433/1 Main Period was 100 U (50 U per eye) and in Study 0003 was 70 U (35 U per eye). (See summary later in the section for the number of patients receiving 50 U per eye.)

With regard to long term exposure, Merz stated that in Study 0433/2 (BEB) OLEX Period, 76 subjects were exposed to NT 201 for 48 weeks or more (ISS, pg. 31). The pooled data from Study 0433/1 (Main Period) and 0433/2 (OLEX Period) are presented by dose and duration of follow-up in the following table.

Table 11: NT 201 Exposure in BEB Study 0433/1 (Main Period) and 0/433/2 (OLEX) by the Number of Injections and the Time the Patient was Monitored in the Trial

(Adapted from Sponsor Table 10, BEB ISS, pg. 17)

Table 10: Summary of NT 201 Exposure in the Study 0433 Main and OLEX Periods by Number of Injections and Observation Period as of 25-Jun-2009 – 120-Day Safety Update Data

Observation Period	Number of Injections						Overall
	1	2	3	4	5	6	
2 to <7 weeks	3 (2.8%)	-	-	-	-	-	3 (2.8%)
7 to <13 weeks	2 (1.9%)	1 (0.9%)	-	-	-	-	3 (2.8%)
13 to <21 weeks	3 (2.8%)	2 (1.9%)	-	-	-	-	5 (4.7%)
21 to <24 weeks	-	1 (0.9%)	1 (0.9%)	-	-	-	2 (1.9%)
24 to <48 weeks	-	1 (0.9%)	1 (0.9%)	1 (0.9%)	6 (5.7%)	3 (2.8%)	12 (11.3%)
48 to <72 weeks	-	2 (1.9%)	2 (1.9%)	8 (7.5%)	28 (26.4%)	26 (24.5%)	66 (62.3%)
72 to <96 weeks	-	-	1 (0.9%)	1 (0.9%)	6 (5.7%)	7 (6.6%)	15 (14.2%)
Overall	8 (7.5%)	7 (6.6%)	5 (4.7%)	10 (9.4%)	40 (37.7%)	36 (34.0%)	106 (100%)

Data are presented as number of subjects (percent of subjects).

“-” indicates category not applicable. OLEX: Open-label Extension Period.

Source: Table 1.10, Section 5.3.5.3, Appendix K.

Reviewer comment: *The sponsor’s table above does not account for time between injections. For instance, if the patient receives one dose and is followed for a year, this should not be considered a year of exposure.*

The sponsor reported that in the “Main and OLEX Periods of Study 0433 combined over half of the subjects had received 5 or 6 doses of study medication, and were followed for 48 weeks or more. (BEB ISS).” As of the time of this review, information from the sponsor is pending regarding the number of patients receiving multiple consecutive doses at specific dose levels.

Reviewer comment: *Using study data, the primary reviewer for the BEB indication, Dr. Ken Bergman, prepared the following summary of cumulative NT 201 exposure.*

“Using the datasets for Trials 0433/1 and 0433/2, the intervals between sequentially administered treatments (numbers of days from one injection to the next injection) were summed. The interval of exposure to active drug in the double blind trial was carried over into the open label extension as these patients were rolled over without interruption in treatments.

This summed exposure for each subject was converted to weeks to get total duration of exposure. The rounding was downward in direction, e.g. 7 weeks and 6 days was considered 7 weeks. If a subject was lost to follow-up and had no final visit for that treatment session, that injection dose and its interval were dropped from the exposure data set.

Subjects with at least 24 weeks and 48 weeks continuous observation were taken to be supportive of exposure to the lowest dose in that interval. I looked at all combinations to see if a given dose exposure might be supported at some middle interval over the course of a subject’s treatment. For example if a subject received 4 injections of 90, 100, 100, and 90 units at intervals over a year, it might also be supportive of 100 units at 6 months

exposure, but also 90 units at 48 weeks exposure. (The doses are expressed as deciles, e.g.: a dose between 90 and 99 units supported a 90 unit dose).”

Table 12: Cumulative NT 201 Exposure for BEB at 24 and 48 Weeks

(Prepared by Dr. Ken Bergman, Adapted from the BEB Efficacy Review)

NT 201 cumulative dose exposure at 24 and 48 weeks					
Total dose NT201 (both eyes)	Considered supportive of this dose level	24 Weeks		48 Weeks	
		N	Cumulative N at or exceeding this dose level	N	Cumulative N at or exceeding this dose level
100 Units	100 Units	15	15	13	13
90 - 99 Units	90 Units	5	20	4	17
80 - 89 Units	80 Units	11	31	5	22
70 - 79 Units	70 Units	14	45	12	34
60 - 69 Units	60 Units	16	61	14	48
50 - 59 Units	50 Units	17	78	18	66
40 - 49 Units	40 Units	8	86	8	74
30 -39 Units	30 Units	3	89	3	77
29 Units or less	20 Units	3	92	3	80

Reviewer comment: Based on the table above, there were 78 patients within the BEB indication who received a dose of 50-59 Units or higher for 24 weeks, and 66 patients who received 50-59 Units or higher for 48 weeks.

7.2.1.2.2 Demographics : BEB

Merz summarized that NT 201-treated subjects were 22 to 79 years of age, with a mean age of 62 years, were predominantly female (65%), and had a mean time since diagnosis of approximately 5 years. Merz stated that the demographic data of the placebo treated patients were similar to those randomized to NT 201 treatment, as shown in the table below (Clinical Overview, pg. 31; BEB ISS, pg.12). Of note, however, Caucasians made up only 78% of the population of NT201-treated patients in 0433/1 compared to 91% of placebo treated patients.

Table 13: Demographics of the BEB Safety Population: Pooled and by Study

(Adapted from Sponsor Table 4, BEB ISS, pg. 12)

Table 4: Demographic Characteristics of Subjects in the Pooled Benign Essential Blepharospasm Safety Population, Overall and by Study

Characteristic	Pooled Blepharospasm Studies	0433/1 Main Period		0003
	NT 201	NT 201	Placebo	NT 201
Age (years)	N=222	N=74	N=34	N=148
Mean	63.1	61.5	62.6	63.9
(SD)	(9.95)	(11.02)	(8.70)	(9.31)
Min, Max	22, 87	22, 79	44, 79	37, 87
Gender (percent)	N=222	N=74	N=34	N=148
Male	26.1	35.1	35.3	21.6
Female	73.9	64.9	64.7	78.4
Weight (kilograms)	N=222	N=74	N=34	N=148
Mean	73.9	78.6	77.5	71.5
(SD)	(14.81)	(18.07)	(17.56)	(12.28)
Min, Max	41, 149	52, 149	50, 117	41, 103
Body Mass Index (kilograms/meter²)	N=222	N=74	N=33	N=148
Mean	27.4	28.7	28.1	26.7
(SD)	(4.66)	(5.50)	(6.09)	(4.03)
Min, Max	17, 43	20, 43	19, 48	17, 39
Race (percent)	N=222	N=74	N=34	N=148
Caucasian*	91.9	78.4	91.2	98.6
Hispanic/Latino	3.6	10.8	2.9	0
Black/Af. Am.	0.9	2.7	5.9	0
Asian	3.6	8.1	0	1.4
Am. Ind./Al. Nat.	0	0	0	0
Other	0	0	0	0

7.2.1.3. Exposure and Demographics: CD

7.2.1.3.1 Exposure: CD

In the minutes for the pre-BLA meeting between the Division and Merz in February 2009, the following statement was made with regard to the number of CD exposures required:

“85 patients with cervical dystonia will have been treated for one year at 240 units but the data will still be blinded at the filing, which the Division found acceptable as long as long term safety data from the indication with the highest dose and duration was included in the BLA.”

The sponsor table below gives mean NT 201 exposure within the pooled cervical dystonia studies.

Table 14: NT 201 Exposure within the Phase 3 CD Studies

(Adapted from Sponsor Table 5, CD ISS, pg. 16)

Table 5: Summary of NT 201 Exposure (in Units) in the Pooled Cervical Dystonia Studies, Overall and by Study

	Cervical Dystonia N=431	0408/1 MP N=159	9801¹ N=41	0013 N=231
Mean Dose	151.6	181.8	97.8	140.4
(SD)	(60.80)	(62.60)	(42.02)	(51.37)
Median Dose	120	240	90	120
25th and 75th Quartile	100, 200	120, 240	60, 120	100, 186
Minimum Dose	30	87.5	30	50
Maximum Dose	400	400	180	300

¹ In Study 9801, subjects could receive two doses of study therapy. Univariate statistics are presented for the total dose received during the study.

MP: Main Period; SD: standard deviation.

Source: Table 1.2.1.1.1, Table 1.2.1.2.1.1, Table 1.2.1.2.2.1, and Table 1.2.1.2.3.1, Section 5.3.5.3, Appendix H.

The sponsor stated that in Study 0408/2 (CD) Extension Period, a total of 161 subjects were exposed to NT 201 for 48 weeks or more (ISS, pg. 31). As of the time of this review, information from the sponsor is pending regarding the number of patients receiving multiple consecutive doses at specific dose levels.

7.2.1.3.2 Demographics: CD

In studies for the CD indication, NT 201-treated patients were 18 to 75 years of age, with a mean age of 53 years. Placebo treated subjects were 30 to 79 years of age, with a mean age of 52.4 years. In both treatment groups subjects were predominantly female (NT 201 group: 66%; placebo group: 66.2%)(Clinical Overview, pg. 27).

7.2.1.4 Exposure and Demographics: SP

7.2.1.2.1 Exposure: SP

Merz stated that in placebo-controlled Study 0410 (SP), a total of 139 subjects were exposed to NT 201 for 24 weeks (6 months) or more, and 127 subjects were exposed to NT 201 for 48 weeks (about one year) or more. Exposure in the Study 0410/1 Main Period and 0410/2 OLEX Period (SP) by dose and number of injections is summarized in the following table (ISS, pg. 31).

Table 15: NT 201 Dose in Study 0410 Main and OLEX Periods by Dose and Number of Injections

(Adapted from Sponsor Table 5.3.5.3-8, ISS 120 Day Update, pg. 19)

Table 5.3.5.3 - 8: Summary of NT 201 Total Dose, in Units, in the Study 0410 (SP) Main and OLEX Periods

Injection Number	N	Mean Dose (±SD)	Median Dose	Minimum, Maximum
First Injection	147	332 (73.6)	360	170, 435
Second Injection	136	352 (70.6)	398	135, 400
Third Injection	121	361 (67.5)	400	100, 500
Fourth Injection	100	361 (65.4)	400	165, 400
Fifth Injection	51	339 (83.5)	400	95, 400
Sixth Injection	7	343 (97.6)	400	200, 400

OLEX: open-label extension; SD: standard deviation; SP: spasticity.

Source: Table 1.1.1, Section 5.3.5.3, Appendix I.

Reviewer comment: As noted in the meeting with the sponsor in June 2009, only 31 patients received four injections in one year (every twelve weeks), which would represent the appropriate duration of treatment pre-specified by the FDA. The FDA’s response to Merz’s response is contained in Appendix 9.7 of this review.

Table 16: NT 201 Exposure in SP Studies 04010/1 (Main Period) and 0410/2 (OLEX) by Weeks of Observation and Dose

(Adapted from Sponsor Table 11, ISS 120 Day Update, pg. 19)

Table 11: NT 201 Exposure (in Weeks) by Mean Dose Group and Observation Period, Study 0410 (SP) Main and OLEX Periods

Observation Period	>120 to 240 U	>240 to 360 U	>360 U	Overall
7 to <13 wks	-	1 (0.7%)	1 (0.7%)	2 (1.4%)
13 to <21 wks	1 (0.7%)	-	3 (2.0%)	4 (2.7%)
21 to <24 wks	1 (0.7%)	-	1 (0.7%)	2 (1.4%)
24 to <48 wks	1 (0.7%)	5 (3.4%)	6 (4.1%)	12 (8.2%)
48 to <72 wks	5 (3.4%)	22 (15.0%)	51 (34.7%)	78 (53.1%)
72 to <96 wks	2 (1.4%)	24 (16.3%)	23 (15.6%)	49 (33.3%)
Overall	10 (6.8%)	52 (35.4%)	85 (57.8%)	147 (100%)

Data are presented as number of subjects (percent of subjects).

OLEX: open-label extension; SP: spasticity; wks: weeks.

Source: Table 1.5, ISS Appendix I.

The sponsor also presented in the SP indication by weeks of observation and number of injections, as shown in the table below:

Table 17: NT 201 Exposure in Study 0410/1 Main and 0410/2 OLEX by Weeks of Observation and Number of Injections

(Adapted from Sponsor Table ISS 120 Day Update, 12, pg. 19)

Table 12: Summary of NT 201 Exposure in the Study 0410 (SP) Main and OLEX Periods by Number of Injections and Observation Period

Observation Period	Number of Injections						Overall
	1	2	3	4	5	6	
7 to <13 wks	2 (1.4%)	-	-	-	-	-	2 (1.4%)
13 to <21 wks	2 (1.4%)	2 (1.4%)	-	-	-	-	4 (2.7%)
21 to <24 wks	2 (1.4%)	-	-	-	-	-	2 (1.4%)
24 to <48 wks	3 (2.0%)	7 (4.8%)	2 (1.4%)	-	-	-	12 (8.2%)
48 to <72 wks	2 (1.4%)	6 (4.1%)	16 (10.9%)	38 (25.9%)	16 (10.9%)	-	78 (53.1%)
72 to <96 wks	-	-	3 (2.0%)	11 (7.5%)	28 (19.0%)	7 (4.8%)	49 (33.3%)
Overall	11 (7.5%)	15 (10.2%)	21 (14.3%)	49 (33.3%)	44 (29.9%)	7 (4.8%)	147 (100%)

Data are presented as number of subjects (percent of subjects).

"-" indicates category not applicable. OLEX: Open-label Extension Period; SP: spasticity; wks: weeks.

Source: Table 1.10, ISS Appendix I.

Reviewer comment: As noted elsewhere in the review, the appropriate exposure for NT 201 in the SP studies is a function of dose, number of injections and follow-up time, and each of the tables above only reflect two of the three factors. For more details on NT 201 exposure in the SP development program as it relates to an adequate safety review, see Section 7.2.1.4 of this review (b) (4).

7.2.1.4.2 Demographics: SP

The NT 201-treated subjects ranged from 34 to 78 years of age (mean 58 years) and were predominantly male (62%) and Caucasian (98%)(Clinical Overview, pg. 30). The demographic profile of the patients within the SP development program are shown in the table below (SP ISS, pg.15).

Table 18: Demographics of Patients in the NT 201 SP Development Program

(Adapted from Sponsor Table 5, SP ISS, pg. 14)

Table 5: Demographic Characteristics of Subjects in the Pooled NT 201 Spasticity Studies, Overall and by Study

Characteristic	Pooled Spasticity ¹	0410/1 Main Period		0607
	NT 201	NT 201	Placebo	NT 201
Age (years)	N=265	N=73	N=75	N=192
Mean	56.1	58.1	53.3	55.4
(SD)	(13.31)	(10.15)	(13.33)	(14.28)
Min, Max	18, 82	34, 78	23, 79	18, 82
Gender (percent)	N=265	N=73	N=75	N=192
Male	58.9	61.6	66.7	57.8
Female	41.1	38.4	33.3	42.2
Weight (kilograms)	N=263	N=73	N=75	N=190
Mean	74.3	76.4	77.3	73.5
(SD)	(14.08)	(15.30)	(12.65)	(13.54)
Min, Max	41, 115	49, 126	41, 115	44, 120
Body Mass Index (kilograms/meter²)	N=263	N=73	N=75	N=190
Mean	26.2	26.4	26.3	26.2
(SD)	(4.17)	(4.58)	(3.54)	(4.02)
Min, Max	18, 41	20, 41	15, 38	18, 41
Race (percent)	N=231	N=73	N=75	N=158
Am. Ind./Al. Nat.	0	0	0	0
Asian	0.4	0	0	0.6
Black/Af. Am.	0.4	0	0	0.6
Hispanic/Latino	0.9	0	0	1.3
Caucasian	98.3	100	100	97.5
Other	0	0	0	0
Baseline Disease Severity (percent)	N=265	N=73	N=75	N=192
Mild	15.5	12.3	18.7	16.7
Moderate	63.4	69.9	64.0	60.9
Severe	21.1	17.8	17.3	22.4
Missing	0	0	0	0

Table 5: Demographic Characteristics of Subjects in the Pooled NT 201 Spasticity Studies, Overall and by Study

Characteristic	Pooled Spasticity ¹		0410/1 Main Period	
	NT 201	NT 201	Placebo	0607 NT 201
Pre-treatment with Botulinum Toxin (percent)	N=265	N=73	N=75	N=192
Treatment-naive	55.8	83.6	86.7	45.3
Pre-treated	44.2	16.4	13.3	54.7

¹ The placebo group in the pooled spasticity studies is from the Study 0410/1 Main Period, and is shown under that study in this table.

Af. Am.: African American; Al. Nat.: Alaskan native; Am. Ind.: American Indian; SD: standard deviation.

Source: Table 2.1.2.3.1.1, Table 2.3.2.1.1.1, Table 2.3.2.2.1.1, Table 2.3.2.3.1.1, Table 2.3.2.3.2.1.1, Table 2.3.2.3.2.2.1, Table 2.4.2.3.1.2, Table 2.4.2.3.2.1.1, Table 2.4.2.3.2.2.1, Table 2.5.2.3.1.1, Table 2.5.2.3.2.1.1, Table 2.5.2.3.2.2.1, Table 2.6.2.3.1.1, Table 2.6.2.3.2.1.1, Table 2.6.2.3.2.2.1, Table 2.7.2.3.1.1, Table 2.7.2.3.2.1.1, Table 2.7.2.3.2.2.1, Table 2.8.2.3.1.1, Table 2.8.2.3.2.1.1, and Table 2.8.2.3.2.2.1, Section 5.3.5.3, Appendix H.

Reviewer comment: I reviewed the table above and found the demographics to be similar between the two treatment groups (NT 201 and placebo).

7.2.2 Explorations for Dose Response

Reviewer comment: Dose-response analyses should ideally be performed in fixed dose studies, due to confounding by disease severity in flexible dose studies. This limitation should be kept in mind with respect to dose-response analyses in the NT 201 development program.

7.2.2.1 Dose Response: Deaths

Due to the small number of deaths (only three in NT 201-treated patients), a credible dose-response analysis could not be performed.

7.2.2.2 Dose Response: SAEs

7.2.2.2.1 Dose Response: SAEs: Pooled Indications

The sponsor prepared the table below summarizing SAEs (presented by SOC) occurring in the pooled, controlled studies related to NT 201 dose.

Table 19: SOC SAEs by NT 201 Dose Group

(Adapted from Sponsor Table 5.3.5.3-13, ISS, pg. 41)

MedDRA System Organ Class Preferred Term	Overall NT 201 N=1313	Overall NT 201 (Placebo- controlled studies) N=618	Overall Placebo N=346	NT 201 Dose Group (Units) (Placebo-controlled studies)				
				≤40 N=325	>40-120 N=138	>120-240 N=98	>240- 360 N=36	>360 N=21
Subjects with Serious Adverse Events	38 (2.9%)	15 (2.4%)	2 (0.6%)	7 (2.2%)	0	6 (6.1%)	1 (2.8%)	1 (4.8%)
Nervous system disorders	8 (0.6%)	1 (0.2%)	1 (0.3%)	-	-	1 (1.0)	-	-
Gastrointestinal disorders	6 (0.5%)	1 (0.2%)	-	1 (0.3%)	-	-	-	-
Infections and infestations	6 (0.5%)	3 (0.5%)	-	-	-	3 (3.1%)	-	-
Respiratory, thoracic and mediastinal disorders	3 (0.2%)	3 (0.5%)	1 (0.3%)	-	-	2 (2.0%)	-	1 (4.8%)
Vascular disorders	3 (0.2%)	1 (0.2%)	-	-	-	-	1 (2.8%)	-
Ear and labyrinth disorders	2 (0.2%)	1 (0.2%)	-	-	-	-	1 (2.8%)	-
Injury, poisoning and procedural complications	2 (0.2%)	2 (0.3%)	-	2 (0.6%)	-	-	-	-
Neoplasms: malignant, benign, and unspecified	2 (0.2%)	-	-	-	-	-	-	-
Renal and urinary disorders	2 (0.2%)	1 (0.2%)	-	1 (0.3%)	-	-	-	-
Reproductive system and breast dis.	2 (0.2%)	1 (0.2%)	-	1 (0.3%)	-	-	-	-
Skin and subcutaneous tissue dis.	2 (0.2%)	-	-	-	-	-	-	-
Cardiac disorders	1 (0.1%)	-	-	-	-	-	-	-
Congenital, familial and genetic dis.	1 (0.1%)	1 (0.2%)	-	1 (0.3%)	-	-	-	-
Eye disorders	1 (0.1%)	-	-	-	-	-	-	-
General disorders and administration site conditions	1 (0.1%)	1 (0.2%)	-	1 (0.3%)	-	-	-	-
Psychiatric disorders	1 (0.1%)	-	-	-	-	-	-	-

MedDRA System Organ Class Preferred Term	Overall NT 201 N=1313	Overall NT 201 (Placebo- controlled studies) N=618	Overall Placebo N=346	NT 201 Dose Group (Units) (Placebo-controlled studies)				
				≤40 N=325	>40-120 N=138	>120-240 N=98	>240- 360 N=36	>360 N=21
Surgical and medical procedures	1 (0.1%)	1 (0.2%)	-	1 (0.3%)	-	-	-	-

*** indicates that no subject had an event in that category. MedDRA: Medical Dictionary for Regulatory Activities
The pooled, controlled studies were: 0498/1 (CD) Main Period, 0913 (CD), 0410/1 (SP) Main Period, 0607 (SP), 0433/1 (BEB) Main Period, 0093 (BEB), 0520/1 (GFL) Main Period, 0527 (GFL), and 0617 (CF). The pooled, placebo-controlled studies were: 0408/1 (CD) Main Period, 0410/1 (SP) Main Period, 0433/1 (BEB) Main Period, 0520/1 (GFL) Main Period, 0527 (GFL).
Source: Table 3.3.1.1.1 and Table 3.3.9.1.1, Section 5.3.5.3, Appendix H.

Merz cautioned that because the dose of NT 201 varied widely across indications, with oldest (i.e., the BEB population) and sickest (i.e., the post-stroke SP population) subjects represented primarily in the lowest and highest dose groups, it is difficult to assess the incidence of SAEs by total dose group in the pooled, controlled studies. However, when SAEs are examined by total NT 201 dose at the SOC and PT levels, the sponsor stated that the number of individual SAEs was low (most events occurred in only one subject), and no pattern of increased incidence of certain events with higher NT 201 dose could be discerned (see Table 1, ISS Appendix D).

Reviewer comment: I concur with the sponsor's assessment that there are too few events to support a dose-response analysis for SAEs, and that general review of the SAEs does not demonstrate any particular pattern.

7.2.2.2.2 Dose Response: SAEs: BEB

In the Study 0433/1 Main Period and 0433/2 OLEX Period, Merz reported that the incidence of SAEs was higher in subjects who received 10 to 40 U of NT 201, compared with those who received >40 U of NT 201. Six of 27 subjects in the 10 to 40 U group (22.2%), compared with 4 of 79 subjects in the >40 U group (5.1%), experienced SAEs. Although it appears that the incidence of SAEs does not increase with higher NT 201 doses in the treatment of BEB, because

of the small number of subjects with SAEs, it is not possible to draw reliable conclusions based on these data (BEB ISS 120 Day Safety Update, pg. 23).

7.2.2.2.3 Dose Response: SAEs: CD

In the Study 0408/1 Main Period and 0408/2 Extension Period (analyzed together), Merz stated that there were 15 SAEs. These 15 included:

- 2 of 48 subjects (4.2%) in the ≤ 120 U treatment group
- 10 of 118 subjects (8.5%) in the >120 to 240 U group
- 3 of 61 subjects (4.9%) in the group whose dose in Study 0408/2 Extension Period remains blinded (Table 2.2.1.1, ISS Appendix J).

From the limited dose data available, the sponsor concluded that SAEs do not increase with higher NT 201 dose (CD ISS, pg 33).

Reviewer comment: As noted previously, the number of SAEs in any single indication is insufficient to support a dose-response analysis. An analysis of pooled data by SOC, rather than individual SAEs is presented in Section 7.2.2.2.1 of this review.

7.2.2.2.4 Dose Response: SAEs: SP

In the pooled SP studies (the Study 0410/1 Main Period and Study 0607), in the NT 201 treatment group 1 of 16 subjects (6.3%) receiving ≤ 120 U, 3 of 67 subjects (4.5%) receiving >120 to 240 U, and 7 of 121 subjects (5.8%) receiving >240 U experienced SAEs (SP ISS, pg. 33).

Reviewer comment: The risk of SAEs in SP patients treated with NT 201 did not demonstrate a dose-response pattern, but the analysis was based on a small number of patients and events.

7.2.2.3 Dose Response: Common Adverse Events

7.2.2.3.1 Dose Response: Common Adverse Events: Pooled Indications

Reviewer comment: Due to the differences in dosing for the various indications, pooled data should not be used in a dose-response analysis. The effect of dose on common adverse events is therefore discussed in the individual indications below.

7.2.2.3.2 Dose Response: Common Adverse Events: BEB

In the Main Period of Study 0433/1, patients could receive up to 100 U of NT 201 (50 U per eye). Merz stated that patients in this study received a mean dose of 64.8 U of NT 201. The sponsor noted that patients receiving doses >40 U had higher incidences of TEAEs (e.g., eyelid ptosis, 15.4% 10-40 U and 19.7% >40 U), but had “no unexpected toxicity.” Merz noted that the

recommended total dose of NT 201 for the treatment of BEB is up to (b) (4) (BEB ISS, pg. 56). “Common” ($\geq 1\%$) and “Very Common” ($\geq 10\%$) adverse events by dose group summarized below.

Table 20: Common and Very Common Adverse Events in NT 201-Treated Patients within Placebo-controlled Study 0433/1

(Adapted from Sponsor Table 15, BEB ISS, pg. 26)

Table 15: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events in the NT 201 Treatment Group, Study 0433/1 Main Period

MedDRA System Organ Class Preferred Term	NT 201 Overall N=74	Placebo Overall N=34	NT 201 10-40 U N=13	NT 201 >40 U N=61
Subjects with TEAEs	52 (70.3%)	21 (61.8%)	7 (53.9%)	45 (73.8%)
Eye disorders	28 (37.8%)	7 (20.6%)	5 (38.5%)	23 (37.7%)
Eyelid ptosis	14 (18.9%)	3 (8.8%)	2 (15.4%)	12 (19.7%)
Dry eye	12 (16.2%)	4 (11.8%)	3 (23.1%)	9 (14.8%)
Vision blurred	4 (5.4%)	2 (5.9%)	-	4 (6.6%)
Visual impairment	5 (6.8%)	-	-	5 (8.2%)
Lacrimation increased	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Gastrointestinal disorders	22 (29.7%)	5 (14.7%)	5 (38.5%)	17 (27.9%)
Dry mouth	12 (16.2%)	1 (2.9%)	4 (30.8%)	8 (13.1%)
Diarrhoea	6 (8.11%)	-	1 (7.7%)	5 (8.2%)
Dysphagia	3 (4.1%)	2 (5.9%)	1 (7.7%)	2 (3.3%)
Lip disorder	2 (2.7%)	-	-	2 (3.3%)
Infections and infestations	15 (20.3%)	5 (14.7%)	3 (23.1%)	12 (19.7%)
Nasopharyngitis	4 (5.4%)	1 (2.9%)	1 (7.7%)	3 (4.9%)
Respiratory tract infection	4 (5.4%)	1 (2.9%)	-	4 (6.6%)
Gastroenteritis viral	2 (2.7%)	-	-	2 (3.3%)
Urinary tract infection	2 (2.7%)	-	-	2 (3.3%)
Nervous system disorders	10 (13.5%)	3 (8.8%)	2 (15.4%)	8 (13.1%)
Headache	5 (6.8%)	1 (2.9%)	1 (7.7%)	4 (6.6%)
General disorders and administration site conditions	8 (10.8%)	3 (8.8%)	1 (7.7%)	7 (11.5%)
Asthenia	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Injection site haematoma	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Injection site pain	2 (2.7%)	-	-	2 (3.3%)
Musculoskeletal and connective tissue disorders	4 (5.4%)	7 (20.6%)	1 (7.7%)	3 (4.9%)
Respiratory, thoracic and mediastinal disorders	8 (10.8%)	1 (2.9%)	-	8 (13.1%)
Dyspnoea	4 (5.4%)	1 (2.9%)	-	4 (6.6%)
Injury, poisoning and procedural complications	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Muscle strain	2 (2.7%)	-	-	2 (3.3%)
Investigations	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Metabolism and nutrition disorders	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Ear and labyrinth disorders	2 (2.7%)	-	-	2 (3.3%)
Reproductive and breast disorders	2 (2.7%)	-	-	2 (3.3%)

Data are presented as number of subjects (percent of subjects).

“-“ indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: Treatment-emergent adverse event; U: units.

Source: Table 3.1.1.2.2.2.2.2 and Table 3.1.9.2.2.2.2.2, Section 5.3.5.3, Appendix H.

Reviewer comment: In the table above, dyspnea occurs to a greater extent in the NT 201 treatment group (5.4%) compared to the placebo group (2.9%).. Although ptosis and dry mouth

are established AEs associated with botulinum toxin for BEB, the occurrence of dyspnea is not expected.

7.2.2.3.3 Dose Response: Common Adverse Events: CD

Merz reported that common treatment-emergent adverse events (TEAEs) in any NT 201 treatment group) observed in patients who received NT 201 (120 U; 240 U) or placebo in the CD indication included dysphagia (13%; 19%, 3%, respectively), neck pain (6%; 15%, 4%, respectively), muscle weakness (6%; 11%, 1%, respectively), injection site pain (9%; 4%, 7%, respectively), musculoskeletal pain (6%; 4%, 1%, respectively), nausea (3%; 5%, 0%, respectively), headache (3%; 5%, 4%, respectively), and musculoskeletal stiffness (1%; 5%, 1%, respectively)(Clinical Overview, pg. 28).

Reviewer comment: *In the list of adverse events above, with the exception of injection site pain, all of the adverse events show a greater risk when patients are treated with 240 U compared to 120 U, and in all cases the risk with 240 U substantially exceeds placebo.*

Of note is the relatively large number of patients who experience dysphagia when treated with 240 U, nearly 20%, or one in five. The risk of nausea in patients treated with 120 U (3%) and 240 U (5%) was also elevated compared to placebo (0%). These two events raise the question of whether they represent evidence of systemic spread beyond the injection site. Dysphagia is commonly observed after treatment for CD in other development programs. Dysphagia was the most frequently reported adverse reaction in clinical trials for Botox® and one of the most common in the double blind placebo controlled trials for Dysport®, according to the labeling for those drugs.. However, as shown in the table below, the number of patients experiencing these events was small (only 6 NT 201-treated CD patients reported nausea), and the risk estimations are therefore not very robust. For further consideration of whether a dose-response effect is apparent for NT 201 CD development program with respect to adverse events, please see also Section 7.2.2 of this review

The table below displays the Very Common ($\geq 10\%$) and Common (≥ 1) adverse events within the placebo-controlled CD trial 0408.

Table 21: Very Common (Occurring in ≥ 10) and Common Adverse Events (Occurring in $\geq 1\%$) within CD Study 0408 Main Period

(Adapted from Sponsor Table 18, CD ISS, pg. 39)

Table 18: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events by NT 201 Dose Group, Study 0408/1 Main Period

MedDRA System Organ Class Preferred Term	NT 201 120 U ¹ N=77	NT 201 240 U ¹ N=82	Placebo N=74
Subjects with TEAEs	44 (57.1%)	45 (54.9%)	31 (41.9%)
Musculoskeletal and connective tissue disorders	18 (23.4%)	26 (31.7%)	8 (10.8%)
Neck pain	5 (6.5%)	12 (14.6%)	3 (4.1%)
Muscular weakness	5 (6.5%)	9 (11.0%)	1 (1.4%)
Musculoskeletal pain	5 (6.5%)	3 (3.7%)	1 (1.4%)
Muscle spasms	1 (1.3%)	3 (3.7%)	2 (2.7%)
Musculoskeletal stiffness	1 (1.3%)	4 (4.9%)	1 (1.4%)
Back pain	1 (1.3%)	1 (1.2%)	2 (2.7%)
Myalgia	1 (1.3%)	2 (2.5%)	-
Pain in extremity	-	3 (3.7%)	-
Table continues			
Gastrointestinal disorders	14 (18.2%)	20 (24.4%)	3 (4.1%)
Dysphagia	10 (13.0%)	15 (18.3%)	2 (2.7%)
Nausea	2 (2.6%)	4 (4.9%)	-
Dry mouth	1 (1.3%)	1 (1.2%)	-
Toothache	2 (2.6%)	-	-
Nervous system disorders	12 (15.6%)	14 (17.1%)	5 (6.8%)
Headache	2 (2.6%)	4 (4.9%)	3 (4.1%)
Dizziness	2 (2.6%)	2 (2.5%)	1 (1.4%)
Hypoaesthesia	2 (2.6%)	1 (1.2%)	-
Burning sensation	1 (1.3%)	1 (1.2%)	-
Head titubation	1 (1.3%)	1 (1.2%)	-
Somnolence	1 (1.3%)	1 (1.2%)	-
Head discomfort	-	2 (2.5%)	-
Paraesthesia	-	2 (2.5%)	-
Syncope vasovagal	-	2 (2.5%)	-
General disorders and administration site conditions	12 (15.6%)	9 (11.1%)	8 (10.8%)
Injection site pain	7 (9.1%)	3 (3.7%)	5 (6.8%)
Asthenia	1 (1.3%)	2 (2.5%)	-
Influenza like illness	1 (1.3%)	1 (1.2%)	-
Infections and infestations	11 (14.3%)	11 (13.4%)	8 (10.8%)
Sinusitis	2 (2.6%)	3 (3.7%)	2 (2.7%)
Nasopharyngitis	3 (3.9%)	-	5 (6.8%)

Reviewer comment: *In the table above, the overall risk of common adverse event for CD patients is similar across doses: 57% in the 120 U group, 55% in the 240 U group and 42% in placebo. However, when restricted to common adverse events most likely to be caused by the drug (based on the frequency of events, the difference from placebo and past experience with other botulinum toxin products), these events appear to demonstrate a dose-response (For example dysphagia (13% 120U; 19% 240 U, 3% placebo), neck pain (6% 120 U, 15% 240 U, 4% placebo), muscle weakness (6% 120 U; 11% 240 U, 1% placebo).*

I believe that there is a dose-response effect demonstrated within this study, with the 240 U dose having a greater risk of adverse events. I believe the reason that the overall risk is similar for the 120 U and 240 U groups is that the table above includes many incidental adverse events unlikely to be drug related (somnolence, sinusitis, syncope, etc) and these obscure the dose-response in the adverse events that are most likely to be drug related.

The following table summarizes the occurrence of common adverse events in the CD development program stratified by dose and number of injections (CD ISS, pg. 25).

Table 22: Overall Summary of Patients with Adverse Events by Dose and Number of Injections within the CD Placebo-Controlled CD Trial 0408/1

(Adapted from Sponsor Table 12, CD ISS, pg. 25)

Table 12: Overall Summary of Patients with Adverse Events and Patients with Adverse Events by Injection Interval as of 25-Jun-2009, Studies 0408/1(CD) Main Period and 0408/2 (CD) Extension Period – 120-day Safety Update Data

Injection Number	Mean Total Dose Group			Overall
	≤120 Units	>120 to 240 Units	Still Blinded	
TEAEs – Overall	40/48 (83.3%)	99/118 (83.9%)	55/61 (90.2%)	194/227 (85.5%)
Injection Session 1	26/48 (54.2%)	67/118 (56.8%)	31/61 (50.8%)	124/227 (54.6%)
Injection Session 2	18/41 (43.9%)	52/107 (48.6%)	39/59 (66.1%)	109/207 (52.7%)
Injection Session 3	17/38 (44.7%)	39/90 (43.3%)	25/55 (45.5%)	81/183 (44.3%)
Injection Session 4	10/31 (32.3%)	34/79 (43.0%)	27/51 (52.9%)	71/161 (44.1%)
Injection Session 5	7/20 (35.0%)	25/63 (39.7%)	11/39 (28.2%)	43/122 (35.3%)
Injection Session 6	2/7 (28.6%)	14/36 (38.9%)	8/18 (44.4%)	24/61 (39.3%)

Table presents number of patients with TEAEs/number of patients at risk (percent of patients with TEAEs). Subjects are categorized by dose group according to their randomized dose of NT 201 in the Study 0408/2 Extension Period.

CD: cervical dystonia; TEAE: treatment-emergent adverse event

“-” indicates category not applicable.

Source: Table 2.1.1.1 and Table 3.1.1.1, Section 5.3.5.3, Appendix J

Reviewer comment: As noted elsewhere in this review, the apparent lessening of adverse event risk with increasing number of injections is likely a survivor bias, in which patients who experienced bothersome adverse events withdrew from the study prior to receiving additional injections.

7.2.2.3.3 Dose Response: Common Adverse Events: SP

Merz presented adverse events as related to various dose groups in the table below.

Table 23: Common Adverse Events (>1%) in the 410/1 Main Period
(Adapted from Sponsor Table 19, Spasticity ISS, pg. 37)

MedDRA System Organ Class Preferred Term	NT 201 Overall N=73	Placebo Overall N=75	NT 201 >120-240 U N=17	NT 201 >240-360 U N=35	NT 201 >360 U N=21
Subjects with TEAEs	21 (28.8%)	20 (26.7%)	5 (29.4%)	9 (25.7%)	7 (33.3%)
Metabolism and nutrition disorders					
Hyperglycaemia	6 (8.2%)	3 (4.0%)	2 (11.8%)	1 (2.9%)	3 (14.3%)
Hypercholesterolaemia	3 (4.1%)	-	1 (5.9%)	-	2 (9.5%)
Hypercholesterolaemia	2 (2.7%)	1 (1.3%)	1 (5.9%)	-	1 (4.8%)
Nervous system disorders	5 (6.9%)	7 (9.3%)	1 (5.9%)	3 (8.6%)	1 (4.8%)
Headache	2 (2.7%)	1 (1.3%)	-	1 (2.9%)	1 (4.8%)
Epilepsy	2 (2.7%)	-	1 (5.9%)	1 (2.9%)	-
Injury, poisoning and procedural complications	5 (6.9%)	2 (2.7%)	1 (5.9%)	3 (8.6%)	1 (4.8%)
Gastrointestinal disorders	3 (4.1%)	5 (6.7%)	1 (5.9%)	1 (2.9%)	1 (4.8%)
Diarrhoea	2 (2.7%)	2 (2.7%)	-	1 (2.9%)	1 (4.8%)
General disorders and administration site conditions	3 (4.1%)	3 (4.0%)	1 (5.9%)	2 (5.7%)	1 (4.8%)
Infections and infestations	2 (2.7%)	5 (6.7%)	2 (11.8%)	-	-
Investigations	2 (2.7%)	1 (1.3%)	1 (5.9%)	-	1 (4.8%)

Data are presented as number of subjects (percent of subjects).

“-” indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: Treatment-emergent adverse event; U: units.

Source: Table 3.1.1.2.3.2.1.2 and Table 3.1.9.2.3.2.1.2, Section 5.3.5.3, Appendix H.

Reviewer comment: Although the sponsor prepared the table above, they noted that there were two few AEs to perform any analyses at the Preferred Term (PT) level. This next table shows common AEs in the SP indication categorized by SOC and dose groups.

FDA Table 23: Adverse Events Occurring in the Study 0410/1 Main Period and 0410/2 OLEX Period Overall and by MedDRA System Organ Class (Adapted from Sponsor Table 20, SP ISS, pg.37)

Table 20: Treatment-Emergent Adverse Events Occurring in the Study 0410/1 Main Period and 0410/2 OLEX Period as of 25-Jun-2009, Overall and by MedDRA System Organ Class

	Mean Total Dose Group			Overall N=147
	>120 -240 Units N=10	>240 - 360 Units N=52	>360 Units N=85	
Overall	6 (60.0%)	30 (57.7%)	54 (63.5%)	90 (61.2%)
Nervous system disorders	1 (10.0%)	10 (19.2%)	19 (22.4%)	30 (20.4%)
Infections and infestations	1 (10.0%)	11 (21.2%)	17 (20.0%)	29 (19.7%)
Investigations	2 (20.0%)	5 (9.6%)	7 (8.2%)	14 (9.5%)
Musculoskeletal and connective tissue disorders	1 (10.0%)	3 (5.8%)	10 (11.8%)	14 (9.5%)
Metabolism and nutrition disorders	2 (20.0%)	3 (5.8%)	8 (9.4%)	13 (8.8%)
Gastrointestinal disorders	1 (10.0%)	4 (7.7%)	7 (8.2%)	12 (8.2%)
General disorders and administration site conditions	-	7 (13.5%)	4 (4.7%)	11 (7.5%)
Injury, poisoning and procedural complications	-	7 (13.5%)	3 (3.5%)	10 (6.8%)
Vascular disorders	1 (10.0%)	1 (1.9%)	7 (8.2%)	9 (6.1%)
Psychiatric disorders	-	3 (5.8%)	6 (7.1%)	9 (6.1%)
Blood and lymphatic system disorders	1 (10.0%)	-	5 (5.9%)	6 (4.1%)
Respiratory, thoracic and mediastinal disorders	-	4 (7.7%)	1 (1.2%)	5 (3.4%)
Neoplasms benign, malignant and unspecified	-	2 (3.9%)	2 (2.4%)	4 (2.7%)
Reproductive system and breast disorders	-	2 (3.9%)	2 (2.4%)	4 (2.7%)
Skin and subcutaneous tissue disorders	-	1 (1.9%)	3 (3.5%)	4 (2.7%)
Endocrine disorders	1 (10.0%)	1 (1.9%)	1 (1.2%)	3 (2.0%)
Renal and urinary disorders	-	1 (1.9%)	2 (2.4%)	3 (2.0%)
Cardiac disorders	-	-	2 (2.4%)	2 (1.4%)
Eye disorders	-	-	2 (2.4%)	2 (1.4%)
Surgical and medical procedures	-	-	2 (2.4%)	2 (1.4%)
Congenital, familial and genetic disorders	-	1 (1.9%)	-	1 (0.7%)
Ear and labyrinth disorders	-	-	1 (1.2%)	1 (0.7%)

Data are presented as number of subjects (percent of subjects).

MedDRA: Medical Dictionary for Regulatory Activities; OLEX: Open-label Extension Period.

Source: Table 2.1.1.1, ISS Appendix I.

Reviewer comment: *The only SOC showing a potential dose-response pattern is Nervous System Disorders, with 10% of patients receiving 120 to 240 U with AEs, 19% of patients receiving between 240 and 360 U, and in 22% of patient receiving >360 Units. It is worth noting, however, that the 120 to 240 U category has only 1 patient, compared to 52 and 85 patients in the other two dose categories.*

7.2.3 Special Animal and/or In Vitro Testing

The sponsor performed several preclinical studies regarding cardiac function (including hERG channel screening) and animal studies addressing prenatal exposure. These studies are discussed in this review in Section 7.4.4.1 and Section 7.6.3 of this review, respectively.

Additional preclinical studies related to drug safety performed by the sponsor are summarized below¹²:

- **Genotoxicity:** No mutagenicity studies have been conducted in accordance with the guidance.
- **Carcinogenicity:** No carcinogenicity studies have been conducted, likewise in accordance with the guidance.
- **Single dose toxicity studies.** These were done in mouse and Sprague Dawley rats. The LD 50 ranged from 50 (given intravenously) to 100,000 (orally) with the maximum lethal dose causing death within 48 hours to 5 days. All animals at 150 LDU/kg died prematurely 3 to 8 days after injection and one treated with 50 LDU/kg died prematurely on day 5. There was also a decrease in body weight and body weight gain at doses of 50 and 150 LDU/kg. The calculated LD 50 of 41 and 87 LDU/kg was established for males and females respectively. The results indicated that 5 LDU/kg can be considered as the NOAEL for a single intramuscular injections of NT 201 in mice, however, there was no LD 50 determined on the IM administration. In male Sprague-Dawley rats, maximum paralysis score was reached by all animals from 48 to 96 hours after treatment at 32 and 64 LDU/kg.
- **Repeat dose toxicity studies:** Doses given above 10 LDU/kg every 2 to 4 weeks caused death when given intramuscularly in the rabbits. Repeat dose toxicity studies done in the cynomolgus monkeys who were given doses as high as 12 LDU/kg in 4 weeks for 10 injections resulted in atrophied gastrocnemius muscle fibers. There were no treatment related effects on ophthalmology, cardiovascular function, food consumption, hematology, serum chemistry and urinary parameters. Based on this dose, the NOAEL for toxicity is >4 times higher than the maximal recommended human dose.
- **Local tolerance toxicity:** No clinically relevant local injection site reactions after repeated intramuscular injection up to 40 LDU/kg or repeated intradermal administration up to 8.34 LDU/kg.
- **Locomotor activity:** The results were dose dependent and the reduction in motility parameters was observed starting at 20 LDU/kg. The NOAEL for motility parameters after a single IV injection is 9 LDU/kg which is approximately 1.3 fold greater than maximum clinical dose in humans (7.24 LDU/kg for 60 kg patient).
- **CNS Toxicity:** No specific studies were done to assess for CNS toxicity. Studies in the mouse at repeated doses with an approximate D 50 of 50 LDU/kg showed clinical signs of piloerection, ptosis, lacrimation, mydriasis, reduced motility, muscular tonus, ataxia, hypothermia and dyspnea.

¹² The description of some of the preclinical studies in this section were adapted from the review of NT 201 efficacy for the CD indication, prepared by Dr. Anne Constantino. The source information is from the sponsor's summary, and not from the FDA's Pharmacology-Toxicology review.

- **GI toxicity:** NT 201 did not show any effect on intestinal transit. The NOAEL of a single intramuscular injection of NT 201 for effects on gastro-intestinal motility in rats is 32 LDU/kg which is 4.5 fold greater than the maximum human clinical dose.
- **Dose-Response:** In the first study, the sponsor stated that after repeated administration of NT 201 to rabbits, no neutralizing antibodies were formed in the NT 201 group. In contrast, Merz stated that in each Botox group, at least 20% of animals developed neutralizing antibodies (Clinical Overview, pg. 15). A second relevant animal study comparing NT 201, Dysport® and Botox® found that the degree and duration of hind limb muscle paralysis in rodents was dose-dependent. Merz stated that the effects of the selected doses of NT 201 and Botox® were almost equipotent in terms of strength and length of the paralysis. The time to onset of paralysis was not found to be dose-related and the sponsor reported that onset did not differ between NT 201, Botox® and Dysport®. The maximal paralytic effect was reached within days after the injections with all three botulinum toxin preparations (Clinical Overview, pg. 14/Nonclinical Overview, pg. 8).
- **Time to Effect Onset:** Merz analyzed the paralytic effect of NT 201 and Botox® through electromyography (EMG) *in vivo* in Cynomolgus monkeys. NT 201 induced a maximum inhibition of EMG activity one week after treatment (Nonclinical Overview, pg. 5).

The sponsor also includes the following summary of animal testing in their proposed labeling (Labeling Section 13.2, Animal Toxicology and/or Pharmacology):



7.2.4 Routine Clinical Testing

7.2.4.1 Routine Clinical Testing: BEB

Merz stated that safety monitoring in the BEB studies included physical examination, neurological examination, adverse event assessment, routine hematology and chemistry, vital signs, Dysphagia Score (DS), Investigator’s Global Assessment of Tolerability (GAT), and assays for Botulinum toxin antibodies (Clinical Overview, pg. 37). Safety testing performed in the BEB studies are shown below.

Table 24: Safety Assessments in the NT 201 BEB Studies

(Adapted from Sponsor Table 3, 0433 Final Study Report, pg. 37)

Table 3: Safety Assessments Performed in the NT 201 Benign Essential Blepharospasm Studies

Assessment	Study			
	0433/1 MP	0433/2 OLEX	0003	0703
Physical and neurological exam	X	X	X	X
Adverse events	X ¹	X ¹	X	X
Hematology and biochemistry	X	X	X	X
Vital signs	X	X	X	X
Electrocardiogram ²	X	X	X	-
Investigator’s Global Assessment of Tolerability	X	X	X	X
Antibodies to Botulinum toxin ³	X	X	X	X

¹ In accordance with the FDA request during a Special Protocol Assessment for Study 0433 (Special Protocol Assessment Response Letter, Protocol MRZ6021-0433, October 31, 2005), subjects were questioned at every study visit about the following events: drooping of the eyelid, problems with his/her vision, dry mouth, swallowing difficulties, speech problems, shortness of breath, respiratory infection, local weakness, facial weakness, general body weakness, stomach or bowel disturbances.

Reviewer comment: In response to an FDA request, Merz specified that vital signs and other testing were performed prior to injection during the study visits (See also Section 7.4.3 of this review).

7.2.4.2 Routine Clinical Testing: CD

Table 25: Safety Assessments in the NT 201 SP Studies

(Adapted from Sponsor Table 3, BEB ISS, pg. 11)

Table 3: Safety Assessments Performed in the NT 201 Benign Essential Blepharospasm Studies

Assessment	Study			
	0433/1 MP	0433/2 OLEX	0003	0703
Physical and neurological exam	X	X	X	X
Adverse events	X ¹	X ¹	X	X
Hematology and biochemistry	X	X	X	X
Vital signs	X	X	X	X
Electrocardiogram ²	X	X	X	-
Investigator's Global Assessment of Tolerability	X	X	X	X
Antibodies to Botulinum toxin ³	X	X	X	X

¹ In accordance with the FDA request during a Special Protocol Assessment for Study 0433 (Special Protocol Assessment Response Letter, Protocol MRZ6021-0433, October 31, 2005), subjects were questioned at every study visit about the following events: drooping of the eyelid, problems with his/her vision, dry mouth, swallowing difficulties, speech problems, shortness of breath, respiratory infection, local weakness, facial weakness, general body weakness, stomach or bowel disturbances.

7.2.4.3 Routine Clinical Testing: CD

Merz stated that safety monitoring in the CD studies included physical examination, neurological examination, adverse event assessment, routine hematology and chemistry, vital signs, Dysphagia Score (DS), Investigator's Global Assessment of Tolerability (GAT), and assays for Botulinum toxin antibodies (Clinical Overview, pg. 27).

The table below shows the testing performed in the individual CD studies.

Table 26: Safety Assessments in the NT 201 CD Studies

(Sponsor Table 3, CD ISS, pg. 12)

Table 3: Safety Assessments Performed in the NT 201 Cervical Dystonia Studies

Assessment	0408/ 1 MP	0408/ 2 EXT	0013	9801	0605/ 1 MP	0605/ 2 OLE X
Physical and neurological exam	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Hematology and biochemistry	X	X	X	X	X	X
Vital signs	X	X	X	-	X	X
Electrocardiogram	X ¹	X ¹	X	-	X ¹	X ¹
Dysphagia score	X	X	X	X	X	X
Investigator's Global Assessment of Tolerability	X	X	X	X	-	-
Antibodies to Botulinum toxin ²	X	X	X	-	-	-

¹ In Studies 0408 and 0605, electrocardiograms were performed at Screening/study entry only.

² Subjects in Study 0408 were screened at each visit using the Fluorescence Immuno Assay for Antibodies. Subjects in Study 0013 were screened using enzyme-linked immunosorbent assay. All samples that tested positive, at any time point, underwent confirmatory testing for neutralizing antibodies using the mouse *ex vivo* hemidiaphragm assay.

X: indicates that the assessment was performed; - indicates that the assessment was not performed.

EXT: Extension (Period); MP: Main Period; OLEX: Open-label Extension (Period).

7.2.4.4 Routine Clinical Testing: SP

The sponsor stated that Safety monitoring within the BEB studies included physical examination, neurological examination, adverse event assessment, routine hematology and chemistry, vital signs, Investigator's Global Assessment of Tolerability, and assays for Botulinum toxin antibodies (Clinical Overview, pg. 29).

7.2.5 Metabolic, Clearance, and Interaction Workup

After systemic absorption, Merz explained that the NT 201 neurotoxin is rapidly metabolized to smaller molecular structures. White blood cells play a role in the disposal of circulating toxin type A as shown for other proteins. The neurotoxin is then degraded intracellularly. Like all proteins, Botulinum toxin type A is rapidly metabolized by proteases and molecular components are recycled through normal metabolic pathways.

Both bioavailability and storage ability of BoNT/A are affected by accompanying complex proteins. (b) (4) (b) (4) (b) (4)

Pharmacokinetic interactions between proteins and NT 201 after intramuscular injections are not expected.¹³

¹³ This paragraph adapted from the CD efficacy review prepared by Dr. Anne Constantino.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Within this review, adverse events that were evaluated in detail due to their occurrence in other botulinum toxin products are:

1. Adverse Events of Special Interest (AESIs) as defined by a list created by the FDA and the sponsor during the pre-BLA period (see Section 7.3.5 of this review)
2. Any symptom or pattern suggesting systemic spread (see Section 7.3.5.2 of this review)
3. Hyperglycemia (See Section 7.3.5.3 of this review)
4. Elevation in Alkaline Phosphatase (See Section 7.3.5.4 of this review)

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 Death Overview

There were a total of six deaths in patients within the NT 201 development program for all indications (including the non-neurologic indications): two in patients treated with placebo, one in a patient treated with Botox® and three in patients treated with NT 201. The three deaths in the NT 201-treated patients all occurred within the spasticity indication studies, and all three were during the OLEX period.

Reviewer comment: The sponsor noted that Subject 1001 in Study 0607 (SP) experienced a fatal myocardial infarction during the screening period of the study prior to receiving drug treatment. The sponsor did not include this deaths in the list of analyzable deaths, and I agree with this exclusion.

The table below summarizes the deaths within the NT 201 development program. More detailed narratives are provided in Appendix 7.3.1.2 of this review.

FDA Table 25: Total Deaths within the Xeomin Development Program

(Adapted from Sponsor Text, ISS 120-Day Safety Update, pg. 41-45)

INDICATION: SPASTICITY
Xeomin-Treated Patients

Patient ID # Study*	Age/ Gender/ Total Injections and Dosing*	Cause of Death	Days from Last Inj. Until Death (Last dosage)	Clinical Summary
Patient 1054 Study 0410 OLEX	72/ Male 1 injection in OLEX phase	Died in Sleep, Cause Unknown	136 days (375 U)	Died in sleep without autopsy. History of multiple CV risk factors: CAD, hypertension, prior aortic aneurysm, and a former smoker. History of CVA prior to the study and experienced a second CVA one week prior to death. Treated with Botox prior to study.
Patient 1058 Study 0410 OLEX	67/ Male 2 injs. in OLEX phase	“Cardiac Arrest”	44 days (400 U)	Patient’s past medical history significant for hypertension, cerebrovascular accident approximately 2.5 years prior and being a former smoker. A screening ECG was assessed as normal. The patient was Botox naïve.
Patient 1169 Study 0410 OLEX	71/ Male 2 injs. in OLEX phase	CVA**	21 days (400 U)	Died of a severe CVA. History of prior CVA, hypertension, and being a former smoker. No post-mortem examination was performed. Prior treatment with Botox.
Placebo-treated Patients				
Patient ID # Study*	Age/ Gender	Cause of Death	Days from Last Inj. Until Death	Clinical Summary
101 Study 0528	85/ Male	Myocardial Infarction	42	This patient with spasticity participated in Study 0528 and had a history of hypertension and hyperlipidemia.
1088 Study 0410 Main	71/ Female	Intracranial Hematoma	23	Died of intracranial hematoma

INDICATION: CERVICAL DYSTONIA				
Botox-treated Patients				
Patient ID # Study*	Age/ Gender	Cause of Death	Days from Last Inj. Until Death	Clinical Summary
0602 Study (b) (4)	59/ Female	Colon Cancer	22	Died of metastatic colon cancer

*The study indicated in this column is the study the patient was in at the time of death.

** CVA = Cerebrovascular Accident

7.3.1.2 Deaths Narratives

There were six deaths in the NT 201 development program. Five occurred in the spasticity indication (three drug-treated and two placebo patients) and one in a Botox-treated patient within the CD indication. Abridged narratives for the six deaths are presented below.

1. **Patient 1054 (Xeomin-treated, SP indication, Study 0410 OLEX):** This 72-year-old man with post-stroke spasticity participated in the Main and OLEX Periods of Study 0410. During the Main Period, he received a single treatment with NT 201 on June 23, 2006. The patient had a past medical history significant for ischemic stroke approximately six years earlier, arrhythmia, ventricular pacemaker, hypothyroidism, coronary artery disease, hypertension, and aortic aneurysm. He was also a former smoker. He had received six Botulinum toxin treatments before study entry. An ECG performed at Screening was abnormal (the subject had a ventricular pacemaker)..

At entry into the OLEX Period of the study, the patient's medications were digoxin, warfarin, levothyroxine, tamsulosin, ramipril, naftidrofuryl, and piratecam.

In the OLEX Period of the study, the subject received 375 U of NT 201 on January 15, 2007. On (b) (6) the patient was hospitalized and diagnosed with a pulmonary embolism, which was treated and resolved. On (b) (6), the subject experienced a cerebrovascular accident. His hospitalization was complicated by progressive apathy and malnutrition. He began to refuse oral medication. (b) (6), the subject died in his sleep of an unknown cause. A post-mortem examination was not performed.

Reviewer comment: *This patient died following a cerebrovascular accident (CVA). Given that he had a previous CVA prior to entering the study, the occurrence of a second CVA is not unexpected, which considerably lessens, although does not exclude, the chance that the death was drug related.*

2. **Patient 1058 (Xeomin-treated, SP indication, Study 0410 OLEX):** This 67-year-old man with post-stroke spasticity participated in the Main and OLEX Periods of Study 0410. The patient had not been treated previously with Botulinum toxin. His past medical history was significant for hypertension, cerebrovascular accident approximately 2.5 years previously, hemiparesis and being a former smoker. An electrocardiogram performed at screening was assessed as normal.

In the OLEX period of the study, the patient received treatment with NT 201 on November 9, 2006 and March 15, 2007. On (b) (6), approximately six weeks after the last administration of NT 201, the patient died as a consequence of a “severe cardiac arrest.”

Reviewer comment: The sponsor’s narrative did not specify whether this cardiac arrest death was verified by autopsy or laboratory results. A request for information was sent to the sponsor, and the response is shown below:

1. FDA Question: For patient 1058 (Xeomin-treated, SP indication, Study 0410 OLEX) whose cause of death was attributed to “severe cardiac arrest,” was the cardiac arrest verified by either laboratory findings or autopsy?

Merz Response: Patient S1058 was a 68-year-old male subject who died of severe cardiac arrest six weeks after the last administration of NT201 study medication for post-stroke spasticity. It was reported that the patient’s wife found her husband without any signs of life. She called the rescue service which stated death by cardiac arrest. As the patient was already dead upon arrival of the rescue services, no laboratory or diagnostic tests could be done. An autopsy was not performed (BLA Amendment 0019, dated February 4, 2010).

The sponsor’s reply confirms that no testing was performed to verify that this was a death due to cardiac arrest, and this attribution appears to have been made by the ambulance crew. I would consider the cause of death in this patient to be unknown, as the patient had a history of cerebrovascular events, and a catastrophic CVA or other causes of sudden death have not been ruled out.

3. **Patient 1169 (Xeomin-treated, SP indication, Study 0410 OLEX):** This 71-year-old man with post-stroke spasticity participated in the Main and OLEX Periods of Study 0410. The subject received the first dose of NT 201 on July 18, 2006. The subject’s past medical history was significant for ischemic cerebrovascular accident approximately 4.4 years earlier, hypertension, and hemiparesis. He was also a former smoker. The subject had been treated for upper limb spasticity with Botulinum toxin before entering the study. An ECG performed at Screening was normal.

In the OLEX Period of the study, the patient received four injections of NT 201 on October 13, 2006, January 8, 2007, April 2, 2007 and June 25, 2007. On (b) (6), approximately (b) (6) after the last administration of NT 201, the subject suffered a

severe cerebrovascular accident at home and died as a consequence. A post-mortem examination was not performed.

***Reviewer comment:** The sponsor's narrative for Patient 1169 did not provide details on how the determination of CVA was made given that no autopsy was performed and the patient died at home. A request for additional information was sent to the sponsor, who replied¹⁴ that the investigator attempted to contact the patient after he missed a study visit, and was informed by his wife that he had died of a CVA. The sponsor stated they did not have any medical records in support of the CVA. I believe that the patient's wife likely provided accurate information on cause of death, but the fact that the CVA diagnosis was not verified should be taken into consideration.*

1.4 Deaths in the CD Indication

- Patient 0602 (Botox-treated, Cervical Dystonia, Study 9801):** This 59-year-old female received two injections of Botox on April 9, 1999 and April 23, 1999, as per protocol. She was admitted to hospital on (b) (6) due to jaundice, passage of fresh blood per rectum, nausea, vomiting, and shortness of breath on exertion. She had experienced pale loose stools for three months, which had progressed to almost hourly bowel movements. Advanced, metastatic colon carcinoma, a large, hemorrhagic duodenal ulcer, and decompensated myocardial insufficiency were diagnosed. The subject developed hepatorenal failure and died (b) (6) of her malignant disease.

***Reviewer comment:** The diagnosis of advanced cancer within several months of entering the study does not suggest a causal relationship with NT 201 treatment.*

7.3.1.3 Comparison of Death Rates: Drug Versus Placebo

Due to the small number of deaths and the fact that all three NT 201-treated deaths occurred in the open-label portion of studies, a comparison in death rates between drug and placebo treatment groups could not be performed.

7.3.1.4 Relationship of Death to Dose

***Reviewer comment:** The small number of deaths in Xeomin-treated patients (N=3), as well as overall (N=6 total deaths), precluded a formal analysis of deaths in relation to dose. Nevertheless, to thoroughly examine the deaths, the role of dose in the deaths should at least be considered. However, the relationship to dose is confounded by indication, as subjects in the spasticity indication both received higher doses and were older and more medically compromised than in other indications. I would therefore conclude that the data within the Xeomin development program neither supports nor refutes a dose-response relationship for NT 201 and fatal outcome.*

¹⁴ Response via e-mail, received May 18, 2010.

7.3.1.5 Sponsor Conclusions with Reviewer Discussion

In their assessment of the deaths within the NT 201 development program, the sponsor reached the following conclusion:

“In NT 201-treated subjects, fatal events show a strong association with the subjects’ underlying state of health, and no pattern of increased incidence of fatal events with higher NT 201 dose or number of treatments is noted (ISS, pg. 40).”

Reviewer comment: *I generally agree with the sponsor’s assessment that the deaths within the NT 201 studies do not show a pattern suggestive of a relationship with NT 201 treatment. I base this conclusion on the following:*

Nature of the deaths: *The three Xeomin-treated patients who died were older patients with risk factors associated with their cause of death. For example, Patient 1169 died from a severe CVA, and had entered the SP development program with a history of prior CVA. Clearly, some deaths from CVA and MI would be expected any study tracking older patients during the time period covered by the studies, and particularly when patients entered the study with a prior history of CVA, as was true for the SP indication.*

A concern with previously approved Botulinum toxins has been adverse events stemming from systemic spread of toxin. None of the three NT 201-treated deaths were characteristic of a fatality from systemic spread of botulinum toxin. The possible exception is Patient 1054, who died in his sleep of unknown causes with no autopsy performed. Although this could conceivably represent an atypical presentation of systemic spread, this is unlikely due to the timing of the death (136 days after last NT 201 treatment) and the lack of escalating symptoms of systemic spread prior to death. The likelihood of this death being due to systemic spread is even lower considering that this patient had a CVA approximately nine days before his death

Timing of deaths: *The three deaths in NT 201-treated patients occurred 21 days (presumed cerebrovascular accident), 44 days (“cardiac arrest”) and 136 days (unknown cause of death). The latter case has a latency that is outside of the expected length of NT 201 effect, but the other deaths took place during the time period in which NT 201 would have an effect.*

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 SAEs: Pooled Indications

7.3.2.1.1 SAEs: Pooled Indications – All Data

Reviewer comment: *A tabular listing of all SAEs within the entire NT 201 development program (including SAEs within non-neurologic indications) is presented in Appendix 9.5 of this review.*

Notable events are discussed within their respective indications within the SAE section of this review.

In the pooled completed studies and ongoing studies of NT 201, SAEs were reported in 43 of 1476 (2.9%) of subjects who received NT 201, 5 of 356 (1.4%) of subjects who received placebo, and 12 of 471 (2.5%) of subjects who received Botox (Clinical Overview, pg. 27).

Table 27: SAEs in the NT 201 Development Program – All Studies

(Adapted from Sponsor Table 5.3.5.3 - 12, ISS, 120-Day Safety Update, pg. 43)

Table 5.3.5.3 - 12: Summary of Serious Adverse Events Overall and by Demographic Characteristics, Completed, Single-Dose² NT 201 Studies

	NT 201 ³	NT 201 (Placebo-controlled Studies) ⁴	Placebo	Botox ²
	N=1476	N=632	N=356	N=471
Subjects with SAEs	43 (2.9%)	17 (2.7%)	5 (1.4%)	12 (2.5%)
Relationship				
Subjects with SAEs Assessed as Related ¹ to Treatment	0	0	0	0
Outcome:				
Subjects who Died	0	0	2 (0.6%)	1 (0.2%)
Subjects who Recovered with Sequelae	2 (0.1%)	0	0	0
Subjects with Not resolved/Ongoing Events	7 (0.5%)	2 (0.3%)	0	4 (0.8%)
Subjects with Severe SAEs	11 (0.7%)	6 (0.9%)	3 (0.8%)	3 (0.6%)

Reviewer comment: *It is notable that the risk of SAE with NT 201 (2.9% for all data, 2.7% in placebo-controlled studies) is similar to the risk in Botox®-treated patients. In addition, in the active-controlled studies (0003 [BEB] and 0013 [CD]) common adverse events were essentially equivalent in the NT 201 group compared to the Botox group (56 and 62 AEs in 40 and 45 patients, respectively)(120-day safety update, pg. 38).*

In the pooled studies in the NT 201 development program, SAEs were distributed among SOCs as shown below.

Reviewer comment: *I searched the AE dataset for the BEB, CD and SP indications combined for serious adverse events within the Designated Medical Events list, including hepatic failure, hepatitis, Stevens Johnson syndrome, toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, pancytopenia, and aplastic anemia. The search identified one case of hepatitis C and one of aplastic anemia (Study 0013). The aplastic anemia occurred in a placebo patient.*

Table 28: SAEs by SOC within the Pooled NT 201 Development Program

(Adapted from Sponsor Table 5.3.5.3-13, 120-Day Safety Update, pg. 45)

MedDRA System Organ Class	Overall NT 201 N=1313	Overall NT 201 (Placebo- controlled Studies) N=618	Overall Placebo N=346
Subjects with SAEs	38 (2.9%)	15 (2.4%)	2 (0.6%)
Nervous system disorders	8 (0.6%)	1 (0.2%)	1 (0.3%)
Gastrointestinal disorders	6 (0.5%)	1 (0.2%)	-
Infections and infestations	6 (0.5%)	3 (0.5%)	-
Respiratory, thoracic and mediastinal disorders	3 (0.2%)	3 (0.5%)	1 (0.3%)
Vascular disorders	3 (0.2%)	1 (0.2%)	-
Ear and labyrinth disorders	2 (0.2%)	1 (0.2%)	-
Injury, poisoning and procedural complications	2 (0.2%)	2 (0.3%)	-
Neoplasms malignant, benign, and unspecified	2 (0.2%)	-	-
Renal and urinary disorders	2 (0.2%)	1 (0.2%)	-
Reproductive system and breast dis.	2 (0.2%)	1 (0.2%)	-
Skin and subcutaneous tissue dis.	2 (0.2%)	-	-
Cardiac disorders	1 (0.1%)	-	-
Congenital, familial and genetic dis.	1 (0.1%)	1 (0.2%)	-
Eye disorders	1 (0.1%)	-	-
General disorders and administration site conditions	1 (0.1%)	1 (0.2%)	-
Psychiatric disorders	1 (0.1%)	-	-
Surgical and medical procedures	1 (0.1%)	1 (0.2%)	-

Appears this way on original

Reviewer comment: Of note, even when subjects from all indications are pooled, and when the adverse events are collapsed into SOC categories, there was frequently a single event in the NT 201 patients. The table above illustrates the difficulties in performing sub-analyses with regards to SAEs, as even when presented by SOC there are so few patients in each strata that examination by dose or risk modifiers is not possible.

7.3.2.1.2 SAEs: Pooled Indications – Placebo-Controlled Studies

Merz reported that patients receiving NT 201 in the placebo-controlled studies had a slightly higher incidence of SAEs overall (17 SAEs/632 patients; 2.7%), compared with subjects who received placebo (5 SAEs, 346 patients; 1.4%)(120-Day Safety Update, pg. 41).

Merz performed a number of analyses to examine risk modifiers for SAEs. In the placebo-controlled studies, the sponsor found that male subjects who received NT 201 had a higher incidence of SAEs (5.9%), compared with the male subjects who received placebo (1.7%). However, because the number of patient in the demographic subgroups was small, it is difficult to draw reliable conclusions based on these data. No imbalance between treatment groups was seen for age or previous treatment status (120-Day Safety Update, pg. 43).

Reviewer comment: SAE data from open-label, multiple dose studies are presented within the sections for their specific indications below.

7.2.3.2 SAEs: BEB

7.2.3.2.1 SAEs in Pooled BEB Studies

7.2.3.2.2 SAEs in the Placebo-Controlled BEB Trials

Merz stated that in the placebo-controlled Study 0433/1 (BEB) Main Period, only one patient, who received placebo, experienced an SAE (dyspnea)(Clinical Overview, pg. 29).

7.2.3.2.3 SAEs in the OLEX BEB Trials

In the open-label study for BEB (0433/2), Merz reported that there were 16 SAEs among 10 patients. These are summarized in the following table (BEB ISS, pg 20).

Table 29: Summary of SAEs within the 0433/2 OLEX Period

(Adapted from Sponsor Table 13, BEB ISS 120 Day Update, pg. 21)

Subject #	Cumulative NT 201 Dose (Main + OLEX Period) <i>Botulinum Toxin Pre-Treatment Status</i>	Event as MedDRA Preferred Term
2001 75, male	600 U (100 U + 500 U) <i>Pre-treated</i>	Colon cancer Streptococcal bacteraemia
2045 60, male	280 U (Placebo + 280 U) <i>Pre-treated</i>	Pancreatitis
2064 78, male	160 U (Placebo + 160 U) <i>Pre-treated</i>	Gastroenteritis Atrial fibrillation Cardiomyopathy ¹ Cardiac failure congestive ¹ Dyspnoea
2108 65, female	350 U (70 U + 280 U) <i>Pre-treated</i>	Staphylococcal infection Chest pain
2122 75, female	250 U (Placebo + 250 U) <i>Pre-treated</i>	Pharyngoesophageal diverticulum
2146 59, female	340 U (55 U + 285 U) <i>Pre-treated</i>	Thyroid neoplasm
2162 63, male	270 U (Placebo + 270 U) <i>Pre-treated</i>	Diverticulitis
2174 22, female	40 U (20 U + 20 U) <i>Pre-treated</i>	Convulsion
2179 72, female	30 U (Placebo + 30 U) <i>Pre-treated</i>	Spinal compression fracture
2223 52, female	300 U (Placebo + 300 U) <i>Pre-treated</i>	Bronchitis

MedDRA: Medical Dictionary for Regulatory Activities; OLEX: open-label extension (period); U: units.

¹ These events were reported as serious before the cut-off date of 25-Jun-2009; however, they were not coded in the clinical database by that date, and therefore do not appear in the summary tables for the study.

Reviewer comment: The SAE of dyspnea occurred in a 78-year-old man (Patient 2064) with a past medical history of vertigo, hypertension, peptic ulcer, partial thyroidectomy, cholecystectomy, melanoma of the eye, prostate resection, polypectomy and low hemoglobin

related to peptic ulcer. Concomitant medications included verapamil, terazosin, enalapril, simvastatin, omeprazole, amoxicillin, and moxifloxacin. During the course of the study, the patient was diagnosed with cardiomyopathy and congestive heart failure (ventricular ejection fraction 30%).

Four months after receiving 40 U of NT 201 in Study 0433/2, the patient was hospitalized for treatment of atrial fibrillation. He presented with complaints of chest pressure and shortness of breath. A CT scan showed cardiomegaly, and an echocardiogram revealed a left ventricular ejection fraction of 25%. He was treated with warfarin and amiodarone, and the event was reported to resolve (0433/2 Study Report, pg. 198).

The clinical scenario described is consistent with dyspnea as a result of congestive heart failure, and does not have any other characteristics, such as muscular paralysis, associated with systemic spread of botulinum toxin. In addition, the event occurred four months following the last dose with NT 201. I would therefore not consider this event to be a result of systemic spread of NT 201.

(Please see Section 7.3.2.5 of this review for comments on the occurrence of convulsion as an SAE in NT 201-treated patients.)

7.2.3.2.4 SAEs in the Other BEB Studies

In BEB Study 0003, Merz stated that three of 148 subjects (2.0%) in the NT 201 group, and five of 152 subjects (3.3%) in the Botox® group, experienced SAEs. The three SAEs in the NT 201-treated patients were abdominal pain, enterocolitis and hemorrhagic intestinal diverticulum. No SAEs occurred in Study 0703.

Reviewer comment: *After neurologic events, the second most common SOC for SAEs in all (placebo-controlled plus open-label) NT 201-treated patients are gastrointestinal disorders (See FDA Table 28 above). The narratives of the cases above did not specify if the AEs of abdominal pain and enterocolitis were related to constipation or diarrhea. Although it was the second most frequent SOC, in the placebo-controlled trials (for all indications) there was only 1 gastrointestinal SAE in a NT 201-treated patient, compared to none in placebo patients.*

For the three gastrointestinal SAEs in Study 0003, the patient's ages were 46 years (abdominal pain), 72 years (enterocolitis) and 74 years (hemorrhagic diverticulum).

7.3.2.3 SAEs: CD

7.3.2.3.1 SAEs: CD Placebo-Controlled Trials

In the Main Period of Study 408/1, Merz stated that four subjects in the NT 201 group in the Study 0408/1 Main Period experienced SAEs (2.5 %), compared with no subject in the placebo

group (0%). The events were appendicitis, asthma, chronic obstructive pulmonary disease, and staphylococcal infection (CD ISS, pg. 25).

Table 30: SAEs in CD Study 0408/1 Main

(Adapted from Sponsor Table 13, CD ISS, pg. 25)

Table 13: Summary of Serious Adverse Events in Study 0408/1 Main Period

Subject # (Link to narrative)	NT 201 Treatment Group <i>Botulinum Toxin Pretreatment Status</i>	Event (MedDRA Preferred Term)	Relationship to Treatment	Intensity	Outcome
1016 50, male	240 U <i>Pre-Treated</i>	Appendicitis	Not related	Severe	Resolved
1044 51, male	240 U <i>Pre-Treated</i>	Asthma	Not related	Severe	Resolved
1128 58, male	240 U <i>Pre-Treated</i>	Chronic obstructive pulmonary disease	Not related	Severe	Resolved
1235 38, male	240 U <i>Pre-Treated</i>	Staphylococcal infection	Not related	Severe	Resolved

MedDRA: Medical Dictionary for Regulatory Activities; U: units.
Source: Table 3.3.4.2.1.2.2.1, Study 0408/1 CSR, Section 5.3.5.1.

Reviewer comment: *As with the other indications, there were too few SAEs to compare the NT 201 and placebo groups by individual SAEs, or even reliably by SOC.*

I reviewed the case of COPD to assess ensure that it was indeed COPD and not some other form of respiratory compromise. This patient (0408/1 1128) had a history of COPD and presented with a four-day history of productive cough. His condition improved with treatments for COPD (IV solumedrol, albuterol/atrovent nebulizer). He did not have any neurologic symptoms that would suggest a spread of toxin effect.

7.3.2.3.2 SAEs: CD: Open-Label Studies

Merz stated that in the Extension Period of Study 0408/2 (CD), 11 subjects experienced 16 SAEs (CD ISS, 26).

Table 31: SAEs in Study 0408/2 OLEX Period

(Adapted from Sponsor Table 14, CD ISS, pg. 27)

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Subject # Age (years), Gender	Main Period/ Extension Period Treatment (Cumulative NT 201 dose, number of NT 201 doses) <i>Botulinum Toxin Pretreatment Status Main Period</i>	Event (MedDRA Preferred Term)
1032 69, male	NT 201 120 U / 240 U (1080 U, 5 injections) <i>Treatment-Naive</i>	Cholecystitis
		Pancreatitis
1046 43, female	NT 201 240 U/NT 201 (<i>Still blinded</i>) (5 injections) <i>Treatment-Naive</i>	Suicidal ideation
1077 61, female	NT 201 240 U/120 U (840 U, 6 injections) <i>Pre-Treated</i>	Accidental overdose (<i>not NT 201</i>)
		Basal cell carcinoma
1095 51, male	NT 201 120 U/240 U (1320 U, 6 injections) <i>Pre-Treated</i>	Non-cardiac chest pain
1116 66, male	Placebo/NT 201 240 U (480 U, 2 injections) <i>Pre-Treated</i>	Colonic polyp
		Appendiceal abscess
		Respiratory failure
1122 49, female	NT 201 240 U/240 U (660 U, 5 injections) <i>Pre-Treated</i>	Herpes zoster
1155 59, female	NT 201 120 U/120 U (600 U, 5 injections) <i>Pre-Treated</i>	Chest injury

1162 57, male	NT 201 120 U/120 U (480 U, 4 injections) <i>Pre-Treated</i>	Pancreatitis
1241 67, female	NT 201 240 U/120 U (600 U, 4 injections) <i>Pre-Treated</i>	Compression fracture Lung neoplasm malignant
1271 66, female	NT 201 120 U/240 U (600 U, 3 injections) <i>Treatment-Native</i>	Small intestinal obstruction
1316 72, female	NT 201 240 U/NT 201 (<i>Still blinded</i>) (4 injections) <i>Pre-Treated</i>	Hip fracture

MedDRA : Medical Dictionary for Regulatory Activities; U: units.
Source: Table 2.2.1.2, Section 5.3.5.3, Appendix J.

Reviewer comment: *As noted by the sponsor, the SAEs generally occurred in only one patient, and no discernable pattern was apparent. One SAE of note was respiratory failure which occurred (Patient 1116). I reviewed the case report, which involved a 67-year-old man with a past medical history of hypertension, hyperlipidemia, two episodes of hepatitis, arthritis, erectile dysfunction, musculoskeletal pain, and prostate cancer. Concomitant medications included vitamins, acetylsalicylic acid, ibuprofen, diazepam, Vytorin, dyazide, and sildenafil.*

In the OLEX Period, the subject received NT 201 on December 5, 2007. About (b) (6) later, (b) (6) the patient underwent an appendectomy and removal of a benign colonic polyp. Two days later, he returned to surgery due to possible intra-abdominal bleeding. He was found to have approximately 150 cc of liquefied blood (clots) and 100 cc of old blood with a retroperitoneal hematoma, but no site of active bleeding was noted. The patient received 3 units of packed red blood cells and transferred to the intensive care unit on a ventilator (0408/2 Final Study Report).

Given the surgery-related events described, I would not consider this event to be related to NT 201 administration.

For the two patients with pancreatitis, in one (Patient 1032) the pancreatitis occurred in the setting of calculi blockage of the gall bladder and common bile duct. The patient underwent a laproscopic cholecystectomy. In the second patient (Patient 1162), the pancreatitis was reported to have occurred in a patient with high alcohol consumption (0408/2 Final Study Report).

7.3.2.3.2 SAEs: CD: Other Studies

In the other CD studies, including Study 9801, Study 0013, the Main Period of Study 0605/1, and in the OLEX Period of ongoing Study 0605/2, Merz reported that a total of 23 subjects experienced 30 SAEs. Seventeen of the subjects with SAEs had received NT 201, and six had received Botox (CD ISS, pg. 29).

These events are shown in the table below.

Table 32: Summary of SAEs in Other Studies (Study 9801, Study 0013, the Main Period of Study 0605/1, and in the OLEX Period of ongoing Study 0605/2) in the CD Indication

(Adapted from Sponsor Table 15, CD ISS, pg. 29)

Study Subject # Age, Sex	Treatment Cumulative Dose <i>Botulinum Toxin Pretreatment Status</i>	Event (MedDRA Preferred Term)
Study 0013 (CD)		
003 50, male	NT 201 120 U <i>Pre-Treated</i>	Vertigo Cerebral disorder ¹ Haematoma
011 40, male	Botox 100 U <i>Pre-Treated</i>	Anxiety
051 73, female	NT 201 200 U <i>Pre-Treated</i>	Neoplasm (<i>ovarian tumor</i>)
170 50, male	NT 201 100 U <i>Pre-Treated</i>	Eczema
207 51, female	Botox 60 U <i>Pre-Treated</i>	Transient ischaemic attack Aphasia
309 50, female	NT 201 100 U <i>Pre-Treated</i>	Metrorrhagia
347 52, female	Botox 200 U <i>Pre-Treated</i>	Leukaemia
444 34, female	Botox 100 U <i>Pre-Treated</i>	Cerebral ischaemia ²
549 46, female	Botox 150 U <i>Pre-Treated</i>	Agitation

Study 0605/1 (CD) Main Period		
1082 58, female	NT 201 220 U <i>Treatment-Naive</i>	Renal abscess
1088 60, male	NT 201 100 U <i>Treatment-Naive</i>	Foot fracture
Study 0605/2 (CD) OLEX Period		
1007 66, male	NT 201 460 U <i>Pre-Treated</i>	Myocardial infarction
1012 55, female	NT 201 663 U <i>Treatment-Naive</i>	Retinal detachment Eye haemorrhage
1020 65, male	NT 201 825 U <i>Pre-Treated</i>	Myocardial infarction Arrhythmia
1037 52, female	NT 201 320 U <i>Treatment-Naive</i>	Femoral neck fracture
1047 59, male	NT 201 410 U <i>Pre-Treated</i>	Mood disorder due to a general medical condition
1048 60, male	NT 201 580 U <i>Pre-Treated</i>	Squamous cell carcinoma
1079 52, female	NT 201 400 U <i>Pre-Treated</i>	Alcoholism
1091 69, female	NT 201 490 U <i>Pre-Treated</i>	Radius fracture
1094 61, female	NT 201 575 U <i>Pre-Treated</i>	Hodgkin's disease Pneumonia
Study 9801 (CD)		
0602 59, female	Botox, 90 U ³ <i>Treatment-Naive</i>	Jaundice Colon cancer
0608 61, female	NT 201, 60 U ³ <i>Treatment-Naive</i>	Nephrolithiasis
0801 47, male	NT 201, 90 U ³ <i>Treatment-Naive</i>	Neoplasm (Malignant neoplasm of the pharynx)

Reviewer comment: For all the CD studies, the SAEs which occurred in more than one patient in the CD indication were neoplasm (7 patients), myocardial infarction (three patient), transient ischemic attacks(TIA)/cerebrovascular accident (CVA) (3 patients),and pancreatitis (two patients). However, with the exception of pancreatitis, these are generally the most prevalent SAEs in any patient population, including in the general background population not treated with any botulinum toxin. Due to the small number of events, however, a formal comparison to background rates would not be a very robust analysis.

7.3.2.4 SAEs: Spasticity

7.3.2.4.1 SAEs: Placebo-Controlled Spasticity Studies

In the Study 0410/1 Main Period, four of 73 subjects (5.5%) in the NT 201 group and one of 75 subjects (1.3%) in the placebo group experienced SAEs. The table below shows the SAEs which occurred in the NT 201-treated patients (0410/1 Final Study Report, pg 21).

Table 33: Summary of SAEs in Study 0410/1 Main Period

(Adapted from Sponsor Table 11, 0410/1 Final Study Report, pg. 21)

Subject # Age (years), Gender	Treatment Group Botulinum Toxin Pretreatment Status	Event as MedDRA Preferred Term
1008 56, male	NT 201 380 U Treatment-Naive	Bronchitis chronic
1036 62, male	NT 201 170 U Treatment-Naive	Cellulitis
1088 71, female	Placebo Treatment-Naive	Intracranial haematoma
1119 49, male	NT 201 170 U Treatment-Naive	Epilepsy Paraparesis Status epilepticus
1140 34, male	NT 201 310 U Treatment-Naive	Hypertension Vertigo

MedDRA: Medical Dictionary for Regulatory Activities; U: units.

Reviewer comment: Due to the small number of SAEs, it was not possible to compare specific SAEs between the drug and placebo groups. Only overall risk could be compared, and it was

considerably higher in the NT 201-treated patients (5.5% in NT 201-treated patients versus 1.3% in placebo-treated patients).

7.3.2.4.2 SAEs: SP- OLEX Studies

In the OLEX period of Study 0410/2, Merz reported that 26 of 145 subjects (17.9%) experienced 38 SAEs. The events experienced are summarized in the table below.

Table 34: SP SAEs in OLEX Study 0410/2

(Adapted from Sponsor Table 29, 0410/2 Final Study Report, pg. 62)

Subject # Age (years), Gender	Cumulative Dose (Main Period + OLEX Period) <i>Botulinum Toxin</i> <i>Pretreatment Status</i>	Event as MedDRA Preferred Term
1002 32, female	1600 U (Placebo + NT 201 1600 U) <i>Treatment-Naive</i>	Hydrocephalus
1007 49, male	1200 U (Placebo + NT 201 1200 U) <i>Treatment-Naive</i>	Hemiparesis Coronary artery bypass
1009 65, female	1600 U (Placebo + NT 201 1600 U) <i>Treatment-Naive</i>	Diabetes mellitus inadequate control
1027 55, female	1800 U (NT 201 300 U + 1500 U) <i>Treatment-Naive</i>	Tracheobronchitis
1028 55, male	1470 U (Placebo + NT 201 1470 U) <i>Treatment-Naive</i>	Rehabilitation therapy ¹ Anaemia
1029 45, male	1425 U (NT 201 210 U + 1215 U) <i>Treatment-Naive</i>	Extradural hematoma Epilepsy
1033 45, male	1895 U (Placebo + NT 201 1895 U) <i>Pre-Treated</i>	Epilepsy
1054 72, male	685 U (NT 201 310 U + 375 U) <i>Pre-Treated</i>	Death Pulmonary embolism Transient ischaemic attack
1058 67, male	800 U (NT 201 400 U + 400 U) <i>Pre-Treated</i>	Cardiac Arrest

Subject # Age (years), Gender	Cumulative Dose (Main Period + OLEX Period) <i>Botulinum Toxin</i> <i>Pretreatment Status</i>	Event as MedDRA Preferred Term
1076 50, male	1165 U (Placebo + NT 201 1165 U) <i>Treatment-Naïve</i>	Calculus ureteric
1079 52, male	1500 U (Placebo + NT 1500 U) <i>Treatment-Naïve</i>	Subileus
1100 60, male	600 U (NT 201 300 U + 300 U) <i>Treatment-Naïve</i>	Renal cell carcinoma stage I Prostate Cancer
1116 61, male	1600 U (Placebo + NT 201 1600 U) <i>Treatment-Naïve</i>	Cardiovascular insufficiency Cardiomyopathy
1121 45, male	710 U (NT 201 310 U + 400 U) <i>Treatment-Naïve</i>	Dizziness Headache
1124 51, male	1195 U (Placebo + NT 201 1195 U) <i>Treatment-Naïve</i>	Intervertebral disc protrusion
1131 61, female	1500 U (NT 201 300 U + 1200 U) <i>Treatment-Naïve</i>	Colonoscopy
1136 65, female	1085 U (NT 201 310 U + 775 U) <i>Treatment-Naïve</i>	Hyperparathyroidism Rehabilitation Therapy ²
1139 55, male	730 U (Placebo + NT 201 730 U) <i>Treatment-Naïve</i>	Muscle spasticity

Subject # Age (years), Gender	Cumulative Dose (Main Period + OLEX Period) <i>Botulinum Toxin Pretreatment Status</i>	Event as MedDRA Preferred Term
1140 34, male	740 U (NT 201 340 U + 400 U) <i>Treatment-Naïve</i>	Hemiparesis
1160 47, female	800 U (Placebo + NT 201 800 U) <i>Treatment-Naïve</i>	Femur fracture
1162 28, male	1305 U (Placebo + NT 201 U 1305 U) <i>Treatment-Naïve</i>	Epilepsy Muscle spasticity
1165 58, female	1080 U (Placebo + NT 201 1080 U) <i>Treatment-Naïve</i>	Muscle spasticity
1169 70, male	1920 U (NT 201 325 U + 1595 U) <i>Pre-Treated</i>	Cerebrovascular Accident
1176 59, male	1600 U (Placebo + NT 201 1600 U) <i>Treatment-Naïve</i>	Rectal cancer
1196 61, male	1600 U (Placebo + NT 201 1600 U) <i>Treatment-Naïve</i>	Pneumonia
1197 64, female	670 U (NT 201 270 U + 400 U) <i>Pre-Treated</i>	Colon cancer Peritonitis Preternatural anus ³

Reviewer comment: The SAEs in the table above generally those typical of an older population, including cancers, pulmonary infections and cardiac insufficiency issues.

7.3.2.5 SAEs: SP – Other Studies

Merz reported that total of 17 subjects in Studies (b) (4) 0607 (b) (4) experienced a total of 23 SAEs (SP ISS, pg. 31).

Reviewer comments: *A tabular listing of all the SAEs within the NT 201 development program is contained in Appendix 9.5 of this review, including those from SP Studies (b) (4). I reviewed these SAEs, and as with the other NT 201 studies, the SAEs were typical of an older patient population with a history of a prior CVA (including myocardial infarction, CVA/TIA and pulmonary issues).*

Of note, in the spasticity indication there were six cases of “epilepsy” and one case of “convulsion” among the SP SAEs. I reviewed the case reports for these patients:

- 1. Patient 161 (b) (4) had a history of epilepsy for one year prior to study entry.*
- 2. Patient 1004 (Study 0607) (a 56-year-old man) had a single seizure 125 days after his last treatment with NT 201. He had recently discontinued a benzodiazepine derivative drug (clobazem) which likely contributed to the seizure.*
- 3. Patient 1116 (b) (4) experienced a single seizure 87 days after receiving 400 U of NT 201. He was hospitalized and evaluated but no likely trigger of the seizure was identified.*
- 4. Patient 1138 (Study 0607) had a history of “epileptic aura” for which he was being treated prior to entering the NT 201 study.*
- 5. Patient 1119 (Study 0410/1) On (b) (4) (31 days after administration of NT 201,) the patient experienced “severe status epilepticus” and moderate paraparesis for which he was hospitalized. The sponsor’s narrative refers to this event as status epilepticus, but states that it resolved after a 25 days, which is inconsistent with status epilepticus. The patient was treated with metoclopramide, valproate sodium, diazepam, piracetam, and mannitol. The subject’s epilepsy medication was also altered in the aftermath of these SAEs: “Status epilepticus” resolved on (b) (4). The patient was subsequently diagnosed with moderate epilepsy. He was hospitalized and topiramate (50 mg p.o./daily) was later added for this event.*
- 6. Patient 1029 (0410/2) had a history of epilepsy prior to study entry.*
- 7. Patient 0607 (0410/2) experienced a single seizure seven days after treatment with NT 201. He did not have a history of epilepsy prior to the study.*

CVA can cause epilepsy, with the healed lesion acting as a nidus for seizure activity. As such, the analysis of drug-relatedness in the SP indication is confounded by this association. There were no cases of epilepsy in the other indication (BEB, CD) In addition, in many of the reports there was a pre-existing history of epilepsy/seizures or other contributing factors. I therefore consider the epilepsy/seizures as likely not related to NT 201 treatment.

7.3.2.6 SAEs: SP – Anaphylaxis

After the BLA submission, there was a post-marketing report of anaphylaxis following Xeomin® administration.

1. Anaphylaxis Case reported to MedWatch (b) (4) # 09-0991): On August 24, 2009, a 56-year old British nurse (who was both the patient and reporter) was treated with NT 201 (Xeomin®) 50 IU for glabellar line/wrinkle reduction. It was reported to be the subject's first treatment with Xeomin®, although she had five prior treatments with Botox®. Within three to five minutes after the injections, she experienced an anaphylactic reaction characterized by palpitations, faintness, and nausea lasting for 36 hours. The report stated hay fever, and allergic reactions to wasp stings and penicillin. The subject was not using any concomitant medication at the time of the event. In the opinion of the investigator, the event was medically significant and related to Xeomin® administration. The report stated that there were no concomitant medications.

Reviewer comment: Although designated a case of anaphylaxis, the case above is unusual in that the no treatment was mentioned and the symptoms lasted for 36 hours.

Reviewer comment: I performed a literature search for case reports of anaphylaxis following botulinum toxin use. The search yielded only the single case below.

Li M, Goldberger BA, Hopkins C. Fatal case of Botox-related anaphylaxis? J Forensic Sci 2005; 50(1):169-72. This case report documents the first death associated with a Botox-lidocaine mixture given to a woman for chronic neck and back pain. Based on the medical records, autopsy, and laboratory findings, the cause of death was determined to be anaphylaxis to the Botox-lidocaine mixture. The history, indications, off-label uses and possible future applications of Botox are reviewed as well as the uses and complications of lidocaine. The author acknowledges that anaphylaxis cannot be definitively proven to be due to Botox alone.

Reviewer comment: Dr. Marc Stone's review of the Dysport® BLA does not mention any cases of anaphylaxis. Botox labeling includes anaphylaxis and immediate hypersensitivity reactions in the postmarketing section and in Warnings and Precautions.

7.3.2.7 SAEs: Reviewer Summary

The SAEs in the NT 201 development program were generally those expected for the background population of the same age group. There were two SAEs of respiratory of failure and dyspnea, but neither fit the clinical presentation of systemic botulinum toxin spread and both cases had clear alternate causes (such as post-surgery blood loss). There were 6 cases of epilepsy and 1 case of convulsion among the SAEs, all within the spasticity indication. Some of these patients were known to have pre-existing epilepsy, but in others there was no history of epilepsy. CVA's may lead to subsequent seizures, and all of the patient sin the SP indication had experienced a prior CVA. There has been a post-marketing report of anaphylaxis occurring in a British patient.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Discontinuations: Pooled Indications

Merz provided the following summary of discontinuations for all causes for the pooled NT 201 development program data.

Reviewer comment: To assess whether discontinuations due to adverse event were mistakenly classified into other discontinuation categories (withdrawal of consent, patient decision, investigator decision, etc.), I read the narratives for non-AE discontinuations within the NT 201 development program (ISS 120-Day Safety Update, Appendix D, pg, 180). Although some of the narratives lacked details, I was not able to find any instances in which a withdrawal due to AE had been miscoded.

In the pooled controlled studies, Merz stated that six of 1313 subjects (0.5%) in the NT 201 treatment group discontinued due to a TEAE, compared with 1 of 396 (0.3%) Botox-treated subjects and 1 of 346 (0.3%) placebo-treated subjects (ISS, pg 140).

Reviewer comment: There are a relatively small number of patients who discontinued the study due to adverse event (0.5%) given the number of patients treated (N=1313). For reference, this was comparable to development programs for other botulinum toxins. In the Dysport® development program, there were relatively few withdrawals as well, as shown by the quote from Dr. Stone's¹⁵ safety review below:

There were only two adverse events associated with dropouts. In Study 020, a 52 year-old woman reported a number of complaints which started three days after injection, including headache, heavy eyelids as well as nervousness and irritability. All the events were recorded as lasting for approximately four weeks. In open-label Study 731, a 53 year-old woman experienced severe dysphagia six days after treatment, resolving 20 days later (pg. 12).

Merz reported that events leading to drop-out in the NT 201 treatment group included muscular weakness (two subjects), dizziness, neck pain, musculoskeletal pain, and nausea (one subject each). In the placebo patient, the event leading to drop-out was intracranial hematoma (ISS 120-Day Safety Update, pg. 139). The sponsor summarized all the adverse events leading to discontinuations within the NT 201 development program in the table below.

15 Clinical Safety Review BLA 125274 (Dysport®). Prepared by Dr. Marc Stone. Dated August 19, 2008.

Table 35: Adverse Events Leading to Discontinuation in the Pooled NT 201 Studies

(Adapted from Sponsor Table 5.3.5.3-14, ISS 120-Day Safety Update, pg. 140)

Table 5.3.5.3 - 14: Summary of Treatment-Emergent Adverse Events Leading to Drop-Out in the NT 201 Studies

Subject # Age, Gender	NT 201 Treatment Group <i>Botulinum Toxin</i> Pretreatment Status	Event (MedDRA Preferred Term)	Relationship to Treatment (Assessed by Investigator)	Intensity	Outcome
Cervical Dystonia					
Study 0408/1 Main Period					
1076 34, female	NT 201 240 U <i>Treatment-Naïve</i>	Muscular weakness	Related	Severe	Resolved
1332 46, female	NT 201 240 U <i>Treatment-Naïve</i>	Muscular weakness	Related	Moderate	Resolved
		Musculoskeletal pain	Related	Moderate	Resolved
		Neck pain	Related	Moderate	Resolved
1033 70, male	NT 201 120 U <i>Pre-Treated</i>	Dizziness	Related	Severe	Resolved
		Nausea	Related	Moderate	Resolved
Study 0013					
540 32, female	Botox <i>Pre-Treated</i>	Ankle fracture	Not related	Mild	Resolved
Study 9801					
801 47, male	NT 201 90 U <i>Pre-Treated</i>	Neoplasm	Not related	Severe	Not resolved
Spasticity					
Study 0410/1 Main Period					
1119 49, male	NT 201 <i>Treatment-Naïve</i>	Paraparesis	Not related	Moderate	Not resolved
1088 71, female	Placebo <i>Treatment-Naïve</i>	Intracranial haematoma	Not related	Severe	Death
Study 0410/2 OLEX Period					
1054 72, male	NT 201 / NT 201 <i>Pre-Treated</i>	Death	Not related	Severe	Death
1058 67, male	NT 201 / NT 201 <i>Pre-Treated</i>	Cardiac arrest	Not related	Severe	Death
1095 51, male	Placebo / NT 201 <i>Treatment-naïve</i>	Injection site pain	Related	Moderate	Resolved

Table continues

Table 5.3.5.3 - 14: Summary of Treatment-Emergent Adverse Events Leading to Drop-Out in the NT 201 Studies

Subject # Age, Gender	NT 201 Treatment Group Botulinum Toxin Pretreatment Status	Event (MedDRA Preferred Term)	Relationship to Treatment (Assessed by Investigator)	Intensity	Outcome
Study 0410/2 OLEX Period (continued)					
1117 51, male	NT 201 / NT 201 Treatment-naïve	Injection site pain	Related	Moderate	Resolved
1142 74, male	NT 201 / NT 201 Pre-Treated	Dysphagia	Related	Mild	Resolved
1169 71, male	NT 201 / NT 201 Treatment-naïve	Cerebrovascular accident	Not related	Severe	Death
1186 73, female	NT 201 / NT 201 Pre-Treated	Hypokinesia	Not related	Moderate	Not resolved
1197 64, female	NT 201 / NT 201 Pre-Treated	Colon cancer	Not related	Severe	Resolved with Sequelae
Study 0607					
1025 69, male	NT 201 Pre-Treated	Transient ischaemic attack	Not related	Mild	Recovered
(b) (4)					
114 74, female	Placebo Treatment-Naïve	Carotid artery stenosis	Not related	Moderate	Recovered

U: Units

MedDRA: Medical Dictionary for Regulatory Activities.

Source: Listing 3.1.21.1.3; Study 0408/1 Main Period CSR, Section 5.3.5.1; Study 0013 CSR, Study 9801 CSR, Study 0410/1 Main Period CSR, and Study 0410/2 OLEX Period CSR, and Study 0607 CSR, Section 5.3.5.1.

Reviewer comment: *The sponsor commented that the number of subjects in the NT 201 treatment group who dropped out of the pooled, controlled studies because of a TEAE is too small (six subjects) to allow for meaningful analysis by age, gender, race, dose group, baseline disease severity or Botulinum neurotoxin pre-treatment status, with which I concur.*

7.3.3.2 Discontinuations: BEB

7.3.3.2.1 BEB Discontinuations in Placebo-Controlled Studies

Merz stated that in the placebo-controlled portion Study 0433/1 Main Period, the incidence of drop-outs in the NT 201 and placebo groups was similar. Seven subjects discontinued Study 0433/1 (Main Period), including 5 of 75 subjects (6.7%) in the NT 201 group and 2 of 34 subjects (5.9%) in the placebo group. Of the subjects in the NT 201 group who dropped out, three developed or experienced withdrawal criteria, one was mistakenly given open-label study treatment, and one was randomized but never treated because she was found not to meet the study entry criteria. No subject in the Study 0433/1 Main Period withdrew due to a TEAE (BEB 120 Day ISS, pg. 24).

Reviewer comment: *Per the sponsor's descriptions of discontinuations, no NT 201-treated patients discontinued due to adverse events.*

7.3.3.2.2 BEB Discontinuations in Open-Label Studies

In the Study 0433/2 OLEX period, the sponsor reported that a total of 19 subjects discontinued the study. Merz stated that only one of these patients discontinued due to an adverse event. Merz noted that Patient 2007 withdrew because of “post-procedural pain and malignant breast lump removal,” stating that anesthesia was not permitted per the protocol, and the subject was withdrawn from the study)(BEB 120 Day ISS, pg. 24).

7.3.3.2.3 BEB Discontinuations in All other Studies

The sponsor reported that no patient in Study 0003 or Study 0703 discontinued due to adverse event (BEB 120 Day ISS, pg. 24).

Reviewer comment: *I reviewed the narratives for all the patients who withdrew from the BEB studies, including those who withdrew due to reasons other than adverse event. I did not find any discontinuations due to adverse events that were inappropriately attributed to other reasons. Due to the small number of discontinuations, no pattern in withdrawals was discernable.*

7.3.3.3 Discontinuations: CD

7.3.3.3.1 CD Discontinuations in Placebo-Controlled Studies

Following a request by the FDA, the sponsor provided the following table categorizing patient discontinuations from the CD studies 0408/1, 9801, and 0013.

Table 36: Categorization of Discontinuations within BEB Studies 0408/1, 9801 and 0013
(Submitted via e-mail on May 27, 2010)

<i>Withdrawals: Summary of Patients and Reasons</i>				
<i>MAIN(Main reason)</i>	<i>TRT(Treatment)</i>			<i>Total</i>
	<i>NT</i>	<i>Placebo</i>	<i>Botox</i>	
<i>Frequency</i>	<i>201</i>			
<i>Percent</i>				
<i>Col Pct</i>				
<i>Withdrawal criteria occurred</i>	0	1	0	1
	0.00	0.13	0.00	0.13
	0.00	1.35	0.00	
<i>Lack of efficacy</i>	3	3	2	8
	0.40	0.40	0.27	1.07
	0.70	4.05	0.82	
<i>Adverse event</i>	4	0	2	6
	0.53	0.00	0.27	0.80
	0.93	0.00	0.82	
<i>Consent withdrawn</i>	2	1	0	3
	0.27	0.13	0.00	0.40
	0.46	1.35	0.00	
<i>Lost to follow-up</i>	7	1	1	9
	0.93	0.13	0.13	1.20
	1.62	1.35	0.41	
<i>Other</i>	2	0	3	5
	0.27	0.00	0.40	0.67
	0.46	0.00	1.23	
<i>Completer</i>	413	68	236	717
	55.14	9.08	31.51	95.73
	95.82	91.89	96.72	
<i>Total</i>	431	74	244	749
	57.54	9.88	32.58	100.00

Reviewer comment: *The table above shows that about twice as many NT 201-treated patients (N=4, 0.53) as Botox-treated patients (N=2, 0.27) discontinued. However, the number of withdrawals was small.*

In the Main Period of Study 0408/1, a total of 14 subjects dropped out, including 5 of 81 subjects (6.2%) in the NT 201 240 U group, 3 of 78 subjects (3.8%) in the NT 201 120 U group, and 6 of 74 subjects (8.1%) in the placebo group. Of these, three subjects withdrew due to TEAEs: 2 of 81 subjects (2.5%) in the 240 U group (Subject 1076: muscular weakness; Subject 1332: muscular weakness, neck pain, and musculoskeletal pain) and 1 of 78 subjects (1.3%) in the 120 U group (Subject 1033: dizziness and nausea). All of the TEAEs leading to drop-out were considered related to study treatment (CD ISS, pg. 34).

Merz noted that no subject in the Main Period of Study 0605/1 withdrew because of a TEAE.

7.3.3.3.2 CD Discontinuations in Other Studies

In the other CD studies, Merz reported that five subjects withdrew due to a TEAE, three of which were treated with NT 201.

1. In the Study 0408/2 Extension Period, Subject 1232 withdrew because she was pregnant.
2. In Study 9801, Subject 0801, who had received NT 201, was diagnosed with a malignant neoplasm of the pharynx, and withdrew because of postsurgical pain and scarring which precluded further treatment
3. In the Study 0605/2 OLEX Period, Subject 1007, who had received NT 201 in the Main and OLEX Periods of the study, withdrew because of a myocardial infarction.

7.3.3.3 Sponsor Analysis of CD Discontinuations

The sponsor examined adverse events leading to discontinuation by Botulinum toxin pretreatment status. Among the CD studies, only Study 0408 enrolled both Botulinum toxin pre-treated and treatment-naïve subjects. In the Study 0408/1 Main Period, Merz noted that the three patients who withdrew due to a TEAE included two of the 72 treatment-naïve subjects (2.8%) and 1 of the 87 pre-treated subjects (1.2%). Sub-analyses by demographic characteristics were not possible due to the small number of discontinuations.

7.3.3.4 Discontinuations: SP

7.3.3.4.1 SP Discontinuations: Placebo-Controlled Studies

The sponsor summarized the reasons for study withdrawal within placebo-controlled Study 0408/1 and Study 0607 in the table below.

FDA Table 37: Reasons for Study Discontinuation in SP Studies 0408/1 and 0607 Combined (Adapted from Sponsor Table 3, submitted following FDA request, received May 27, 2010))

<i>Withdrawals: Summary of Patients and Reasons</i>			
<i>MAIN(Main reason) (Treatment Code)</i>			
<i>Frequency</i>			
<i>Percent</i>			
<i>Col Pct</i>	<i>NT 201</i>	<i>Placebo</i>	<i>Total</i>
<i>Adverse event</i>	2	1	3
	0.59	0.29	0.88
	0.75	1.33	
<i>Consent withdrawn</i>	3	0	3
	0.88	0.00	0.88
	1.13	0.00	
<i>Lost to follow-up</i>	2	0	2
	0.59	0.00	0.59
	0.75	0.00	
<i>Other</i>	7	0	7
	2.06	0.00	2.06
	2.64	0.00	
<i>Completer</i>	251	74	325
	73.82	21.76	95.59
	94.72	98.67	
<i>Total</i>	265	75	340
	77.94	22.06	100.00

In the main period of Study 0410/1, Merz stated that a total of three patients discontinued from Study 0410/1 (Main Period), only one of which was in an NT 201-treated patient (Patient 1119, paraparesis). One NT 201-treated patient also withdrew consent and discontinued (Subject 1180)(0410/1 Study Report, pg. 97).

7.3.3.4.2 SP Discontinuations: Open-Label Studies

In the Study 0410/2 OLEX Period, Merz stated that eight subjects discontinued due to TEAE. Three of these discontinuations were due to patient death (discussed in Section 7.3.1 of this review). The sponsor stated that seven NT 201-treated patients discontinued Study 0410/2 OLEX Period because of a TEAE.

The other seven adverse events leading to discontinuation in SP 0410/2 were injection site pain, dysphagia, CVA, hypokinesia and colon cancer. Merz concluded that overall there was no pattern to the events leading to discontinuation, and most were related to the subjects' medical history and underlying health status (SP ISS, pg. 34).

Reviewer comment: *I reviewed the narrative for the spasticity patient who withdrew from 0410/2 due to dysphagia (Patient 1142), as this is not an expected AE within the spasticity indication. The event occurred in a 74-year-old man, and the narrative was lacking in detail,*

stating only (b) (6), the subject developed the TEAE dysphagia. The event, which was mild in intensity, resolved on an unspecified date. The study drug was withdrawn as a consequence of this event.” (ISS Appendix D, pg. 202).

Reviewer comment: A request was made to the sponsor for additional information on this case, including the timing of dysphagia with regard to NT 201 treatment. The sponsor responded with the following enhanced narrative:

Subject 1142 (Adverse Event: DYSPHAGIA): This 74-year-old male subject (height 176 cm, weight 68.5 kg, BMI 22.1) was an ex-smoker and had a past medical history significant for ischaemic cerebrovascular accident. At entry to the Main Period (baseline) it had been 1.3 years since the occurrence of the ischemic stroke and since the first diagnosis of upper limb spasticity. The subject was Botulinum toxin treatment-naïve. An ECG was performed at Screening and the results were abnormal and clinically relevant (Flat T-Wave in T2-T4 leads). The subject entered the Main Period on 03-Jul-2006 and received a first injection with 330 U of NT 201 on 10-Jul-2006, injected under EMG stimulator control for the treatment of the clinical patterns of Flexed Wrist, Clenched Fist, Flexed Elbow and Thumb in Palm. No adverse events were reported for the subject during the Main Period. At entry to the OLEX Period on 02-Oct-2007, the following concomitant diseases and medications were ongoing in this subject: hypertension (amlodipine 10 mg p.o./daily and enalapril 30 mg p.o./daily); hypercholesterolemia; hemiparesis; drug hypersensitivity; electrocardiogram Q wave abnormal; facial paresis; hypoglossal nerve paresis; and hyperreflexia. The subject was also receiving treatment with acetylsalicylic acid (75 mg p.o./daily) for cerebrovascular accident prophylaxis. On 02-Oct-2006 and 02-Jan-2007, the subject received 310 U and 325 U of NT 201, respectively, injected under EMG stimulator control for the treatment of the clinical patterns of Flexed Elbow, Flexed Wrist and Clenched Fist.

On 11-Oct-2006 the subject experienced an episode of dysphagia that was assessed as mild in intensity and related to study treatment by the investigator. The event resolved on an unknown date. On 03-Jan-2007, one day after the last injection with NT 201, the subject developed a second TEAE dysphagia. The event, which was also mild in intensity, resolved on an unspecified date. The study drug was withdrawn as a consequence of this event. The last study visit was on 19-Jul-2007. The Investigator assessed the event as related to the study treatment, no further details regarding both episodes of dysphagia were reported.

Reviewer comment: Although the narrative above was somewhat unclear on this point, this event describes a SP patient, who received NT 201 injection in the upper extremity, who twice experienced dysphagia following NT 201 treatment (310 U and 320 U for the first and second adverse events, respectively). Further, the event appeared temporally related to NT 201 administration, occurring 9 days after treatment in the first event and one day after treatment in the second event. This case raises concern of systemic spread of toxin effect, and is also discussed in Section 7.3.5.1 (AESIs) of this review.

7.3.3.4.2 SP Discontinuations: Other Studies

Merz stated that no patients in Study (b) (4) withdrew due to a TEAE. In Studies 0607 and (b) (4), a total of three NT 201-treated patients withdrew due to TEAE.

- Patient 1025 experienced cerebral haemorrhage and transient ischemic attack in Study 0607
- Patient 114 experienced carotid artery stenosis in Study (b) (4)
- Patient 101 in Study (b) (4) experienced a myocardial infarction (described in Section 7.3.1 of this review)

Reviewer comment – Summary of Discontinuations: *Although the number of discontinuations due to AE is low in the NT 201 development program, it is consistent with that seen in other botulinum toxin development programs. The number of discontinuations due to adverse event was (0.5% (6/1313 patients) in the NT 201 treatment group, 0.3% (1/396 patients) Botox-treated subjects and 0.3% (1/346 patient) among placebo-treated patients. During the course of the safety review, I did not notice a pattern among the patients discontinuing due to adverse event. I audited the narratives of patients who discontinued for reasons other than adverse events (such as withdrawal of consent and loss to follow-up).*

7.3.4 Significant Adverse Events

Any adverse event that is included among the symptoms of spread of toxin effect were closely examined within this review. Primary among these were adverse events related to pulmonary difficulties and respiratory distress. The patients in the NT 201 development program who experienced dyspnea or respiratory failure are discussed in Section 7.3.2 (SAEs) and Section 7.4.1 (Common AEs) of this review.

During the review of the primary submission, a case report of a report was received describing anaphylaxis shortly after NT 201 use for glabellar frown lines, This case and other information related to the possibility of anaphylaxis is discussed in further detail in Section 9.6 of this review.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Adverse Events of Special Interest (AESIs)

During the planning of the NT 201 development program, the FDA requested that Merz monitor studies for Adverse Events of Special Interest (AESIs). A list of AESIs was developed based on adverse events that had been observed for other botulinum toxin products.

During the planning of the NT 201 development program, the FDA requested that Merz monitor studies for Adverse Events of Special Interest (AESIs). This list of AESIs was developed based on adverse events that had been observed for other botulinum toxin products. The FDA provided the guidance below to the sponsor following a sponsor question on the analysis of AESIs :

“The pooling of datasets for the above analyses should be for each indication and across all indications. In addition to the analysis based on the list of Adverse Events of Special Interest in the briefing book, please perform another analysis based on the following terms: Botulism, muscular weakness, muscle paresis, paralysis, paralysis flaccid, areflexia, hyporeflexia, hypotonia, peripheral nerve palsy, peripheral paralysis, cranial nerve palsies multiple, paresis cranial nerve, cranial nerve paralysis, bulbar palsy, facial paresis, facial palsy, accommodation disorder, diplopia, eyelid function disorder, eyelid ptosis, pupillary reflex impaired, vision blurred, vocal cord paralysis, vocal cord paresis, speech disorder, dysphonia, dysarthria, dysphagia, aspiration, pneumonia aspiration, dyspnea, respiratory depression, respiratory failure, respiratory arrest, diaphragmatic paralysis, bradycardia, dry mouth, constipation, ileus paralytic, pelvic floor muscle weakness, and urinary retention.” (FDA Minutes for Sponsor Meeting on December 12, 2008)

7.3.5.1.1 AESIs: Pooled Indications

In the placebo-controlled studies of NT 201, Merz reported that the overall incidence of AESIs in the NT 201 treatment group was higher than in the placebo group.

At the PT level, the only AESI that occurred with a greater incidence in the NT 201 group, compared with the placebo group, with a difference of $\geq 2\%$ was dysphagia (28 of 701 subjects, 4.0%, vs. 5 of 346 subjects, 1.5%)(ISS, pg. 72).

7.3.5.1.2 AESIs: BEB

In the BEB Study 0433/1 Main Period, Merz noted that 32 of 74 subjects (43.2%) in the NT 201 group and 9 of 34 subjects (29.5%) in the placebo group experienced adverse events of special interest (AESIs). For subjects in the NT 201-treated group, the most common of these events were eyelid ptosis (14 subjects, 18.9%), dry mouth (12 subjects, 16.2%), vision blurred (4 subjects, 5.4%) and dyspnea (4 subjects, 5.4%). For subjects in the placebo-treated group, the most common AESIs were eyelid ptosis (3 subjects, 8.8%), vision blurred, dysphagia, and muscular weakness (each in 2 subjects, 5.9%). The sponsor stated that all other AESIs occurred in <1% of subjects in the NT 20 treatment group (BEB ISS, pg. 39).

Reviewer comment: *It is notable that just under 10% of the patients in the placebo group reported ptosis. One would expect this to be a paralytic effect of NT 201, but the occurrence in the placebo group suggests it may also be injection dependent or related to patient expectations.*

Reviewer comment: See also Section 7.5.3.2.2 of this review for details of an analysis of AESI's by age group.

When the OLEX data from study 433/2 was combined with the data from Study 0433/1 Main, the results were similar to those for the Study 0433/1 Main Period. (BEB ISS, pg. 40).

7.3.5.1.3 AESIs: CD

In the Main Period of Study 0408/1, the sponsor stated that the overall incidence of AESIs was higher in NT 201- treated subjects (37 [23.3%] of 159) than in placebo-treated subjects (3 [4.1%] of 74). In the pooled CD studies (Study 0408/1 Main Period, 9801, and 0013), Merz reported that 69 of 431 subjects (16.0%) in the NT 201 treatment group, and 3 of 74 subjects (4.1%) in the placebo group, experienced AESIs. For NT 201-treated subjects, the most common of these events were dysphagia (12.3%) and muscular weakness (4.2%). All other AESIs occurred in <1% of subjects in the NT 201 treatment group (CD ISS, pg. 28).

Merz examined a number of risk modifiers for the association of AESIs in the CD indication. Merz stated that no difference in AESI incidence by age or gender was observed. However, the incidence of AESIs appears to decrease in NT 201-treated subjects with moderate to severe disease at baseline, compared with those with mild disease. Although the reason for this relationship was unclear, the sponsor hypothesized the following:

“One possible explanation is that subjects with moderate and severe CD often have substantial muscle hypertrophy due to the continuous muscle activity. Botulinum neurotoxin administration usually targets these hypertrophic muscles. These hypertrophic muscles present a substantial tissue mass that the Botulinum neurotoxin must diffuse across before reaching non-targeted muscles to cause AESIs. Conversely, in subjects with mild disease, the targeted muscles have relatively less tissue, and thereby present less of a barrier to diffusion. The proposed clinical administration of NT 201 includes flexible dosing to adjust for the mass of the targeted muscle (see Section 1.14.1.3, Package Insert, Section 2.4.1, Dosage). However, in the clinical trials, there was substantially less flexibility in the dosing; patients with mild, moderate, and severe disease received similar, protocol-specified doses of NT 201; because subjects with more severe disease most likely had more muscle mass, these subjects may have been less likely to experience AESIs.”(CD ISS, pg. 30)

Reviewer comment: The sponsor's hypothesis above seems a reasonable explanation of the apparent inverse relationship between disease severity and the occurrence of AESIs.

In the Main Period of Study 0408/1, Merz stated that the incidence rates of AESIs with NT 201 treatment also “appears” higher in patients who were treatment-naïve at baseline and hypothesized that this was most likely due to enrollment bias (i.e., subjects who are pretreated and enroll in this study are preferentially subjects who had no adverse experience with previous Botulinum toxin administration)(CD ISS, pg. 57).

Reviewer comment: *The sponsor's hypothesis regarding the association of pre-treatment status and AESIs is plausible.*

7.3.5.1.4 AESIs: SP

In the Study 0410/1 Main Period, Merz reported that 1 of 73 subjects (1.4%) in the NT 201 group (reported AE terms: constipation and paraparesis) and 1 of 75 subjects (1.3%) in the placebo group (reported AE term: dysphagia) experienced AESIs (SP ISS, pg. 43).

Reviewer comment: *The lack of a difference between AESIs in the placebo and treatment group is unexpected. In addition, it is inconsistent with the findings in the other indications: the risk of AESIs in the BEB indication was about twice as high in treated patients and about four times as high in the CD indication. However, in the pooled SP studies (described in the text immediately below) AESIs show a two-fold increase consistent with the other indications.*

In the pooled SP studies (the Study 0410/1 Main Period and Study 0607), Merz stated that 6 of 265 subjects (2.3%) in the NT 201 treatment group, and 1 of 75 subjects (1.3%) in the placebo group, experienced adverse events of special interest (AESIs). For NT 201-treated subjects, the most common of these events was muscular weakness (3 subjects, 1.1%). All other AESIs (i.e., dysphagia, constipation, dysarthria, and paraparesis) occurred in only one subject in the NT 201 treatment group (SP ISS, pg. 43).

In the Study 0410/2 OLEX Period, Merz reported that nine subjects treated with NT 201 experienced AESIs. The events experienced by these subjects were muscular weakness (5 subjects), hemiparesis (2 subjects), dysphagia (1 subject), and dry mouth (1 subject). Merz performed a number of sub-analyses and stated that the incidence of AESIs did not increase with greater number of NT 201 injections or longer observation period (SP ISS, pg. 44).

7.3.5.2 Spread of Toxin Effect

Merz conducted two studies specifically to examine the diffusion potential of NT 201: Study 0709 CSR, and the Study 0113.

Merz asserted that, as shown in the descriptions of the most common adverse events, no symptoms indicative of clinically important systemic diffusion of NT 201 (e.g., general or respiratory muscle paresis, diplopia, dysarthria) were observed in NT 201 development program. The sponsor also stated that other potential indicators (e.g., non-specific muscular weakness, dyspnea, paresthesia, dysesthesia) occurred in a small number of subjects and the only adverse event suggestive of local diffusion that occurred more often in NT 201 patients, compared to placebo, with a difference of $\geq 2\%$, was dysphagia (5.0% vs. 1.5%) (Clinical Overview, pg. 32).

Reviewer comment: *In addition to the general review of AEs, I searched the indication specific (BEB, CD, SP) summaries for cases "dyspnea," "respiratory" and "paralysis" in an attempt to*

capture all AEs that may be related to severe systemic spread of NT 201. This search revealed a number of cases of dyspnea and respiratory difficulty (pulmonary embolism, chronic bronchitis, asthma exacerbation, etc.), but none fit the pattern of systemic botulinum toxin spread. These cases are discussed in Section 7.3.2 (SAEs) and 7.4.1 (Common Adverse Events).

One case that raised concern of systemic spread occurred in an SP patient (Patient 1142) who received NT 201 injection in the upper extremity, who twice experienced dysphagia following NT 201 treatment (310 U and 320 U for the first and second adverse events, respectively). Further, the event appeared temporally related to NT 201 administration, occurring nine days after treatment in the first event and one day after treatment in the second event.

Reviewer Conclusion: *I recommend that the Boxed Warning describing systemic spread of toxin effect contained in the label of other botulinum toxin class members also be included in the NT 201 labeling.*

7.3.5.3 Hyperglycemia

7.3.5.3.1 Background

During the review of another botulinum toxin product (Dysport®) a small elevation of blood glucose was observed in drug-treated compared to placebo-treated patients. The Dysport® label contains the following statement in the “Laboratory Findings” section:

“Subjects treated with DYSPORT® exhibited a small increase from baseline (0.23 mol/L) in mean blood glucose relative to placebo-treated subjects. This was not clinically significant among subjects in the development program but could be a factor in patients whose diabetes is difficult to control.”

Due to this finding in the Dysport® review, the FDA requested¹⁶ that the sponsor perform expanded analyses of glucose within the NT 201 development program.

7.3.5.3.2 Hyperglycemia: Pooled Indications

At the request of FDA¹⁷, Merz performed additional analyses of the effects of treatment with NT 201 on blood glucose, by dose and duration, were performed for the pooled NT 201 safety database.

The sponsor stated that an analysis of mean changes from baseline to the primary endpoint assessment and final visits by NT 201 dose group “did not reveal a trend.” However, in the >360 U NT 201 treatment group, Merz reported that the mean (SD) change in blood glucose level in

¹⁶ Meeting minutes (December 12, 2008 Meeting)

¹⁷ Request sent 2008

NT 201-treated patients from baseline to the primary endpoint assessment visit was 1.1 (1.38) mmol/L. Merz noted that this increase in glucose did not persist when the change from baseline to the final visit was analyzed 0.32 (1.56) mmol/L. The sponsor noted that the >360 U NT 201 group patients were all from the SP studies. In the pooled SP studies, the sponsor reported that “a similar but more pronounced increase in blood glucose values occurred in the placebo group for the same time period.”

Reviewer comment: *I reviewed the tables referenced by the sponsor¹⁸ and concurred with the sponsor’s description summarized above. For the pooled data, the picture is mixed. Although there was a slight increase with NT 201 treatment to primary assessment, the effect did not persist to the final study visit, and a larger increase was also observed in the placebo group.*

Merz asserted that there were no clinically meaningful difference in mean changes from baseline to the primary endpoint assessment and final visit between subjects followed for >2 to ≤24 weeks, and those followed for >24 to ≤48 weeks (ISS 120-Day Safety Update, pg. 89).

Reviewer comment: *In the specific indications summarized in the sections below, and throughout their safety documents, Merz presented glucose data with the placebo-controlled and open-label data combined.*

Table 37: Change in Glucose from Baseline to Final Study Visit in the Placebo-Controlled Phase of Study0433 (BEB), Study 0408 (CD) and Study 0410 (SP)

(Adapted from Sponsor Text and Sponsor Tables supplied in Response to FDA Request)

BEB		
Controlled Study Name (Length of Study)	Baseline Mean Glucose (N)	Mean Glucose at Final Visit
0433/1 Length: Up to 20 weeks	NT 201: 5.34 (N=74) Placebo: 5.28 (N=34)	NT 201: 5.47 Placebo: 5.74
CD		
Controlled Study Name (Length of Study)	Baseline Mean Glucose (N)	Mean Glucose at Final Visit
0408/1 (8 to 20 weeks)	NT 201: 5.29 (N=154) Placebo: 5.27	NT 201: 5.34 Placebo: 5.46

¹⁸ The tables referenced by the sponsor were ISS Tables 6.4.1.1, 6.4.2.1, 6.4.3.1, 6.4.4.1 and 6.4.1.2.3.1.

	(N=70)	
SP		
Controlled Study Name (Length of Study)	Baseline Mean Glucose (N)	Glucose at Final Visit
0410/1 (12 to 20 weeks)	NT 201: 5.64 (N=73) Placebo: 5.85 (N=75)	NT 201: 5.90 Placebo: 6.26

Reviewer comment: *The table above shows that the mean glucose was usually higher at the final visit compared to baseline. However, this trend occurs in both the NT 201 and the placebo-treated patients, and is more pronounced in the placebo patients. However, as with the vital signs analysis (Section 7.4.3), the laboratory testing at the final visit was drawn weeks after the previous NT 201-treatment, and hence at a time when the effect of NT 201 had waned.*

7.3.5.3.3 Hyperglycemia: BEB

Merz presented serum glucose data as mean values and shifts from the previous injection within the BEB Study 0433/1 Main Period and Study 0433/2 OLEX Period (analyzed together), and asserted that “no trend toward an increase in mean serum glucose values over time, or increases in serum glucose in the groups of subjects with higher numbers of NT 201 injections, versus lower numbers of injections, was observed.” Further, Merz stated that there were no clinically meaningful differences in serum glucose values between the dose groups and no pattern of clinically meaningful shifts in serum glucose values from the previous study visit (ISS, 120 Day Update, pg. 63).

Reviewer comment: *I reviewed the tables the sponsor quoted (ISS Appendix K, 5.1.1.1, and 5.2.1.1) and verified that glucose levels over the course of the study and between the NT 201 and placebo treatments groups were essentially equivalent.*

Two patients in the BEB Study 0433/1 Main Period and Study 0433/2 OLEX Period had high a “clinically significant” serum glucose value:

1. **Patient 2011** was a 48-year-old man who received a single dose of NT 201 in the Main Period of the study, and five doses of NT 201 in the OLEX Period. The patient did not report a previous history of hyperglycemia or diabetes mellitus. The patient’s serum blood glucose values at screening and before the second injection of study treatment were within normal limits (normal range: 68 to 110 mg/dL). Before the third injection, on April 23, 2007, the subject’s serum glucose value was 140 mg/dL. The patient also had elevated glucose values of 160 mg/dL before the 5th injection, and 198 mg/dL at the final visit. The subject received a total of six injections, and completed the study.

***Reviewer comment:** The patient above (Patient 2011) is notable for an apparently escalating blood glucose with subsequent injections (Normal at baseline, 140 mg/dL before the third injection, 160 mg/dL before the fifth injection, and 198 mg/dL at final visit. Based on this single case, however, it is not possible to make a conclusion regarding causality.*

2. **Patient 2129** was a 68-year-old woman who received a single dose of NT 201 in the Main Period of the study, and one dose of NT 201 in the OLEX Period. She was noted to have hyperglycemia at screening for the Main Period of the study, with a serum glucose value of 126 mg/dL (normal range 68 to 110 mg/dL). She did not report a previous history of hyperglycemia or diabetes mellitus. The patient had elevated serum glucose values of 173 and 126 mg/dL before the 2nd injection and last observation visit respectively. The patient was withdrawn from the study because of a protocol violation (the subject was mistakenly given open-label NT 201, instead of randomized, double-blind treatment with NT 201 or placebo, at the first injection).

7.5.3.3.4 Hyperglycemia: CD

Merz stated that in the Main Period of Study 0408/1, there were “no clinically important mean changes or shifts from baseline to the final visit in NT 201-treated patients.”

***Reviewer comment:** I reviewed the sponsor’s tables displaying the glucose-related data in the placebo-controlled CD study 0408/1 (Table 6.4.1.2.1.2.2, Table 6.4.3.2.1.2.2, 0408/1 Study Report) and agreed that there were no apparent changes in mean glucose over time.*

Merz also analyzed serum glucose mean values and shifts from the previous injection for the Study 0408/1 Main Period and Study 0408/2 Extension Period (analyzed together). The sponsor found no trend toward an increase in mean serum glucose values over time, or increases in serum glucose in the groups of subjects with higher numbers of NT 201 injections, versus lower numbers of injections. For the 153 subjects who completed the Study 0408/2 Extension Period as of October 2008, and have unblinded NT 201 dose data, the sponsor stated that there was no clinically meaningful difference in mean serum glucose values between the ≤ 120 U group and the >120 to 240 U group, or from prior study visit (ISS, 120 Day Update, pg. 62).

In the Study 0408/1 Main Period and Study 0408/2 Extension Period, a total of seven subjects experienced CS abnormal serum glucose values. However, for five of these patients the value was a baseline test prior to NT 201 treatment. The two treatment-emergent cases are shown below (ISS 120 Day Update, pg. 63):

1. **Patient 1107** had a CS high serum glucose value of 7.5 mmol/L (normal range 3.8 to 6.1 mmol/L) before injection 4. The subject’s serum glucose value before the 5th injection was within normal limits. This subject received NT 201 120 U in the Main Period, and 240 U in the Extension Period. She had elevated hepatic alkaline phosphatase, total cholesterol, and LDL cholesterol values, and a normal serum glucose value, at screening

for the Main Period. Her past medical history did not include diabetes or glucose intolerance, and she did not report medications for the treatment of these conditions during the study. The subject's TEAEs were musculoskeletal pain, neck pain, headache, pain in extremity, and joint swelling.

2. **Patient 1049** had a CS low serum glucose (2.9 mmol/Labeling) at the last study visit. She had received six injections and had no other CS abnormalities in serum glucose values during the study.

7.5.3.3.5 Hyperglycemia: SP

Within the SP indication, the sponsor stated Patient 1009 in the Study 0410/2 OLEX Period experienced a SAE classified as "diabetes mellitus inadequate control." She had a history of diabetes as well as elevated glucose prior to the first injection, (137 mg/dL). At Visit 8, the patient's glucose value of 432 mg/dL, and she was hospitalized for control of her diabetes mellitus. The patient's medications were adjusted and the event resolved. At Visit 10, following the resolution of the event, the subject had a low, not CS glucose value of 57 mg/dL. Merz stated that the subject's remaining on-study glucose values were normal (97 mg/dL at Visit 12), or high but not clinically significant (CS) by the investigator (115 mg/dL at Visit 14 and 174 mg/dL at Visit 18). The sponsor stated that no action was taken with the study drug (ISS 120 Day Update, pg. 63).

Reviewer comment: Although this patient's pre-existing diabetes could explain the glucose levels noted above, it is also possible that treatment with NT 201 exacerbated her already high glucose levels (137 mg/dL) to an even higher level (432 mg/dL).

In the Study 0410/1 Main Period and Study 0410/2 OLEX Period (analyzed together), Merz reported that six patients who had serum glucose values at the first injection visit that were within normal limits experienced abnormalities in serum glucose values while receiving NT 201 during the study. However, five of the patients had a pre-existing history of diabetes. Study

Appears this way on original

Reviewer comment – Overall Reviewer Conclusions: The data linking NT 201 to an effect on glucose levels is mixed. There were cases of elevated blood glucose in NT 201-treated patients, including one in the spasticity indication that was classified as an SAE due to the need for hospitalization. Within the placebo-controlled trials, there were also more clinically significant glucose values in the NT 201 compared to the placebo treated patients, but the overall number of patients with events in each group was small. (For example, in the spasticity indication, 3 cases in the NT 201 group compared to none in the placebo group). When mean glucose value was compared from the initial study visit to the primary endpoint visit and the final visit with the placebo-controlled trials, the values for NT 201, placebo and Botox® were similar (both over time and between groups).

7.3.5.4 Alkaline Phosphatase

7.3.5.4.1 Alkaline Phosphatase: Pooled Indications

Because of a slight elevation of alkaline phosphatase in the safety review of a different botulinum toxin product, alkaline phosphatase has been evaluated in recent submissions of botulinum toxin products. In prior botulinum toxin products, the safety reviews there was a concern of elevated alkaline phosphatase levels, although the safety data was not sufficient to include any statement on the subject in either the Dysport® or the Botox® label.

Reviewer comment: As with the glucose analysis, the sponsor performed a variety of analyses to assess alkaline phosphatase levels in the NT 201 development program, including by indication, injection number, dose groups and over time. These were performed on the placebo-controlled and open-label data combined. The analyses typically involved shift changes and trends in alkaline phosphatase levels in the NT 201 treated group by various parameters. Because these tables were difficult to access and interpret, the sponsor was asked to complete the table below.

Table 38: Change in Alkaline Phosphatase from Baseline to Final Study Visit in the Placebo-Controlled Phase of Study0433 (BEB), Study 0408 (CD) and Study 0410 (SP)

(Adapted from Sponsor Text and Sponsor Tables supplied in Response to FDA Request)

BEB		
Controlled Study Name (Length of Study)	Baseline Mean AP (N)	Mean AP at Final Visit
0433/1 Length: Up to 20 weeks	NT 201: 79.2 (N=74) Placebo: 74.2 (N=34)	NT 201: 81.1 Placebo: 75.4
CD		
Controlled Study Name (Length of Study)	Baseline Mean AP (N)	Mean AP at Final Visit
0408/1 (8 to 20 weeks)	NT 201: 72.0 (N=154) Placebo: 73.4 (N=70)	NT 201: 72.0 Placebo: 73.2
SP		
Controlled Study Name (Length of Study)	Baseline Mean AP (N)	Mean AP at Final Visit
	NT 201: 74.6	NT 201: 73.5

0410/1 (12 to 20 weeks)	(N=73) Placebo: 75.4 (N=75)	Placebo: 74.4

Reviewer comment: Based on the table above, the mean alkaline phosphatase does not show a difference between the NT 201 and placebo-treated patients when compared from baseline to final visit (alkaline phosphatase testing was not performed at the primary endpoint visit).

7.3.5.4.2 Alkaline Phosphatase: BEB

Merz stated that an analysis of alkaline phosphatase mean values and shifts from the previous injection was performed for the Study 0433 (BEB) Main and OLEX Periods (analyzed together). The sponsor asserted that “no trend toward an increase in alkaline phosphatase over time, or of higher mean values in the groups of subjects with higher numbers of NT 201 injections, compared with those with lower numbers of injections. The sponsor maintained that there were also no clinically meaningful differences in mean alkaline phosphatase values between the NT 201 dose groups” (Table 5.1.1.2, ISS Appendix K)(ISS, pg. 60).

Reviewer comment: I reviewed the table referenced by the sponsor for the statements in the paragraph above (Table 5.1.1.2, ISS Appendix K) and found them to be accurate.

Merz stated that two subjects had elevated alkaline phosphatase values, but that only one of these was treatment-emergent (the other was present before the patient received their first injections). The sponsor reported that Subject 2106 had a high, CS abnormal alkaline phosphatase value before Injection 2 (169 U/L; normal range 36-118 U/L). The sponsor noted, however, that this patient also had a high alkaline phosphatase value (135 U/L) before the first injection (ISS 120 Day Update, pg. 60).

7.3.5.4.3 Alkaline Phosphatase: CD

Merz performed an analysis of alkaline phosphatase mean values and shifts from the previous injection for NT 201-treated patients in the Study 0408/1 Main Period or 0408/2 Extension Period (analyzed together) and found “no trend toward an increase in alkaline phosphatase over time, or of higher mean values in the groups of subjects with higher numbers of NT 201 injections, compared with those with lower numbers of injections” was observed. For the 166 subjects whose treatment assignment was unblinded, Merz reported that there was no clinically meaningful difference in mean alkaline phosphatase values or shifts from the previous injection, between the ≤120 U group and the >120 to 240 U group (CD ISS, pg. 70).

Merz stated that in the open-label extension period (0408/2), two NT 201-treated patients had elevated alkaline phosphatase levels (CD ISS, pg. 60):

1. **Subject 1107:** This 57-year-old woman, had an elevated alkaline phosphatase value of 140 U at screening (normal range 36-118 U), and elevated values of 132 U, 127 U and 136 U at the final visit of the Main Period, the 4th injection visit, and the 5th injection visit, respectively. At the trial termination visit the value was slightly elevated (122 U). The patient received one injection of NT 201 (120 U) during the Main Period, and four additional injections of NT 201 (240 U) during the Extension Period, and completed the study.
2. **Subject 1316:** This a 72-year-old woman, had alkaline phosphatase values that were within normal limits (normal range 36-118 U) at all study visits until the final visit of the Extension Period, when her alkaline phosphatase value was 134 U. During the study, the patient also had multiple elevated gamma-glutamyltransferase values: 53 U/L (normal range 8 to 49 U/L) at screening; 53 U/L before the 3rd injection, and 70 U/L before the 4th injection, and 142 U/L at the final visit. The patient received NT 201 (240 U) in the Main Period and three injections of NT 201 (still blinded) during the Extension Period, and completed the study.

Reviewer comment: *Because these elevations occurred in the OLEX study 0408/2, it is difficult to tell if they represent an elevated risk in the drug-treated patients compared to non-treated patients.*

7.3.5.4.4 Alkaline Phosphatase: SP

In the Study 0410 (SP) Main and OLEX Periods (analyzed together), Merz stated that there were no clinically meaningful mean changes from baseline or the previous injection, or shifts from baseline or the previous injection, for alkaline phosphatase values. One NT 201- treated patient who did not have a CS abnormality in alkaline phosphatase at study entry developed a CS abnormality during the study. Merz provided the following summary narrative (ISS 120 Day Update, pg. 61).

Subject 1132 received placebo in the Main Period of Study 0410/1. The patient had a high, not CS alkaline phosphatase value of 136 U/L (normal range 35 to 123 U/L) before the first NT 201 injection, followed by normal values (115 U/L and 120 U/L at the primary endpoint analysis visit 4 weeks after injection, and before the second injection, respectively), and a CS high value of 172 U/L before the 4th injection. The patient's remaining values during the study were on the high end of the normal range (121 U/L at Visit 14 and 117 U/L at Visit 16).

Reviewer comment: *There was no additional information following the patient's completion of the study to determine whether the alkaline phosphatase level returned to normal.*

7.3.5.4.5 Alkaline Phosphatase: Non-Neurologic Indications

Merz noted that one patient in the glabellar frown line studies had a CS alkaline phosphates value following treatment with NT 201, as presented below:

Subject 2033 is a 56-year-old white woman who was initially enrolled in Study 0520. The subject entered Study 0609 and received the first treatment with NT 201 in that study on October 5, 2007. She received a total of 4 cycles of treatment in Study 0609. Her medical history was significant for diverticulosis, sigmoidectomy, diabetes mellitus, and hypothyroidism. Concomitant medications included levothyroxine. At screening, on September 7, 2007, the patient's alkaline phosphatase value was 82 U/L (normal range 20 to 125 U/L). On October 6, 2008, at the 12-month evaluation visit, the subject experienced a CS high alkaline phosphatase value of 171 U/L. She experienced two AEs during the studies: bile duct stone which required hospitalization and moderate gastritis (ISS 130 Day Safety Update, pg. 37).

7.4 Supportive Safety Results

As discussed in Section 7.3.5.2 of this review, the sponsor conducted two studies to examine systemic spread of NT 201 by measuring concentrations at different body sites.

7.4.1 Common Adverse Events

Reviewer comment: A phenomena has been observed in other drug development programs in which the risk of adverse events in studies conducted in North America are higher than those in studies conducted outside North America. For some drugs, the difference was limited to common adverse events, but in others a difference was observed for both common and serious adverse events. A comparison of AE risk in NT 201 studies conducted inside and outside of North American is contained in Section 7.5 of this review ("Other Safety Explorations").

7.4.1.1 Definition of Common Adverse Events

For the sponsor's analysis within the ISS, Merz utilized the following definitions:

- **Common adverse events** were defined as those occurring in $\geq 1\%$ of subjects.
- **Common Treatment Emergent Adverse Events (TEAEs)** were defined as those with a difference of $\geq 3\%$ to placebo at the SOC level and a difference $\geq 2\%$ to placebo at the PT level.
- **Very common adverse events** were defined as those occurring in $\geq 10\%$ of subjects

Reviewer comment: In their analyses, Merz typically presents the chance of adverse events in the form of risk (percent), rather than rate (events per time). In the placebo-controlled Main period of the studies one would expect exposures (dose, number of injections, follow-up time) to be relatively equivalent between groups due to similar discontinuation rates (0.5% NT 201, 0.3% placebo). However, some analyses pooled placebo-controlled and open-label data, and in these analyses the NT 201-treated patients have spent more time in the study than placebo patients. This additional time provides more opportunity for NT 201 patient to experience an adverse

event, whether related to NT 201 or not. This presentation is acceptable, however, as this is a conservative method of analysis that is biased against the drug.

7.4.1.2 Common Adverse Events: Pooled Indications

Reviewer comment: *Explorations for dose-response and the presence of possible risk modifiers for common AEs are contained in Sections 7.5.1 (Drug-Dose Interaction) and 7.5.2 (Drug-Demographic Indication) respectively.*

The following table presents common ($\geq 1\%$) and very common ($\geq 10\%$) adverse events in the pooled placebo-controlled studies within the total NT 201 development program (Clinical Overview, pg. 27).

Table 39: Common ($\geq 1\%$) and Very Common ($\geq 10\%$) Adverse Events in the Pooled Placebo-Controlled Studies within the NT 201 Development Program

(Sponsor Table 5.3.5.3-15, ISS, pg. 46)

Table 5.3.5.3 - 15: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects) Adverse Events in the NT 201 Treatment Group - Pooled, Placebo-Controlled Studies

MedDRA System Organ Class Preferred Term	NT 201 N=701	Placebo N=346
Subjects with TEAEs	368 (52.5%)	140 (40.5%)
Infections and infestations	130 (18.5%)	55 (15.9%)
Nasopharyngitis	40 (5.7%)	27 (7.8%)
Sinusitis	14 (2.0%)	5 (1.5%)
Influenza	13 (1.9%)	7 (2.0%)
Bronchitis	10 (1.4%)	0
Upper respiratory tract infection	7 (1.0%)	4 (1.2%)
Nervous system disorders	102 (14.6%)	40 (11.6%)
Headache	68 (9.7%)	25 (7.2%)
Musculoskeletal and connective tissue disorders	86 (12.3%)	21 (6.1%)
Neck pain	20 (2.5%)	3 (0.9%)
Muscular weakness	15 (2.1%)	3 (0.9%)
Musculoskeletal pain	11 (1.6%)	1 (0.3%)
Back pain	10 (1.4%)	4 (1.2%)
Muscle disorder	9 (1.3%)	0
Musculoskeletal stiffness	8 (1.1%)	2 (0.6%)
Gastrointestinal disorders	78 (11.1%)	20 (5.8%)
Dysphagia	28 (4.0%)	5 (1.5%)
Dry mouth	14 (2.0%)	1 (0.3%)
Diarrhoea	10 (1.4%)	3 (0.9%)
Nausea	10 (1.4%)	1 (0.3%)
Eye disorders	50 (7.1%)	10 (2.9%)
Eyelid ptosis	16 (2.3%)	3 (0.9%)
Dry eye	14 (2.0%)	4 (1.2%)
Respiratory, thoracic and mediastinal disorders	46 (6.6%)	7 (2.0%)
Oropharyngeal pain	12 (1.7%)	2 (0.6%)
Dyspnoea	7 (1.0%)	1 (0.3%)
General disorders and administration site conditions	43 (6.1%)	20 (5.8%)
Injection site pain	12 (1.7%)	6 (1.7%)

Table continues

Table 5.3.5.3 - 15: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects) Adverse Events in the NT 201 Treatment Group - Pooled, Placebo-Controlled Studies

MedDRA System Organ Class Preferred Term	NT 201 N=701	Placebo N=346
Injury, poisoning and procedural complications	31 (4.4%)	11 (3.2%)
Investigations	29 (4.1%)	5 (1.5%)
Skin and subcutaneous tissue disorders	27 (3.9%)	6 (1.7%)
Reproductive system and breast disorders	14 (2.0%)	2 (0.6%)
Psychiatric disorders	12 (1.7%)	2 (0.6%)
Insomnia	7 (1.0%)	0
Metabolism and nutrition disorders	11 (1.6%)	5 (1.5%)
Vascular disorders	10 (1.4%)	6 (1.7%)
Hypertension	7 (1.0%)	2 (0.6%)
Immune system disorders	8 (1.1%)	0

The pooled, placebo-controlled studies were: 0408/1 (CD) Main Period, 0433/1 (BEB) Main Period, 0410/1 (SP) Main Period, 0520/1 (GFL) Main Period, 0527 (GFL), and 0617 (CF).

MedDRA: Medical Dictionary for Regulatory Activities.

Source: Table 3.7.1.1.2, Section 5.3.5.3, Appendix H.

Reviewer comment: *A table of common adverse event is particularly poorly suited to pooling indications because the AEs are indication specific. For example, dysphagia is a common AE in NT 201-treated CD patients, but not in other indications. Likewise for ptosis, which is a common AE for BEB but not for the other indications. Combining the indications dilutes AEs that are indication specific and therefore biases the results.*

Keeping this limitation in mind, in the pooled placebo-controlled trials the AEs with the largest difference between NT 201 and patients were dysphagia (4.0% NT 201 vs. 1.5% placebo), neck pain (2.9% NT 201 vs. 0.9% placebo), muscular weakness (2.1% NT 201 vs. 0.9% placebo), musculoskeletal pain (1.6 % vs. 0.3%), dry mouth (2.0% versus 0.3%), and ptosis 2.3% vs. 0.9%). These AEs are expected within the botulinum toxin class. There was also an increase in NT 201 risk relative to placebo for diarrhea (1.4% NT 201 vs. 0.9% placebo) and nausea (1.4% NT 201 versus 0.3% placebo), which are not well known to be associated with botulinum toxin products (Diarrhea is mentioned in the post-marketing events in the Botox® label and Dysport® label).

Merz acknowledged that in the pooled, placebo-controlled studies, a higher percent of subjects in the NT 201 treatment group experienced TEAEs, compared with the placebo group. The SOCs in which a greater percent of subjects in the NT 201 treatment group compared with the placebo group experienced TEAEs, with a difference of ≥3%, were Nervous system disorders, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, Eye disorders, and Respiratory, thoracic and mediastinal disorders. The TEAEs that occurred in a greater percent of subjects in the NT 201 group, compared with the placebo group, with a difference of ≥2% were headache and dysphagia (ISS, pg. 46).

7.4.1.3 Common Adverse Events: BEB

In the BEB indication, 41.4% of all NT 201-treated patients (all BEB studies combined), 70.3% of NT 201-treated patients in placebo-controlled studies and 61.8% of placebo patients experienced TEAEs.

7.4.1.3.1 Common Adverse Events: BEB – Pooled Studies

In the pooled studies within the BEB indication, 41.1% of all NT 201-treated patients experienced a TEAE, 70.3% of NT 201-treated patients in the placebo-controlled trials, and 61.8% of patients in the placebo-treated patients experienced TEAEs.

Table 40: Adverse Events in the Pooled in the BEB Studies, Overall and by Population
(Adapted from Sponsor Table 9, ISS Appendix B, pg. 17)

	Pooled Blepharospasm Studies		0433/1 Main Period	
	NT 201 N=222	NT 201 N=74	Placebo N=34	NT 201 N=148
Subjects with TEAEs	92 (41.4%)	52 (70.3%)	21 (61.8%)	40 (27.0%)
Subjects with severe TEAEs	7 (3.2%)	4 (5.4%)	0	3 (2.0%)
Subjects with SAEs	3 (1.4%)	0	1 (2.9%)	3 (2.0%)
Subjects who died	0	0	0	0
Subjects with TEAEs leading to dropout	0	0	0	0

SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Source: Table 3.1.1.2.2.1.1, Table 3.1.1.2.2.2.1.2, Table 3.1.1.2.2.2.2.1, Table 3.1.2.2.2.1.1, Table 3.1.2.2.2.2.1.1, Table 3.3.1.2.2.2.1.1, Table 3.3.1.2.2.2.1.1, Table 3.3.1.2.2.2.2.1, Table 3.1.22.1.3, Table 3.6.1.2.2.1.1, Section 5.3.5.3, Appendix H.

The table below displays AE data for the Main and Extension Period of BEB study 0433 by SOC, stratified by number of injections.

Table 41: Common Adverse Events (≥1) in BEB Study 0433 Main and Extension Period by SOC)

(Adapted from Sponsor Table 16, BEB ISS, pg. 22)

Table 16: Common (Occurring in ≥1% of Subjects in Any Category) Adverse Events in the Study 0433 (BEB) Main and Extension Periods, by System Organ Class and Injection

MedDRA System Organ Class	Injection 1 NT 201 N=106	Injection 2 NT 201 N=98	Injection 3 NT 201 N=91	Injection 4 NT 201 N=86	Injection 5 NT 201 N=76	Injection 6 NT 201 N=36
Subjects with TEAEs	70 (66.0%)	42 (42.9%)	47 (51.7%)	32 (37.2%)	27 (35.5%)	14 (38.9%)
Eye disorders	36 (34.0%)	17 (17.4%)	21 (23.1%)	14 (16.3%)	12 (15.8%)	7 (19.4%)
Gastrointestinal disorders	27 (25.5%)	11 (11.2%)	7 (7.7%)	8 (9.3%)	3 (4.0%)	1 (2.8%)
Infections and infestations	18 (17.0%)	5 (5.1%)	12 (13.2%)	9 (10.5%)	9 (11.8%)	3 (8.3%)
Nervous system disorders	15 (14.2%)	7 (7.1%)	5 (5.5%)	3 (3.5%)	4 (5.3%)	2 (5.6%)
General disorders and administration site conditions	12 (11.3%)	3 (3.1%)	3 (3.3%)	2 (2.3%)	4 (5.3%)	-
Respiratory, thoracic and mediastinal disorders	9 (8.5%)	2 (2.0%)	2 (2.2%)	1 (1.2%)	2 (2.6%)	-
Investigations	8 (7.6%)	5 (5.1%)	3 (3.3%)	-	3 (4.0%)	2 (5.6%)
Musculoskeletal and connective tissue disorders	6 (5.7%)	9 (9.2%)	6 (6.6%)	2 (2.3%)	3 (4.0%)	1 (2.8%)
Injury, poisoning and procedural complications	5 (4.7%)	2 (2.0%)	-	3 (3.5%)	1 (1.3%)	-
Skin and subcutaneous tissue disorders	-	3 (3.1%)	1 (1.1%)	5 (5.8%)	2 (2.6%)	-
Metabolism and nutrition disorders	3 (2.8%)	2 (2.0%)	-	-	-	-
Reproductive system and breast disorders	2 (1.9%)	-	1 (1.1%)	-	1 (1.3%)	-
Ear and labyrinth disorders	2 (1.9%)	-	-	-	-	-
Neoplasms, benign, malignant and unspecified	2 (1.9%)	1 (1.0%)	1 (1.1%)	2 (2.3%)	-	-
Hepatobiliary disorders	1 (0.9%)	-	-	-	1 (1.3%)	-
Psychiatric disorders	1 (0.9%)	1 (1.0%)	2 (2.2%)	-	1 (1.3%)	-
Renal and urinary system disorders	1 (0.9%)	-	1 (1.1%)	1 (1.2%)	2 (2.6%)	1 (2.8%)
Immune system disorders	1 (0.9%)	1 (1.0%)	-	1 (1.2%)	1 (1.3%)	-
Vascular disorders	1 (0.9%)	2 (2.0%)	1 (1.1%)	-	1 (1.3%)	-
Cardiac disorders	-	-	-	1 (1.2%)	-	-
Surgical and medical procedures	-	-	-	1 (1.2%)	-	-

Table continues

Table 16: Common (Occurring in ≥1% of Subjects in Any Category) Adverse Events in the Study 0433 (BEB) Main and Extension Periods, by System Organ Class and Injection

MedDRA System Organ Class	Injection 1 NT 201 N=106	Injection 2 NT 201 N=98	Injection 3 NT 201 N=91	Injection 4 NT 201 N=86	Injection 5 NT 201 N=76	Injection 6 NT 201 N=36
Blood and lymphatic system disorders	-	-	-	-	1 (1.3%)	-

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject had a TEAE in that category.

BEB: benign essential blepharospasm; MedDRA: Medical Dictionary for Regulatory Activities; OLEX: open-label extension (period); TEAE: Treatment-emergent adverse event.

Source: Table 3.1.1.1, ISS Appendix J.

7.4.1.3.2 Common Adverse Events: BEB Placebo-Controlled Studies

Merz reported that the adverse events occurring in ≥3% of NT 201-treated subjects compared to placebo in Study 0433/1 Main Period were eyelid ptosis (19% vs. 9%), dry eye (16% vs. 12%), dry mouth (16% vs. 3%), diarrhea (8% vs. 0%), headache (7% vs. 3%), visual disturbance (7% vs. 6%), dyspnea (5% vs. 3%) and nasopharyngitis (5% vs. 3%) (Clinical Overview, pg. 29). Other common adverse events are shown in the following table.

Table 42: Common and Very Common Adverse Events in NT 201-Treated Patients within Placebo-controlled Study 0433/1

(Adapted from Sponsor Table 15, BEB ISS, pg. 26)

Table 15: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events in the NT 201 Treatment Group, Study 0433/1 Main Period

MedDRA System Organ Class Preferred Term	NT 201 Overall	Placebo Overall	NT 201 10-40 U	NT 201 >40 U
	N=74	N=34	N=13	N=61
Subjects with TEAEs	52 (70.3%)	21 (61.8%)	7 (53.9%)	45 (73.8%)
Eye disorders	28 (37.8%)	7 (20.6%)	5 (38.5%)	23 (37.7%)
Eyelid ptosis	14 (18.9%)	3 (8.8%)	2 (15.4%)	12 (19.7%)
Dry eye	12 (16.2%)	4 (11.8%)	3 (23.1%)	9 (14.8%)
Vision blurred	4 (5.4%)	2 (5.9%)	-	4 (6.6%)
Visual impairment	5 (6.8%)	-	-	5 (8.2%)
Lacrimation increased	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Gastrointestinal disorders	22 (29.7%)	5 (14.7%)	5 (38.5%)	17 (27.9%)
Dry mouth	12 (16.2%)	1 (2.9%)	4 (30.8%)	8 (13.1%)
Diarrhoea	6 (8.11%)	-	1 (7.7%)	5 (8.2%)
Dysphagia	3 (4.1%)	2 (5.9%)	1 (7.7%)	2 (3.3%)
Lip disorder	2 (2.7%)	-	-	2 (3.3%)
Infections and infestations	15 (20.3%)	5 (14.7%)	3 (23.1%)	12 (19.7%)
Nasopharyngitis	4 (5.4%)	1 (2.9%)	1 (7.7%)	3 (4.9%)
Respiratory tract infection	4 (5.4%)	1 (2.9%)	-	4 (6.6%)
Gastroenteritis viral	2 (2.7%)	-	-	2 (3.3%)
Urinary tract infection	2 (2.7%)	-	-	2 (3.3%)
Nervous system disorders	10 (13.5%)	3 (8.8%)	2 (15.4%)	8 (13.1%)
Headache	5 (6.8%)	1 (2.9%)	1 (7.7%)	4 (6.6%)
General disorders and administration site conditions	8 (10.8%)	3 (8.8%)	1 (7.7%)	7 (11.5%)
Asthenia	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Injection site haematoma	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Injection site pain	2 (2.7%)	-	-	2 (3.3%)
Musculoskeletal and connective tissue disorders	4 (5.4%)	7 (20.6%)	1 (7.7%)	3 (4.9%)
Respiratory, thoracic and mediastinal disorders	8 (10.8%)	1 (2.9%)	-	8 (13.1%)
Dyspnoea	4 (5.4%)	1 (2.9%)	-	4 (6.6%)
Injury, poisoning and procedural complications	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Muscle strain	2 (2.7%)	-	-	2 (3.3%)
Investigations	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Metabolism and nutrition disorders	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Ear and labyrinth disorders	2 (2.7%)	-	-	2 (3.3%)
Reproductive and breast disorders	2 (2.7%)	-	-	2 (3.3%)

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: Treatment-emergent adverse event; U: units.

Source: Table 3.1.1.2.2.2.2 and Table 3.1.9.2.2.2.2, Section 5.3.5.3, Appendix H.

Reviewer comment: Ptosis and dry eye would be expected with NT 201 treatment of BEB, and in the NT 201 development program they do have an elevated risk substantially higher risk relative to placebo. Diarrhea also shows a higher rate in the NT 201 group (8% versus 0% placebo)

which as noted previously is not expected, although it is based on a small number of patients (0 in placebo patients versus 1 NT 201 patients).

In response to an FDA request for additional information, the sponsor submitted full narratives for all the patients in Study 0433/1 who experienced either dyspnea or dry mouth. These narratives are contained in full in Appendix 9.8 of this review. A table summarizing doses and days until onset of the AE is presented below.

Table 43: Patients with Dry Mouth or Dyspnea within BEB Study 0433

(Adapted from full narratives presented in Appendix 9.8 of this review)

Patient Number	Event	Dose Prior to Event	Days to Event*
5704	Dry Mouth	100 U	13
5875	Dry Mouth	63 U	23
5710	Dry Mouth	50 U	21
5711	Dry Mouth	60 U	7
5884	Dry Mouth	32.5 U	15
5872	Dyspnea	55.5 U	31
5733	Dry Mouth	40 U	15
5737	Dry Mouth	40 U	29
5741	Dry Mouth, Dyspnea	90 U	14
5852	Dry Mouth	100 U	29
5863	Dyspnea	80 U	21
5770	Dyspnea	50 U	17
5751	Dry Mouth	69 U	70
5766	Dry Mouth	100 U	41

* Days to event from most recent NT 201 dose.

Reviewer comment: *The table above shows that dry mouth occurring after a wide range of NT 201 doses, from 32.5 Units to 100 Unites. The onset of dry mouth or dyspnea was generally between two and four weeks, which is suggestive of a causal association.*

7.4.1.3.3 Common Adverse Events: BEB – Open-Label Studies

Reviewer comment: *For the BEB indication, the sponsor presented the open-label AE data combined with the AE data from the placebo-controlled portion of the study.*

Merz stated that the most common AEs in the repeated dose BEB studies were eyelid ptosis (18.9%), dry eye (16.2%), dry mouth (16.2%), and visual disturbance (6.8%)(BEB ISS, pg. 26).

7.4.1.4 Common Adverse Events: CD

7.4.1.3.1 Common Adverse Events: CD – Pooled Studies

In pooled Main and Extension data from CD Study 0408/1, Merz stated that 194 of 227 subjects (85.5%) experienced TEAEs. In the Study 0410/1 Main Period and 0410/2 OLEX Period combined, the sponsor reported that TEAEs most frequently occurred in the nervous system disorders (30 of 147 subjects, 20.4%), infections (29 of 147 subjects, 19.7%), Investigations, and musculoskeletal/connective tissue disorders (14 subjects, 9.5%, each) SOCs. At the PT level, the sponsor reported that the common AE profile was similar to that in the placebo-controlled trial, and including muscle spasticity (15 subjects, 10.2%), upper respiratory tract infection, hypertension, epilepsy, and depression (7 subjects, or 4.8%, each) as the most frequent AEs (CD ISS, pg. 37).

Reviewer comment: Two patients within the CD indication experienced common adverse events classified as dyspnea. Narratives for these two patients are shown below:

1. **Patient 5537:** This 51-year-old female subject (white, weight 119 lb, height 64 in) was an ex-smoker. Her medical history was significant for surgery to right scapula post MVA (motor vehicle accident) in 1981, concomitant diseases included constipation since 1971, panic/anxiety disorder since 1971, and intermittent left calf swelling since 1996. Concomitant medications were Correctol 2 tabs prn for constipation and Xanax 1 mg prn for anxiety, as well as several vitamin and mineral supplements. During the trial the generalized headache was treated with Aspirin 2-4tabl prn.

Torticollis was first diagnosed in March 2006. Estimated Duration of CD was 10 years. Before entering the study the subject had not been treated with any botulinum toxin. In the MP, the subject received 240 U of NT 201 on 25-OCT-2006. On 28-OCT-2006 the subject experienced stiff neck, which was rated as severe in intensity and related to treatment by the investigator. This event resolved after three days. On 08-NOV-2006 the subject suffered from mild dyspnea which was considered to be related to treatment and resolved after nine days. An investigator comment described this event as “two episodes when stair climbing”. Other non-serious adverse events that occurred on the same day were generalized headache (moderate), head tremors (mild), mumbled speech (mild, reported were intermittent episodes 4-5 times), neck weakness (severe), and left arm weakness (moderate). All of these events were considered treatment-related and for all events the outcome was reported as resolved. The subject continued in the extension period.

2. **Patient 5047:** This 19-year-old male subject (white, weight 210.40 lb, height 70 in) was a non-smoker. His medical history was significant for enlarged heart in 2001 [sic] and pneumonia in 2006. His concomitant diseases included allergic rhinitis since 2005 and restless legs since 24-MAY-2007. At study entry, his concomitant medications comprised Requip 1 mg/day(25-MAY-2007 - 11- SEP-2007) for restless legs. During the main period,

the subject took Advil every 4 hrs prn, doxycycline 100 mg bid, Robitussin DM 2 tbsps 6 times a day, and Tylenol, all for bronchial infection (13-SEP-2007 - 30-SEP-2007), and Advair and Singulair (21-OCT-2007 - ongoing) for Asthma. Torticollis was first diagnosed in October 2005. Prior to study entry the subject had been treated with Botox® between 08-DEC-2005 and 24-MAY-2007. In the MP, the subject received 120 U of NT 201 on 30-AUG-2007. On 02-SEP-2007 the subject experienced pain in bilateral shoulders, which was rated as moderate in intensity and related to treatment by the investigator. This event was ongoing but stable at the end of the trial. On the same day he experienced moderate weakness in bilateral shoulders, which was also considered to be treatment-related and resolved after two weeks. On (b) (6) the subject suffered an asthma attack which was moderate in intensity and not considered treatment-related by the investigator. (b) (6) later, on 31-OCT-2007, the subject experienced chest pain due to bronchial infection and shortness of breath. Both events were of mild intensity and assessed as not related to study treatment. Shortness of breath was reported as resolved 16 days after event onset, chest pain due to bronchial infection was ongoing but stable at the end of the trial. The subject continued in the extension period.

Reviewer comment: *Neither of the two cases above are strongly suggestive of dyspnea due to spread of toxin effect, as the first appears to describe exertional dyspnea and in the second patient the event was characterized as an asthma attack/bronchial infection.*

7.4.1.3.2 Common Adverse Events: CD – Placebo-Controlled Studies

Common ($\geq 1\%$) and Very Common ($\geq 10\%$) adverse events in the placebo-controlled phase of Study 0408 are shown in the table below.

Table 44: Common and Very Common Adverse Events Occurring in the NT 201 Treatment Group in Study 0408 Main Period

(Adapted from Sponsor Table 16, CD ISS, pg. 36)

Table 16: Common and Very Common Adverse Events Occurring in the NT 201 Treatment Group, Study 0408/1 Main Period

MedDRA System Organ Class Preferred Term	NT 201 N=159	Placebo N=74
Subjects with TEAEs	89 (56.0%)	31 (41.9%)
Musculoskeletal and connective tissue disorders	44 (27.7%)	8 (10.8%)
Neck pain	17 (10.7%)	3 (4.1%)
Muscular weakness	14 (8.8%)	1 (1.4%)
Musculoskeletal pain	8 (5.0%)	1 (1.4%)
Musculoskeletal stiffness	5 (3.1%)	1 (1.4%)
Muscle spasms	4 (2.5%)	2 (2.7%)
Myalgia	3 (1.9%)	-
Back pain	2 (1.3%)	2 (2.7%)
Pain in extremity	3 (1.9%)	-
Gastrointestinal disorders	34 (21.4%)	3 (4.1%)
Dysphagia	25 (15.7%)	2 (2.7%)
Nausea	6 (3.8%)	-
Dry mouth	2 (1.3%)	-
Nervous system disorders	26 (16.4%)	5 (6.8%)
Headache	6 (3.8%)	3 (4.1%)
Dizziness	4 (2.5%)	1 (1.4%)
Burning sensation	2 (1.3%)	-
Head discomfort	2 (1.3%)	-
Head tingling	2 (1.3%)	-
Paraesthesia	2 (1.3%)	-
Somnolence	2 (1.3%)	-
Syncope vasovagal	2 (1.3%)	-
Hypoesthesia	3 (1.9%)	-
General disorders and administration site conditions	21 (13.2%)	8 (10.8%)
Injection site pain	10 (6.3%)	5 (6.8%)
Asthenia	3 (1.9%)	-
Influenza like illness	2 (1.3%)	-
Infections and infestations	20 (12.6%)	8 (10.8%)
Sinusitis	5 (3.1%)	2 (2.7%)
Nasopharyngitis	3 (1.9%)	5 (6.8%)
Upper respiratory tract infection	2 (1.3%)	-
Respiratory, thoracic and mediastinal disorders	18 (11.3%)	2 (2.7%)
Asthma	4 (2.5%)	-
Oropharyngeal pain	4 (2.5%)	-
Cough	2 (1.3%)	-
Dyspnoea	2 (1.3%)	-
Rhinorrhoea	2 (1.3%)	-
Dysphonia	2 (1.3%)	-
Skin and subcutaneous tissue disorders	6 (3.8%)	3 (4.1%)
Hyperhidrosis	2 (1.3%)	-
Rash	2 (1.3%)	-

Data are presented as number of subjects (percent of subjects).

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event.

Source: Table 3.1.1.2.1.2.2.2, Section 5.3.5.3, Appendix H.

Reviewer comment: *In the table above, the most frequent adverse event occurring more frequently with NT 201 treatment compared to placebo are those expected with botulinum toxin use in the cervical region: neck pain (10.7% NT 201 vs. 4.1% placebo), muscular weakness 14 (8.8% NT 201 vs. 1.4% placebo), musculoskeletal pain 8 (5.0% vs. 1.4%) and musculoskeletal stiffness (3.1% NT 201 vs. 1.4%)(CD ISS, pg. 36).*

As a group, there were more “Respiratory, Thoracic and Mediastinal Disorders” in the NT 201-treated (11.3%) compared to placebo patients (2.7%). The AEs in this category included asthma,

rhinorrhea and cough, which one would expect to be common in the background population. I reviewed the two cases of dyspnea.

7.4.1.3.3 Common Adverse Events: CD – Open-Label Studies

As of December 2008, Merz stated that a total of 177 of 214 subjects (82.7%) had experienced TEAEs in the ongoing Study 0408/2 Extension Period. Merz asserted that the most commonly experienced TEAEs in the Extension Period were similar to those in the placebo-controlled Main Period, and included dysphagia (34 of 214 subjects, 15.9%), sinus infection (16 of 214 subjects, 7.5%), “common cold” (13 of 214 subjects, 6.1%), headache and neck weakness (9 of 214 subjects, 4.2%, each)(CD ISS, pg. 29).

7.4.1.5 Common Adverse Events: Spasticity

7.4.1.4.1 Common Adverse Events: Spasticity – Pooled Studies

In Study 0410 (Main and OLEX data combined), in the NT 201 treatment group Merz reported that TEAEs most commonly occurred in the Nervous system disorders (25 of 265 subjects, 9.4%) and Infections and infestations SOCs (20 of 265 subjects, 7.6%) SOCs. At the PT level, the event with the highest incidence in the NT 201 group was epilepsy (8 of 265 subjects, 3%). The sponsor stated that most TEAEs occurred in only one patient.

Table 45: Common Adverse Events in SP Study 0410 Main and OLEX Periods
(Adapted from Sponsor Table 3.1.1.2.3.1.2, 0410/1 Study Report, pg. 792)

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

System Organ Class Preferred Term	Treatment					
	NT 201		Placebo		Overall	
	No. of Pat. N (%)	Occ. of AEs N (%)	No. of Pat. N (%)	Occ. of AEs N (%)	No. of Pat. N (%)	Occ. of AEs N (%)
Patients at risk	265 (100.00)		75 (100.00)		340 (100.00)	
Patients with AEs	94 (35.47)	170 (100.00)	20 (26.67)	36 (100.00)	114 (33.53)	206 (100.00)
NERVOUS SYSTEM DISORDERS	25 (9.43)	35 (20.59)	7 (9.33)	7 (19.44)	32 (9.41)	42 (20.39)
Epilepsy	8 (3.02)	8 (4.71)	-	-	8 (2.35)	8 (3.88)
Headache	4 (1.51)	6 (3.53)	1 (1.33)	1 (2.78)	5 (1.47)	7 (3.40)
Convulsion	2 (0.75)	2 (1.18)	-	-	2 (0.59)	2 (0.97)
Dizziness	1 (0.38)	1 (0.59)	1 (1.33)	1 (2.78)	2 (0.59)	2 (0.97)
Dysaesthesia	2 (0.75)	2 (1.18)	-	-	2 (0.59)	2 (0.97)
Hypoaesthesia	2 (0.75)	2 (1.18)	-	-	2 (0.59)	2 (0.97)
Muscle spasticity	1 (0.38)	1 (0.59)	1 (1.33)	1 (2.78)	2 (0.59)	2 (0.97)
Syncope	1 (0.38)	1 (0.59)	1 (1.33)	1 (2.78)	2 (0.59)	2 (0.97)
Transient ischaemic attack	2 (0.75)	2 (1.18)	-	-	2 (0.59)	2 (0.97)
Amnesia	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Cerebral haemorrhage	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Dysarthria	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Epileptic aura	1 (0.38)	2 (1.18)	-	-	1 (0.29)	2 (0.97)
Loss of consciousness	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Nerve compression	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Paraesthesia	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Paraparesis	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Status epilepticus	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Intracranial haematoma	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
Ischaemic stroke	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
Partial seizures	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
INFECTIONS AND INFESTATIONS	20 (7.55)	22 (12.94)	5 (6.67)	5 (13.89)	25 (7.35)	27 (13.11)
Nasopharyngitis	3 (1.13)	3 (1.76)	-	-	3 (0.88)	3 (1.46)
Urinary tract infection	3 (1.13)	3 (1.76)	-	-	3 (0.88)	3 (1.46)
Bronchitis	2 (0.75)	2 (1.18)	-	-	2 (0.59)	2 (0.97)
Influenza	1 (0.38)	1 (0.59)	1 (1.33)	1 (2.78)	2 (0.59)	2 (0.97)
Localised infection	2 (0.75)	2 (1.18)	-	-	2 (0.59)	2 (0.97)
Respiratory tract infection	1 (0.38)	1 (0.59)	1 (1.33)	1 (2.78)	2 (0.59)	2 (0.97)

System Organ Class Preferred Term	Treatment					
	NT 201		Placebo		Overall	
	No. of Pat. N (%)	Occ. of AEs N (%)	No. of Pat. N (%)	Occ. of AEs N (%)	No. of Pat. N (%)	Occ. of AEs N (%)
INFECTIONS AND INFESTATIONS	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Acarodermatitis	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Appendicitis	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Cellulitis	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Ear infection	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Furuncle	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Gastrointestinal infection	1 (0.38)	2 (1.18)	-	-	1 (0.29)	2 (0.97)
Implant site infection	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Tonsillitis	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Viral infection	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Pharyngitis	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
Rhinitis	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
Tinea infection	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
GASTROINTESTINAL DISORDERS	15 (5.66)	18 (10.59)	5 (6.67)	8 (22.22)	20 (5.88)	26 (12.62)
Diarrhoea	5 (1.89)	6 (3.53)	2 (2.67)	2 (5.56)	7 (2.06)	8 (3.88)
Nausea	4 (1.51)	4 (2.35)	-	-	4 (1.18)	4 (1.94)
Dysphagia	1 (0.38)	1 (0.59)	1 (1.33)	1 (2.78)	2 (0.59)	2 (0.97)
Constipation	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Diverticulum	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Faecal incontinence	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Faecaloma	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Gastrointestinal haemorrhage	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Haemorrhoidal haemorrhage	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Impaired gastric emptying	1 (0.38)	1 (0.59)	-	-	1 (0.29)	1 (0.49)
Vomiting	-	-	2 (2.67)	2 (5.56)	2 (0.59)	2 (0.97)
Abdominal pain	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
Abdominal pain upper	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
Gastroesophageal reflux disease	-	-	1 (1.33)	1 (2.78)	1 (0.29)	1 (0.49)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	15 (5.66)	18 (10.59)	3 (4.00)	3 (8.33)	18 (5.29)	21 (10.19)

Merz asserted that all the patients with seizures had medical history significant of epilepsy at baseline (SP ISS, pg. 35).

Reviewer comment: *The occurrence of epilepsy as an adverse event in NT 201-treated patients is discussed further in Section 7.3.2 of this review. I reviewed the case reports for the epilepsy patients and confirmed that the patients had a history of seizures prior to study entry.*

7.4.1.4.2 Common Adverse Events: Spasticity – Placebo-Controlled Trials

In the Study 0410/1 Main Period, Merz stated in the NT 201 treatment group, the MedDRA System Organ Classes (SOCs) in which TEAEs most commonly occurred were Metabolism and nutrition disorders (6 of 73 subjects, 8.2%), Nervous system disorders, and Injury, poisoning and procedural complications (5 of 73 subjects, 6.9%, each). At the Preferred Term (PT) level, the most common event in NT 201-treated patients was hyperglycemia (3 of 73 subjects, 4.1%)(SP ISS, pg. 35).

Reviewer comment: *Hyperglycemia has been observed with use of other botulinum toxin products, specifically in the Dysport® development program. Hyperglycemia and glucose (including the three cases above) are discussed in more detail in Section 7.6.2.4 of this review.*

Individual AE events in the NT 201 and placebo treatment groups are displayed in the table below.

Table 46: Adverse Events within the Main Portion of SP Study 0410/1 occurring at a frequency of ≥ 2 Percent

(Adapted from Sponsor Table 51, 0410/1 Study Report, pg. 174)

Text Table 51: All Reported AEs by System Organ Class and Preferred Term with a Frequency of Occurrence ≥ 2 Patients Overall (EFS Population, N = 148)

System Organ Class Preferred term	NT 201 (N = 73)			Treatments Placebo (N = 75)			Total (N = 148)		
	N	%	E	N	%	E	N	%	E
Nervous System Disorders	5	(6.8)	10	7	(9.3)	7	12	(8.1)	17
	S1119			S1007					
	S1120			S1088					
	S1121			S1093					
	S1140			S1116					
	S1197			S1125					
				S1183					
				S1196					
Headache	2	(2.7)	4	1	(1.3)	1	3	(2.0)	5
Epilepsy	2	(2.7)	2	0	(0.0)	0	2	(1.4)	2
Metabolism and Nutrition Disorders	6	(8.2)	6	3	(4.0)	3	9	(6.1)	9
	S1047			S1082					
	S1049			S1086					
	S1089			S1102					
	S1119								
	S1120								
	S1159								
Hypercholesterolemia	2	(2.7)	2	1	(1.3)	1	3	(2.0)	3
Hyperglycemia	3	(4.1)	3	0	(0.0)	0	3	(2.0)	3
Diabetes Mellitus	1	(1.4)	1	1	(1.3)	1	2	(1.4)	2
Gastrointestinal Disorders	3	(4.1)	3	5	(6.7)	8	8	(5.4)	11
	S1032			S1116					
	S1035			S1125					
	S1119			S1168					
				S1183					
				S1190					
Diarrhea	2	(2.7)	2	2	(2.7)	2	4	(2.7)	4
Vomiting	0	(0.0)	0	2	(2.7)	2	2	(1.4)	2

System Organ Class Preferred term	NT 201 (N = 73)			Treatments Placebo (N = 75)			Total (N = 148)		
	N	%	E	N	%	E	N	%	E
Injury, Poisoning and Procedural Complications	5	(6.8)	6	2	(2.7)	3	7	(4.7)	9
	S1027			S1183					
	S1117			S1190					
	S1123								
	S1131								
	S1180								
Contusion	1	(1.4)	1	2	(2.7)	3	3	(2.0)	4
Infections and Infestations	2	(2.7)	2	5	(6.7)	5	7	(4.7)	7
	S1036			S1034					
	S1101			S1059					
				S1116					
				S1183					
				S1187					
General Disorders and Administration Site Conditions	3	(4.1)	6	3	(4.0)	3	6	(4.1)	9
	S1117			S1033					
	S1121			S1122					
	S1197			S1183					
Investigations	2	(2.7)	2	1	(1.3)	2	3	(2.0)	4
	S1101			S1127					
	S1159								
Vascular Disorders	1	(1.4)	1	2	(2.7)	2	3	(2.0)	3
	S1140			S1125					
				S1185					
Hypertension	1	(1.4)	1	1	(1.3)	1	2	(1.4)	2
Blood and Lymphatic System Disorders	1	(1.4)	2	1	(1.3)	1	2	(1.4)	3
	S1119			S1187					
Musculoskeletal and Connective Tissue Disorders	1	(1.4)	1	1	(1.3)	1	2	(1.4)	2
	S1194			S1127					
Renal and Urinary Disorders	1	(1.4)	1	1	(1.3)	1	2	(1.4)	2
	S1100			S1041					

Data Sources: Table 14.3.3.1 and Listing 14.3.2.

AEs were counted only once per level (preferred term, system organ class, overall).

Body system totals were not necessarily the sum of individual AEs due to patients with more than one AE.

Dictionary: MedDRA 9.1

E: number of events.

Reviewer comment: In the 0410 study report, common AEs were presented as those occurring in more than 2% of patients, as opposed to in 1% of patients in the majority of the NT 201 development program. This is acceptable, however, as it is still an inclusive percent (as opposed to 5%) and reduces some of the “noise” with use of a 1% cut-off.

In reviewing the table above, the AEs in the NT 201-treated group with the largest increase compare to placebo-treated patients were: headache (2.7% NT 201 [N=2] versus 1.3% placebo [N=1]), epilepsy (2.7% NT 201 versus 1.3% placebo) and hyperglycemia (4.1% NT 201 versus 0 placebo). I reviewed the two cases of epilepsy and both patients had a history of epilepsy prior to entering the study.

Hyperglycemia is discussed in Section 7.6.2.4 of this review.

7.4.1.4.2 Common Adverse Events: Spasticity – Open-Label Studies

The sponsor summarized common adverse events within the OLEX Study 0410/2 in the table below.

Table 47: Adverse Events in SP OLEX Study 0410/2 occurring in more than 2% of Patients
(Adapted from Sponsor Table 38, 0410/2 Study Report, pg. 173)

Text Table 38: Summary of TEAEs by System Organ Class and Preferred Term Experienced by ≥ 2 Patients Overall During the OLEX Period (EFS Population, N = 145)

System Organ Class Preferred Term	Treatment previously received during the Main Period						Overall (N = 145)		
	NT 201 Group (N = 71)			Placebo Group (N = 74)			N	%	E
	N	%	E	N	%	E			
TEAEs	38	(53.5)	82	44	(59.5)	98	82	(56.6)	180
Nervous System Disorders	10	(14.1)	13	16	(21.6)	20	26	(17.9)	33
Muscle spasticity	6	(8.5)	7	9	(12.2)	11	15	(10.3)	18
Epilepsy	2	(2.8)	2	3	(4.1)	3	5	(3.4)	5
Hemiparesis	1	(1.4)	1	1	(1.4)	1	2	(1.4)	2
Infections & Infestations	11	(15.5)	13	15	(20.3)	16	26	(17.9)	29
Upper respiratory tract infection	4	(5.6)	5	3	(4.1)	3	7	(4.8)	8
Respiratory tract infection	2	(2.8)	2	2	(2.7)	2	4	(2.8)	4
Urinary tract infection	2	(2.8)	2	2	(2.7)	2	4	(2.8)	4
Influenza	2	(2.8)	2	1	(1.4)	1	3	(2.1)	3
Gastroenteritis	1	(1.4)	1	1	(1.4)	1	2	(1.4)	2
Musculoskeletal & Connective Tissue Disorders	7	(9.9)	10	6	(8.1)	6	13	(9.0)	16
Muscular weakness	3	(4.2)	3	2	(2.7)	2	5	(3.4)	5
Pain in extremity	2	(2.8)	2	1	(1.4)	1	3	(2.1)	3
Investigations	7	(9.9)	7	4	(5.4)	5	11	(7.6)	12
Gamma-glutamyl transferase increased	4	(5.6)	4	2	(2.7)	2	6	(4.1)	6
General Disorders & Administration Site Conditions	5	(7.0)	6	5	(6.8)	8	10	(6.9)	14
Injection site pain	2	(2.8)	2	2	(2.7)	4	4	(2.8)	6
Pyrexia	2	(2.8)	2	1	(1.4)	1	3	(2.1)	3
Edema peripheral	1	(1.4)	1	1	(1.4)	1	2	(1.4)	2
Psychiatric Disorders	6	(8.5)	6	3	(4.1)	4	9	(6.2)	10
Depression	5	(7.0)	5	2	(2.7)	2	7	(4.8)	7
Gastrointestinal Disorders	3	(4.2)	4	6	(8.1)	8	9	(6.2)	12
Dysphagia	1	(1.4)	2	1	(1.4)	1	2	(1.4)	3
Vascular Disorders	2	(2.8)	2	6	(8.1)	6	8	(5.5)	8
Hypertension	1	(1.4)	1	5	(6.8)	5	6	(4.1)	6
Cardiovascular insufficiency	1	(1.4)	1	1	(1.4)	1	2	(1.4)	2
Metabolism & Nutrition Disorders	4	(5.6)	5	4	(5.4)	4	8	(5.5)	9
Hyperglycemia	3	(4.2)	3	0	(0.0)	0	3	(2.1)	3

System Organ Class Preferred Term	Treatment previously received during the Main Period						Overall (N = 145)		
	NT 201 Group (N = 71)			Placebo Group (N = 74)			N	%	E
	N	%	E	N	%	E			
Blood & Lymphatic System Disorders	1	(1.4)	1	4	(5.4)	4	5	(3.4)	5
Anemia	0	(0.0)	0	2	(2.7)	2	2	(1.4)	2
Respiratory, Thoracic & Mediastinal Disorders	3	(4.2)	3	1	(1.4)	1	4	(2.8)	4
Cough	2	(2.8)	2	0	(0.0)	0	2	(1.4)	2
Reproductive System & Breast Disorders	1	(1.4)	1	2	(2.7)	2	3	(2.1)	3
Benign prostatic hyperplasia	1	(1.4)	1	2	(2.7)	2	3	(2.1)	3
Endocrine Disorders	2	(2.8)	2	1	(1.4)	1	3	(2.1)	3
Hypothyroidism	1	(1.4)	1	1	(1.4)	1	2	(1.4)	2

Data Sources: Tables 14.3.4.1.6; Dictionary: MedDRA 9.1; N: number of patients, E: number of events

Reviewer comment: The table above is notable for several reasons. First, although as per the title it presents open-label data, it also presents figures for the placebo group, which were presumably taken from the Main Period (0410/1) of the study. Secondly, the table presents events occurring in $\geq 2\%$ of patients, whereas in the majority of the NT 201 development program 1% was used as the criteria for common adverse events. In reviewing the table above, the most frequent adverse events in OLEX Study 0410/2 were: muscle spasticity (8.5%), depression (7.0%), upper respiratory track infection (5.6%) and muscular weakness (4.2%).

The events of hyperglycemia and increased GGT noted in the table above are discussed in Section 7.6.2.4 (Hyperglycemia) and Section 7.4.2 (Laboratory Findings) of this review.

7.4.2 Laboratory Findings

Reviewer comment: Laboratory results for glucose and alkaline phosphatase are discussed in Section 7.6.2.4 and Section 7.6.2.5 of this review, respectively.

7.4.2.1 Laboratory Values: Pooled Indications

Merz stated that in their safety analysis, laboratory values were summarized as shifts from baseline, and as mean values and changes from baseline, to the visit when the primary efficacy endpoint was assessed (this varied across studies, from 2 to Week 6 following study drug administration) and to the final visit (this also varied across studies, from 8 to 25 weeks following study drug administration)(ISS, pg. 79).

In the pooled controlled studies, Merz summarized that 41 of 1313 NT 201-treated subjects (3.1%) and 14 of 346 subjects (4.0%) in the placebo group, had treatment-emergent, clinically significant (CS) abnormalities of biochemistry parameters. In the NT 201 treatment group, these events were elevated glucose (11 subjects, 0.8%), elevated total cholesterol (9 subjects, 0.7%), elevated LDL cholesterol (9 subjects, 0.7%), elevated gamma-glutamyltransferase (8 subjects, 0.6%), elevated AST (6 subjects, 0.5%), low HDL cholesterol (4 subjects, 0.3%), elevated

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

alanine aminotransferase (4 subjects, 0.3%), elevated urea (4 subjects, 0.3%), elevated bilirubin (3 subjects, 0.2%), low potassium (2 subjects, 0.2%), low sodium, elevated alkaline phosphatase, and elevated creatinine (1 subject, 0.1%, each) (Table 6.3.1)(ISS 120-Day Safety Update, pg. 89).

***Reviewer comment:** I reviewed the sponsor's values for the various biochemistry parameters to be characterized as clinically significant, and found them to be reasonable.*

The mean changes (from baseline to final study visit) in biochemistry parameters in the pooled, placebo-controlled studies are shown in the table below.

Table 48: Mean Changes in Biochemistry Parameters in the Pooled, Placebo-Controlled Studies within the NT 201 Development Program

(Adapted from Sponsor Table 2, 120-Day Safety Update – Appendix E, pg. 4)

Table 2: Biochemistry Values, Changes from Baseline at Primary Endpoint Assessment and Final Visits, NT 201 Treatment Group, Pooled Controlled Studies

Parameter	N	Missing	Mean	SD	Min, Max
Albumin (g/L)					
Baseline	1302	11	45.0	3.27	28, 58
1° Endpoint Visit	482	831	43.7	3.31	35, 56
1° Endpoint Visit - Baseline	472	841	-0.4	2.96	-14, 10
Final Visit	1260	53	44.5	3.13	23, 54
Final Visit - Baseline	1250	63	-0.5	2.84	-23, 11
Alkaline phosphatase (U/L)					
Baseline	1306	7	83.1	34.34	14, 278
1° Endpoint Visit	483	830	106.0	34.49	35, 241
1° Endpoint Visit - Baseline	477	836	-2.3	13.87	-74, 60
Final Visit	1257	56	82.3	33.37	13, 238
Final Visit - Baseline	1251	62	-1.1	13.46	88, 95
Bilirubin total (µmol/L)					
Baseline	1300	13	7.63	4.593	1.7, 47.9
1° Endpoint Visit	482	831	7.96	4.318	1.7, 39.9
1° Endpoint Visit - Baseline	476	837	-0.04	3.089	-16.1, 10.3
Final Visit	1256	57	7.61	4.241	0.6, 37.6
Final Visit - Baseline	1245	68	0.01	3.123	-18.8, 18.5
Calcium (mmol/L)					
Baseline	700	613	2.367	0.1084	2.01, 2.70
1° Endpoint Visit	72	1241	2.311	0.1076	2.12, 2.73
1° Endpoint Visit - Baseline	72	1241	-0.013	0.0786	-0.22, 0.17
Final Visit	679	634	2.361	0.1004	2.08, 2.73
Final Visit - Baseline	678	635	-0.007	0.1050	-0.32, 0.38
Cholesterol HDL (mmol/L)					
Baseline	617	696	1.585	0.4747	0.44, 4.89
1° Endpoint Visit	72	1241	1.404	0.4292	0.59, 2.70
1° Endpoint Visit - Baseline	72	1241	-0.021	0.1551	-0.44, 0.44
Final Visit	599	714	1.556	0.4422	0.55, 3.31
Final Visit - Baseline	598	715	-0.030	0.2455	-2.52, 0.91
Cholesterol LDL (mmol/L)					
Baseline	617	696	3.059	0.9092	0.23, 7.68
1° Endpoint Visit	72	1241	3.203	0.7558	1.76, 5.09
1° Endpoint Visit - Baseline	72	1241	-0.070	0.6039	-2.04, 2.17
Final Visit	599	714	3.015	0.8731	0.28, 6.83
Final Visit - Baseline	598	715	-0.044	0.6283	-2.66, 3.75
Cholesterol total (mmol/L)					
Baseline	617	696	5.303	1.0567	2.78, 10.11
1° Endpoint Visit	72	1241	5.056	0.9183	2.31, 7.27
1° Endpoint Visit - Baseline	72	1241	-0.093	0.6948	-2.38, 2.12
Final Visit	599	714	5.230	1.0179	2.71, 9.26
Final Visit - Baseline	598	715	-0.075	0.6920	-3.09, 3.41

Table continues

Table 2: Biochemistry Values, Changes from Baseline at Primary Endpoint Assessment and Final Visits, NT 201 Treatment Group, Pooled Controlled Studies

Parameter	N	Missing	Mean	SD	Min, Max
Creatine kinase (U/L)					
Baseline	37	1276	67.0	54.41	7, 236
1° Endpoint Visit	40	1273	65.8	45.24	2, 197
1° Endpoint Visit - Baseline	37	1276	-5.9	41.27	-149, 60
Final Visit	33	1280	72.7	41.48	12, 174
Final Visit - Baseline	30	1283	2.9	40.97	120, 114
Creatinine (µmol/L)					
Baseline	1309	4	74.8	15.57	33, 156
1° Endpoint Visit	484	829	76.1	15.68	44, 143
1° Endpoint Visit - Baseline	481	832	0.7	10.15	-35, 44
Final Visit	1259	54	75.6	15.73	34, 178
Final Visit - Baseline	1255	58	0.8	9.77	-53, 53
Gamma-glutamyltransferase (U/L)					
Baseline	1309	4	28.4	46.92	4, 831
1° Endpoint Visit	484	829	24.5	45.32	4, 724
1° Endpoint Visit - Baseline	481	832	-1.1	26.45	-457, 139
Final Visit	1259	54	26.5	35.29	3, 526
Final Visit - Baseline	1255	58	-1.3	23.69	-452, 156
Glucose (mmol/L)					
Baseline	1303	10	5.47	1.615	1.8, 24.1
1° Endpoint Visit	480	833	5.71	1.546	1.7, 16.4
1° Endpoint Visit - Baseline	472	841	-0.01	1.516	-14.0, 6.6
Final Visit	1256	57	5.49	1.457	2.3, 19.2
Final Visit - Baseline	1247	66	0.03	1.447	-11.6, 11.5
Potassium (mmol/L)					
Baseline	1308	5	4.32	0.418	2.3, 9.1
1° Endpoint Visit	438	830	4.32	0.405	3.2, 6.7
1° Endpoint Visit - Baseline	479	834	0.02	0.457	-5.3, 2.4
Final Visit	1256	57	4.33	0.409	2.8, 8.5
Final Visit - Baseline	1251	62	0.01	0.465	-4.6, 4.2
Aspartate aminotransferase (U/L)					
Baseline	1309	4	19.1	12.37	4, 282
1° Endpoint Visit	484	829	12.6	6.70	4, 58
1° Endpoint Visit - Baseline	482	831	-0.2	4.49	-43, 33
Final Visit	1256	57	19.0	13.11	4, 316
Final Visit - Baseline	1252	61	0.1	6.42	-52, 68
Alanine aminotransferase (U/L)					
Baseline	1309	4	19.6	14.82	2, 252
1° Endpoint Visit	484	829	14.6	10.16	4, 98
1° Endpoint Visit - Baseline	482	831	0.2	6.74	-45, 78
Final Visit	1256	57	19.9	15.82	2, 308
Final Visit - Baseline	1252	61	0.4	9.17	-58, 109

Table continues

Table 2: Biochemistry Values, Changes from Baseline at Primary Endpoint Assessment and Final Visits, NT 201 Treatment Group, Pooled Controlled Studies

Parameter	N	Missing	Mean	SD	Min, Max
Sodium (mmol/L)					
Baseline	1310	3	141.6	3.01	130, 158
1° Endpoint Visit	484	829	141.2	3.56	131, 189
1° Endpoint Visit - Baseline	482	831	0.2	3.78	-10, 48
Final Visit	1258	55	141.6	2.97	125, 152
Final Visit - Baseline	1255	58	-0.1	3.50	-17, 13
Urea (mmol/L)					
Baseline	1231	82	7.42	3.960	2.0, 24.4
1° Endpoint Visit	409	904	11.63	4.137	1.7, 24.0
1° Endpoint Visit - Baseline	404	909	0.12	2.810	-10.1, 9.4
Final Visit	1189	124	7.57	3.940	1.7, 25.1
Final Visit - Baseline	1181	132	0.10	2.011	-12.8, 10.5

The pooled controlled studies were: 0408/1 (CD) Main Period, 0410/1 (SP) Main Period, 0433/1 (BEB) Main Period, 0520/1 (GFL) Main Period, 0527 (GFL), and 0617 (CF).

1°: Primary; g/L: grams per liter; max: maximum; min: minimum; mmol/L: millimoles per liter; µmol/L: micromoles per liter; SD: standard deviation; U/L: units per liter.

Source: Table 6.1.1.1.1 through Table 6.1.1.1.17, Section 5.3.5.3, Appendix H.

Reviewer comment: *As stated previously in this review, due to differences in patient populations it is generally not acceptable to pool safety data between the indications. However, in order to obtain a larger number of patients for analysis I believe it is acceptable for laboratory values to be combined across indications.*

Table 1: Hematology Values, Changes from Baseline at Primary Endpoint Assessment and Final Visits, NT 201 Treatment Group, Pooled Controlled Studies

Parameter	N	Missing	Mean	SD	Min, Max
Basophils (10⁹/L)					
Baseline	616	697	0.02	0.036	0, 0.2
1° Endpoint Visit	72	1241	0.01	0.032	0, 0.1
1° Endpoint Visit - Baseline	72	1241	0	0.044	-0.1, 0.1
Final Visit	588	725	0.01	0.035	0, 0.2
Final Visit - Baseline	586	727	0	0.044	-0.2, 0.2
Eosinophils (10⁹/L)					
Baseline	616	697	0.162	0.1170	0, 1.0
1° Endpoint Visit	72	1241	0.181	0.1380	0, 0.8
1° Endpoint Visit - Baseline	72	1241	0.021	0.1034	-0.3, 0.5
Final Visit	588	725	0.176	0.1450	0.1, 1.4
Final Visit - Baseline	586	727	0.015	0.1373	-0.7, 1.3
Erythrocytes (10¹²/L)					
Baseline	1298	15	4.54	0.437	2.82, 6.61
1° Endpoint Visit	475	838	4.56	0.458	2.72, 6.43
1° Endpoint Visit - Baseline	465	848	-0.04	0.227	-0.95, 1.29
Final Visit	1241	72	4.51	0.434	2.72, 6.33
Final Visit - Baseline	1226	87	-0.02	0.225	-1.04, 0.91
Hematocrit (ratio)					
Baseline	699	614	0.413	0.0352	0.31, 0.53
1° Endpoint Visit	72	1241	0.429	0.0385	0.35, 0.51
1° Endpoint Visit - Baseline	72	1241	-0.002	0.0194	-0.05, 0.05
Final Visit	669	644	0.411	0.0351	0.32, 0.53
Final Visit - Baseline	667	646	-0.002	0.0218	-0.09, 0.06
Hemoglobin (g/L)					
Baseline	1298	15	139.1	12.38	96, 186
1° Endpoint Visit	475	838	138.3	12.69	102, 177
1° Endpoint Visit - Baseline	465	848	-0.7	6.28	-30, 24
Final Visit	1241	72	138.3	12.53	137, 176
Final Visit - Baseline	1226	87	6.83	6.83	-34, 27
Leucocytes (10⁹/L)					
Baseline	1298	15	6.67	1.879	1.2, 17.9
1° Endpoint Visit	475	838	6.50	1.613	2.1, 12.5
1° Endpoint Visit - Baseline	465	848	-0.13	1.353	-6.1, 4.6
Final Visit	1239	74	6.65	1.869	2.4, 21.6
Final Visit - Baseline	1224	89	0	1.622	-10.5, 12.3
Lymphocytes (10⁹/L)					
Baseline	616	697	1.977	0.6691	0.7, 5.8
1° Endpoint Visit	72	1241	1.904	0.5393	0.9, 3.2
1° Endpoint Visit - Baseline	72	1241	-0.050	0.4853	-1.6, 1.2
Final Visit	588	725	1.960	0.6337	0.4, 5.2
Final Visit - Baseline	586	727	-0.014	0.4436	-2.2, 1.7

Table continues

Table 1: Hematology Values, Changes from Baseline at Primary Endpoint Assessment and Final Visits, NT 201 Treatment Group, Pooled Controlled Studies

Parameter	N	Missing	Mean	SD	Min, Max
Monocytes (10⁹/L)					
Baseline	616	697	0.388	0.1538	0, 1.3
1° Endpoint Visit	72	1241	0.354	0.1394	0.1, 0.8
1° Endpoint Visit - Baseline	72	1241	-0.015	0.1589	-0.3, 0.5
Final Visit	588	725	0.391	0.1598	0, 1.1
Final Visit - Baseline	586	727	0.005	0.1465	-0.6, 0.7
Neutrophils (10⁹/L)					
Baseline	616	697	4.04	1.430	1.1, 10.7
1° Endpoint Visit	72	1241	4.41	1.384	1.9, 8.3
1° Endpoint Visit - Baseline	72	1241	-0.13	1.031	-3.1, 2.8
Final Visit	588	725	4.03	1.463	1.2, 12.0
Final Visit - Baseline	586	727	0.01	1.383	-6.7, 7.7
Platelets (10⁹/L)					
Baseline	1294	19	258.9	63.59	59, 643
1° Endpoint Visit	474	839	249.6	61.03	51, 671
1° Endpoint Visit - Baseline	464	849	-1.8	37.00	-242, 268
Final Visit	1233	80	258.0	62.38	8, 700
Final Visit - Baseline	1216	97	-1.0	38.51	-230, 466
Reticulocytes Relative (promille)					
Baseline	346	967	10.8	15.25	0, 279
1° Endpoint Visit	53	1260	13.6	5.16	6, 25
1° Endpoint Visit - Baseline	45	1268	-0.7	4.89	-13, 9
Final Visit	326	987	9.9	4.69	1, 25
Final Visit - Baseline	305	1008	-0.9	15.58	-262, 12
Reticulocytes (10⁹/L)					
Baseline	231	1082	48.2	23.30	9, 143
1° Endpoint Visit	0	1313	-	-	-
1° Endpoint Visit - Baseline	0	1313	-	-	-
Final Visit	219	1094	49.4	23.76	7, 140
Final Visit - Baseline	217	1096	1.4	18.27	-75, 75

The pooled controlled studies were: 0408/1 (CD) Main Period, 0410/1 (SP) Main Period, 0433/1 (BEB) Main Period, 0520/1 (GFL) Main Period, 0527 (GFL), and 0617 (CF).

1°: Primary; g/L: grams per liter; max: maximum; min: minimum; SD: standard deviation.

“-“ means that no value is available for the parameter at that time point.

Source: Table 6.1.1.1.19 through Table 6.1.1.1.30, Section 5.3.5.3, Appendix H.

For hematology studies, Merz noted that in the pooled, controlled studies, fewer patients in the NT 201 group than in the placebo group experienced clinically significant laboratory abnormalities; seven of 1313 NT 201-treated subjects (0.5%) had 10 treatment-emergent, clinically significant (CS) hematology abnormalities, compared with 4 of 346 subjects (1.2%) in the placebo group. The abnormalities that occurred in the NT 201-treated subjects were low hemoglobin (3 subjects, 0.2%), low erythrocytes (2 subjects, 0.2%), low platelets (2 subjects, 0.2%), low hematocrit, low relative reticulocytes, and elevated eosinophil count (1 subject, 0.1%, each). The sponsor stated that all of these abnormalities were detected at the final visit of the respective study, which in every study occurred weeks after receipt of a single dose of NT 201 (ISS, pg. 80).

For hematology results, in the pooled subjects in the NT 201 treatment group, in the controlled studies, Merz stated that there were no “clinically meaningful shifts or mean changes from baseline” in “most” biochemistry parameters. These include: albumin, alkaline phosphatase, bilirubin, calcium, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, total cholesterol, creatine kinase, creatinine, gamma-glutamyltransferase (GGT), potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium and urea (ISS, pg. 80).

7.4.2.2 Laboratory Values: BEB

For hematologic tests, Merz stated that in the pooled BEB studies (the Study 0408/1 Main Period, and Studies 0013 and 9801), in the NT 201 treatment group, no “clinically meaningful” shifts or mean changes from baseline were noted for red blood cells, hemoglobin, hematocrit (change from baseline available for final visit only; white blood cells, neutrophils (change from baseline available for final visit only; eosinophils, lymphocyte, basophils, monocytes, reticulocytes (change from baseline available for final visit only; or platelets (BEB ISS, pg. 72).

***Reviewer comment:** Because Merz did not elaborate on the details of the shift and mean changes summarized above, for each indication I examined all laboratory data within the placebo and NT 201 treatment groups during their respective placebo-controlled studies. Below are the hematology results for BEB (Study 0433/1 Study Report).*

Table 49: Hematologic Testing Results at Screening and Final Visit within BEB Study 0433/1 by Treatment Group

(Adapted from Sponsor Table 49, BEB Study 0433/1 Study Report, pg. 149)

Text Table 49: Mean (SD) of Hematology Parameters at Screening and Final Visit, by Treatment Group (EFS Population)

Parameter [SI Units]	Visit	Mean (SD)			
		NT 201 group N=74		Placebo group N=34	
Hematocrit [ratio]	Screening	0.42	(0.037)	0.42	(0.043)
	Final	0.41	(0.035)	0.41	(0.037)
Hemoglobin [g/L]	Screening	139.5	(12.75)	138.6	(16.29)
	Final	136.9	(12.25)	136.3	(13.18)
INR [ratio]	Screening	1.03	(0.139)	1.06	(0.201)
	Final	1.08	(0.244)	1.06	(0.182)
Erythrocytes [$10^{12}/L$]	Screening	4.61	(0.450)	4.59	(0.400)
	Final	4.52	(0.454)	4.49	(0.342)
Reticulocytes [$10^9/L$]	Screening	49.4	(24.64)	46.9	(24.62)
	Final	49.4	(20.48)	43.5	(22.00)
Leukocytes [$10^9/L$]	Screening	6.09	(1.622)	6.51	(1.985)
	Final	5.98	(1.397)	6.33	(2.189)
Neutrophils [$10^9/L$]	Screening	3.66	(1.295)	3.94	(1.666)
	Final	3.52	(1.094)	3.81	(1.784)
Lymphocytes [$10^9/L$]	Screening	1.83	(0.594)	1.91	(0.646)
	Final	1.89	(0.660)	1.89	(0.754)
Monocytes [$10^9/L$]	Screening	0.42	(0.185)	0.44	(0.184)
	Final	0.40	(0.168)	0.43	(0.174)
Eosinophils [$10^9/L$]	Screening	0.16	(0.086)	0.22	(0.165)
	Final	0.16	(0.120)	0.19	(0.181)
Basophils [$10^9/L$]	Screening	0.01	(0.023)	0.01	(0.029)
	Final	0.01	(0.034)	0.00	(0.019)
Platelets [$10^9/L$]	Screening	254.9	(74.35)	268.6	(77.42)
	Final	257.4	(70.73)	260.3	(72.47)

SD=Standard deviation

Source: Table 14.3.4.1.3

Reviewer comment: As seen in the preceding table, hematology values in BEB patients were similar for treatment group and from screening to final visit in Study 0433/1 Main Period. The table above, as for the biochemistry results below, also highlights the small number of patients on which these results are based (74 in the NT 201 group and 34 in the placebo group).

For biochemistry testing, the placebo and NT 201 treatment group results are shown in the table below.

Table 50: Chemistry Testing at Screening and Final Visit in BEB Study 0433/1 by Treatment Group

(Adapted from Sponsor Table 50, BEB Study 0433/1 Study Report, pg. 150)

Text Table 50: Mean (SD) of Clinical Chemistry Parameters at Screening and Final Visit, by Treatment Group (EFS Population)

Parameter [SI Units]	Visit	Mean (SD)			
		NT 201 group N=74		Placebo group N=34	
Sodium [mmol/L]	Screening	141.2	(3.34)	141.1	(3.74)
	Final	140.4	(3.41)	141.2	(4.52)
Potassium [mmol/L]	Screening	4.27	(0.471)	4.23	(0.341)
	Final	4.25	(0.381)	4.22	(0.398)
Calcium [mmol/L]	Screening	2.39	(0.096)	2.40	(0.097)
	Final	2.40	(0.096)	2.39	(0.101)
Glucose [mmol/L]	Screening	5.34	(0.684)	5.32	(0.764)
	Final	5.46	(0.944)	5.74	(1.496)
Urea nitrogen [mmol/L]	Screening	5.82	(1.816)	5.30	(1.866)
	Final	5.90	(1.809)	5.52	(1.647)
Creatinine [µmol/L]	Screening	82.7	(18.24)	83.1	(19.45)
	Final	84.5	(18.14)	83.6	(21.39)
Albumin [g/L]	Screening	44.38	(2.199)	44.70	(2.671)
	Final	44.18	(2.556)	43.72	(2.474)
Bilirubin [µmol/L]	Screening	6.54	(3.030)	7.21	(4.807)
	Final	6.08	(2.216)	7.83	(5.068)
AST [U/L]	Screening	24.2	(6.88)	24.8	(6.18)
	Final	24.7	(8.36)	25.3	(7.10)
ALT [U/L]	Screening	23.8	(10.28)	23.4	(8.80)
	Final	23.8	(10.74)	24.5	(11.03)
AP [U/L]	Screening	78.5	(23.10)	75.8	(21.35)
	Final	80.9	(24.38)	75.4	(22.50)
GGT [U/L]	Screening	25.8	(18.55)	29.1	(28.03)
	Final	27.6	(22.31)	33.2	(34.75)
Total cholesterol [mmol/L]	Screening	5.30	(1.008)	5.40	(1.317)
	Final	5.24	(1.040)	5.25	(1.207)
HDL [mmol/L]	Screening	1.44	(0.417)	1.57	(0.561)
	Final	1.40	(0.390)	1.52	(0.539)
LDL [mmol/L]	Screening	3.07	(0.923)	3.08	(1.042)
	Final	3.01	(0.948)	2.93	(0.951)

SD=Standard deviation
Source: Table 14.3.4.2.3

Reviewer comment: I reviewed the table above and found the results to be similar across treatment groups and from Screening to Final visit.

7.4.2.3 Laboratory Values: CD

At the PT level, the most frequent TEAEs were muscle spasticity (15 subjects, 10.2%), gamma-glutamyltransferase increased (8 subjects, 5.4%), and upper respiratory tract infection, hypertension, epilepsy, and depression (7 subjects, or 4.8%, each) (Table 2.1.1.2, ISS Appendix D).

For hematology laboratory testing, Merz stated that in the pooled CD studies (the Study 0408/1 Main Period, and Studies 0013 and 9801) there were no clinically meaningful shifts or mean changes from baseline in NT 201-treated patients for hemoglobin, hematocrit (change from baseline available for final visit only), white blood cell count, or other relevant testing (CD ISS, pg. 69)

Reviewer comment: *I reviewed both the cut-off values used to identify “clinically meaningful shifts” and the tables prepared by the sponsor summarizing the hematology data, and found the sponsor’s statements above to be accurate.*

For biochemistry laboratory testing, Merz stated that in the pooled CD studies (the Study 0408/1 Main Period, and Studies 0013 and 9801), there were no clinically meaningful shifts or mean changes from baseline in the NT 201 treatment group for glucose, alanine aminotransferase (aspartate aminotransferase, gamma-glutamyltransferase, bilirubin, urea, creatinine, albumin, lipoprotein profile and other routine biochemistry laboratory testing.

Reviewer comment: *Of note, in the CD indication there were no “clinically meaningful shifts” for glucose in the NT 201 treatment group. I reviewed the individual study reports for the exact values used to categorize the clinically meaningful shift, and found the values used to be clinically reasonable. Glucose levels in the NT 201 development program are discussed in more detail in Section 7.3.5.3 of this review.*

As with the hematology testing, I reviewed the laboratory cut-off values and the sponsor’s summary tables and found them to be reasonable and an adequate reflection of the data.

See Section 7.3.5.4 of this review for a discussion of alkaline phosphatase values with in the NT 201 development program.

7.4.2.4 Laboratory Values: SP

In the OLEX period of Study 04010, adverse events that occurred in $\geq 3\%$ of subjects included gamma-glutamyl transferase increased (4.1%).

Reviewer comment: *Glucose and alkaline phosphatase are discussed separately in Section 7.6.2.4 and 7.6.2.5 (respectively) of this review.*

For spasticity patients in the NT 201 treatment group, in the controlled studies, there were no clinically meaningful shifts or mean changes from baseline in albumin, bilirubin, calcium, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, total

cholesterol, creatine kinase, creatinine, gamma-glutamyltransferase (GGT), potassium, aspartate aminotransferase (AST)), alanine aminotransferase (ALT), sodium and urea. The sponsor reported that there were also no significant shift or mean changes for hematology testing (120 Day ISS, pg. 88).

7.4.3 Vital Signs

7.4.3.1 Pooled Indications

Reviewer comment: *In the Dysport® development program, a small effect on heart rate was observed, and the Dysport® label contains the following language within the “Electrocardiographic Findings” section of labeling:*

ECG measurements were only recorded in a limited number of subjects in an open-label study without a placebo or active control. This study showed a statistically significant reduction in heart rate compared to baseline, averaging about three beats per minute, observed 30 minutes after injection.

Reviewer comment: *Although one indication (BEB) showed a slight decrease in heart rate from baseline to final visits, this was not replicated in the other indications (CD and SP). The potential signal for decreased heart rate observed in the Dysport® development program does not appear to be replicated in the NT 201 development program.*

This reviewer made a request to the sponsor regarding the timing of vital sign measurements with regard to NT 201 administration, as this was not readily apparent in the application. The sponsor’s response to this information request is shown below (Sequence 40 within the NT 201 BLA):

“In the placebo-controlled studies for CD (i.e. study 0408), BEB (i.e. study 0433) and SP (i.e. study 0410) according to the trial protocol the vitals signs measurement at baseline were to be performed before randomization and therefore before injection of study medication (see also initial BLA submission, for CD: section 5.3.5.1 MRZ 60201-0408, 16.1.1 Amended Clinical Trial Protocol No. 2, section 9.5.1.4.3 and 9.5.1.4.4; for BEB: section 5.3.5.1 MRZ 60201-0433- 1, 16.1.1 Protocol and Protocol Amendments, section 9.5.1.4.3 and 9.5.1.4.4; for SP: section 5.3.5.1 MRZ 60201-0410-1 (amended report), 16.1.1 Protocol and Protocol Amendments, section 9.5.1.4). In these studies at the injection visits in the extension period all assessments including vital signs were to be performed prior to treatment.

In SP study 0607 the vital signs measurement were not necessarily to be performed before injection according to the trial protocol (see also initial BLA submission, section 5.3.5.1 MRZ 60201-0607, 16.1 Study Information, section 9.1.6).

In the active comparator controlled studies for CD (i.e. study 0013) and BEB (i.e. study 0003) the assessments were expected to be performed in order of appearance and therefore vital signs assessments should have been performed before treatment (see also initial BLA submission, for CD: section 5.3.5.1 MRZ 60201-0013, 16.1.1 Protocol and Protocol Amendments, section 10.2.1; for BEB: section 5.3.5.1 MRZ 60201-0003, 16.1.1 Protocol and Protocol Amendments 3, section 10.2.1). In the active comparator CD study 9801 vital signs were assessed at baseline, no further specification regarding the time point relative to the injection was defined in the trial protocol.”

Reviewer comment: *Based upon the above, in the placebo-controlled studies vital sign measurements were apparently made prior to treatment, both for baseline and for follow-up visits. As such, the vital signs were measured at least twelve weeks subsequent to prior NT 201 administration, at a time when NT 201’s effect had waned. Clearly, this was not the ideal timing for assessing an effect of NT 201 on vital signs.*

In the remaining studies (SP 0607, active-comparator studies), the vital signs were also performed prior to NT 201 injection, with the exception of CD Study 9801 in which (after baseline assessment) “no further specification regarding the time point relative to the injection was defined in the trial protocol.”

I referenced the FDA safety review¹⁹ of Dysport® to ascertain the timing of vital sign studies within the Dysport® development program, which was 30 minutes after injection.

7.4.3.2 Vital Signs: BEB

Merz stated that in the pooled BEB studies, in the NT 201 treatment group, no clinically meaningful changes or shifts in systolic or diastolic blood pressure, heart rate or respiratory rate from baseline to the visit when the primary efficacy endpoint was measured (Week 2 to Week 4) or the final visit were noted. The sponsor further stated that in the unpooled Study 0703, no clinically meaningful changes in these parameters were observed (BEB ISS, 120-Day Update, pg. 55).

Reviewer comment: *I examined BEB placebo-controlled study 0433/1 in order to:*

- *Compare NT 201 and placebo values for vital sign parameters*
- *Review the criteria the sponsor used to determine clinically meaningful changes*

I searched the ISS and the Study 0433/1 study report for the parameters used to determine a “clinically meaningful shift” but did not find this information. A request for clarification was made to the sponsor, who provided the following information:

19 FDA Clinical Safety Review BLA 125274. Dated September 28, 2008. Prepared by Dr. Marc Stone.

“A clinical meaningful shift (too low or too high) is defined as a vital sign that was out of the normal range for the respective parameter after administration. This definition applies for all studies analyzed for the Integrated Summary of Safety.

For example: If a subject has a heart rate as defined in the normal range of 50-120 beats per minutes at screening and develops a tachycardia (per definition a heart rate of > 120 beats per minutes) during the course of the study, this subject would be counted as one subject with a clinical meaningful shift to the group of subjects with a high heart rate at the respective visit (Merz response to FDA question, transmitted via e-mail on January 19, 2010).

Table 51: Criteria for Classifying Vital Signs as Low, Normal and High within the NT 201 Development Program

(Adapted from Sponsor Table 17, ISS Appendix F, pg. 25)

Text Table 17: Classification of Vital Signs

Parameter	Low	Normal	High
Systolic Blood Pressure [mmHg]	< 90	90 - 140	> 140
Diastolic Blood Pressure [mmHg]	< 40	40 - 90	> 90
Heart Rate [/ min]	< 50	50 - 120	> 120
Respiratory Rate [/ min]	< 12	12 - 20	> 20

The difference in vital signs between treatment group and between baseline and final visit for the placebo-controlled period of 0433 are shown below.

Table 52: Vital Signs by Treatment Group and Visit within the Placebo-controlled 0433/1
(Adapted from Sponsor Table 51, 0433/1 Study Report, pg. 152)

Text Table 51: Means (SD) of Vital Signs Parameters and Body Weight by Visit and Treatment Group (EFS Population)

Parameter (SI Units)	Visit	Mean (SD)			
		NT 201 group N=74	Placebo group N=34		
Systolic blood pressure (mmHg)	Screening	131.0	(16.15)	134.6	(14.93)
	Baseline	130.1	(15.90)	129.4	(15.60)
	Visit 3	128.4	(16.81)	130.3	(14.32)
	Visit 4	126.2	(14.74)	127.4	(17.57)
	Final Visit	126.2	(13.75)	128.1	(15.56)
Diastolic blood pressure (mmHg)	Screening	77.9	(8.78)	79.3	(7.42)
	Baseline	77.4	(9.31)	76.2	(9.60)
	Visit 3	77.7	(9.58)	77.1	(8.22)
	Visit 4	76.5	(7.93)	75.9	(8.86)
	Final Visit	76.5	(7.80)	76.4	(8.79)
Heart rate (bpm)	Screening	69.6	(12.31)	70.3	(7.70)
	Baseline	71.9	(11.19)	70.9	(10.67)
	Visit 3	71.0	(9.51)	71.4	(11.42)
	Visit 4	71.0	(9.74)	71.2	(10.00)
	Final Visit	70.2	(9.39)	71.3	(10.19)
Respiration rate (breaths/min)	Screening	16.6	(3.91)	15.7	(2.72)
	Baseline	16.7	(4.36)	16.0	(2.95)
	Visit 3	16.4	(3.91)	15.2	(2.32)
	Visit 4	16.6	(3.61)	15.8	(2.95)
	Final Visit	16.2	(3.25)	16.0	(3.12)
Body weight (lb)	Screening	173.4	(39.85)	171.0	(38.71)
	Final	175.3	(40.11)	168.9	(37.94)

SD=Standard deviation; bpm=Beats per minute

Source: Table 14.3.5.3

Reviewer comment: The table above does not generally demonstrate a difference in vital signs by treatment group or by treatment length. For heart rate, the placebo and NT 201 group begin as essentially equivalent, but by the final visit three is a slight decrease in the NT 201-treated patients (70.2% NT 201, 71.3% placebo).

7.4.3.3 Vital Signs: CD

Merz reported that in the pooled CD studies (the Study 0408/1 Main Period, and Studies 0013 and 9801), in the NT 201 treatment group, no “clinically important mean changes or shifts in systolic or diastolic blood pressure, heart rate or respiratory rate from baseline to the visit when the primary endpoint” was measured (Weeks 2 to 4) or final visit were observed. The sponsor further stated that in the unpooled CD Study 0605/1 Main Period,” no clinically important changes in these parameters were noted” (Study 0605/1 Main Period CSR, Section 5.3.5.1)(CD ISS, pg. 78).

Reviewer comment: I examined CD placebo-controlled study 0408/1 in order to:

- Compare NT 201 and placebo values for vital sign parameters
- Review the criteria the sponsor used to determine clinically meaningful changes

The difference in vital signs between treatment group and between baseline and final visit for the placebo-controlled period of 0433 are shown below.

The table below presents the vital sign data for the CD indication by study visit and treatment group within the placebo-controlled portion of Study 0408.

Table 53: Vital Signs by Treatment Group and Visit within the Placebo-controlled 0408/1
(Adapted from Sponsor Table 56, 0408/1 Study Report, pg. 156)

Text Table 56: Means (SD) of Vitals Signs Parameters and Body Weight Parameters by Visit and Treatment group (Total EFS Population)

Parameter [SI Units]	Visit	Mean (SD)					
		240 U group N=81		120 U group N=78		Placebo group N=74	
Systolic blood pressure [mmHg]	Screening	124.7	(16.46)	128.4	(18.68)	129.4	(16.98)
	Baseline	124.9	(15.49)	128.1	(15.03)	129.8	(17.89)
	Visit 3	123.5	(15.90)	124.7	(14.88)	128.0	(17.99)
	Visit 4	119.9	(13.55)	124.5	(14.07)	127.7	(17.65)
	Final Visit	122.2	(14.17)	124.6	(14.00)	128.9	(20.13)
Diastolic blood pressure [mmHg]	Screening	76.2	(10.24)	77.9	(10.69)	78.6	(8.92)
	Baseline	77.2	(9.88)	77.0	(9.57)	76.9	(10.71)
	Visit 3	75.2	(9.76)	75.7	(8.88)	77.7	(8.99)
	Visit 4	73.7	(9.21)	76.0	(9.65)	76.3	(10.41)
	Final Visit	74.8	(9.71)	76.7	(10.46)	76.5	(9.78)
Heart rate [bpm]	Screening	71.6	(10.27)	72.5	(13.48)	73.6	(10.54)
	Baseline	73.5	(10.10)	74.4	(12.92)	75.6	(11.62)
	Visit 3	73.9	(9.60)	73.3	(10.19)	74.4	(10.47)
	Visit 4	74.5	(10.63)	74.3	(10.72)	73.8	(11.11)
	Final Visit	74.6	(12.14)	72.8	(10.50)	74.2	(11.09)
Respiration rate [breaths/min]	Screening	15.7	(2.60)	16.0	(2.77)	16.0	(2.61)
	Baseline	15.9	(2.46)	16.1	(2.86)	15.9	(2.91)
	Visit 3	15.7	(2.49)	15.8	(2.64)	15.6	(2.69)
	Visit 4	15.6	(2.33)	15.6	(2.41)	15.6	(2.58)
	Final Visit	15.7	(2.11)	15.4	(2.42)	15.6	(2.44)
Body weight [lb]	Screening	160.8	(35.46)	178.6	(36.26)	170.1	(35.52)
	Final	160.3	(34.87)	178.6	(36.25)	170.6	(35.32)

Source: Table 14.3.5.3

Reviewer comment: From the table above, I do not see any affect on vital signs by dose group or from screening to final visit. For heart rate, no decrease was shown in the NT 201 patients compared to the placebo patients, and at the final study visit the mean heart rate was 74.6 in the NT 201-patients and 74.2 in the placebo-patients.

7.4.3.4 Vital Signs: SP

In the pooled SP studies, Merz stated that in the NT 201 treatment group, “no clinically meaningful shifts or mean changes in systolic or diastolic blood pressure, heart rate or respiratory rate” from baseline to Week 4 or the final visit (which varied across studies, from 20 to 69 weeks following treatment with NT 201) were noted. For heart rate, in the pooled studies, the heart rate at baseline was 73.9 bpm NT 201, 73.9 bpm placebo and 72.7 bpm Botox®. For the final visit, these had changed to 73.0 bpm, 72.0 bpm placebo and 71.5 Botox®.

Reviewer comment: I reviewed the BEB, CD and SP study reports to determine when heart rate was measured relative to NT 201 administration. (The decrease in heart rate in the Dysport® development program was observed in a CD study in which measurements were taken 30 minutes after treatment). I reviewed the study reports for the placebo-controlled trials of BEB, CD and SP, and it was unclear when vital signs were measure during the study visit. A request has been made to the sponsor to clarify this.

In the unpoolled Study (b) (4) the sponsor stated that “no clinically meaningful changes” in these parameters were observed (SP ISS 120 Day Update, pg. 57).

Reviewer comment: I reviewed the Study 0410/1 Report to compare vital sign parameters in NT 201 and placebo-treated patients. In the SP indication, the sponsor prepared a separate table for each vital sign parameter. I reviewed each of these tables (also included in the SP ISS 120 Day safety Update, Table 8.1.2.3.1.1, Table 8.1.2.3.1.2, Table 8.2.2.3.1.1, Table 8.2.2.3.1.2, Table 8.3.2.3.1.1, Table 8.3.2.3.1.2, Table 8.4.2.3.1.1, Table 8.4.2.3.1.2). The results were similar between treatment group and over time.

7.4.4 Electrocardiograms (ECGs)

7.4.4.1 Preclinical hERG Channel Testing

The sponsor presented data from a hERG channel study examining the effect of NT 201 on hERG channels using patch clamp recordings. The study also contained positive controls (cisapride and terfenadine) to validate their methods. The authors reported “(b) (4)” (10,000 units per ml) had no effect on hERG tail currents at -20 mV. The authors concluded that negative interactions of (b) (4) and, by implication, NT-201 with hERG channels seems unlikely.

Merz noted that in the hERG channel study, a concentration of 10,000 LDU/mL (b) (4) had no effect on hERG tail currents at -20 mV. This concentration clearly exceeds the therapeutically achievable concentration in human blood even when assuming full systemic availability of the administered dose. Given a mean human blood volume of 65 mL/kg (female) to 75 mL/kg (male) and a clinically recommended maximum dose of 435 LDU per treatment the maximal concentration² that can be achieved clinically is below 1 LDU/mL. Thus, Merz concluded that

the tested concentration in the hERG assay exceeds the maximal achievable concentration in human blood by a factor of at least 10,000. Therefore negative interactions of (b) (4) and, by implication, NT 201 with hERG channels in humans seem to be unlikely (Nonclinical Overview, pg. 11).

Reviewer comment: *The study described above was performed using (b) (4) ” from which the authors extrapolated the results to NT 201.*

7.4.4.2 ECGs: Other In Vivo Preclinical Studies

Merz described the following additional preclinical study related to NT 201 and cardiac function:

The effects of NT 201 and Botox® on electrocardiography (ECG) parameters were analyzed in conscious, non-restrained telemetered male Cynomolgus monkeys after a single intramuscular injection of 16 LDU/kg.

Reviewer comment: *The FDA’s Dr. Barbara Wilcox explained that that the dose of 16 LDU/kg represents 4-times the maximum human dose for CD and 9.4-times the maximum human dose for BEB.*

A decrease in heart rate and interrelated variations of RR and QT intervals (most likely due to the administration under ketamine hydrochloride anesthesia) were observed 2 to 3 hours after the treatment with either NT 201 or Botox®. One week after treatment with either NT 201 or Botox®, while paralysis of the *gluteus* muscle was well established, heart rate was markedly higher than during the pre-test period or during the day of treatment. This effect was associated with concomitant effects on RR and QT interval duration. From study week 4 onwards, ECG parameters returned essentially to baseline levels. Neither NT 201 nor Botox® affected PR interval length or QRS complex duration. NT 201 induced a slight increase in the QTc interval duration corrected with Fridericia’s formula, but no effect was observed on the QTc interval length corrected with Bazett’s formula. As this effect was of low magnitude (less than 20 ms) and only visible after correction with Fridericia’s formula, it is not considered by the sponsor to be biologically relevant. Week to week comparison of QTc values did not reveal any statistically significant difference compared to the pre-test period. Botox ® induced a slight QTc interval increase from 2 to 4 hours post-treatment (Nonclinical Overview, pg. 11).

Reviewer comment: *The FDA’s pre-clinical reviewer for NT 201 noted that a 9-month study in monkeys showed a small but dose -related reduction in heart weight (absolute and relative), but that there were no in-life signals (ECG, BP, HR) or histological correlates.*

7.4.4.3 ECGs: Pooled Indications

Reviewer comment: *Tables comparing ECG values in the placebo-controlled trials for the individual indications (BEB, CD and SP) were difficult to locate in the application, and a request was made to the sponsor for this information. The sponsor's response to the FDA's request is shown below:*

“As stated in the SAP for the initial BLA (see also Integrated Summary of Safety - Appendix F) in the placebo-controlled trials in the indications CD (i.e. study 0408), BEB (i.e. study 0433) and SP (i.e. study 0410) ECGs were assessed at baseline only. An additional ECG assessment was performed if an Adverse Event of the cardiovascular system occurred. This applied to one patient in study 0410 (a further ECG assessment was performed at final visit after a syncope). Table 7.4.2.1.2.2.1 of Appendix H gives the QT analysis for the placebo-controlled CD study 0408 and Table 7.4.2.1.1.1 for all studies of the CD indication (i.e. studies 0013 and 0408). The QT analysis for the placebo-controlled BEB study 0433 is given in Table 7.4.2.2.2.2.1 and for all studies of the BEB indication (i.e. studies 0003 and 0433) in Table 7.4.2.2.1.1. Finally, Table 7.4.2.3.2.1.1 displays the QT analysis of the placebo-controlled SP study 0410. No further SP studies were conducted with ECG assessments.

Please note that in the Type B Meeting on September 14, 2004 it was confirmed by the FDA that there is no need to include ECG evaluation in the design of the long-term study (see page 11, item 6 response under Sponsor Clinical questions and Proposed Responses, Food and Drug Administration, 2004)”

Reviewer comment: *The sponsor's summary of the ECG protocol within the NT 201 development program highlights the difficulty in preparing a table comparing ECG parameters in the NT 201 and placebo groups within the placebo-controlled trials. As shown in the tables below, the sponsor's ECG analysis largely consists of examining changes in NT 201-treated patients between study visits.*

The table below summarizes the changes in ECG parameters for NT 201-treated patients within the pooled, placebo-controlled studies from baseline to final study visit.

Table 54: ECG Parameters in the Pooled, Controlled Trials in the NT 201 Treatment Group
(Adapted from Sponsor Table 5.3.5.3-26, Pooled ISS, pg. 10)

Table 5.3.5.3 - 27: Electrocardiogram Parameters in the Controlled Studies, NT 201
Treatment Group

	N	Mean (SD)	Median	25%, 75%	Min	Max
Heart Rate (bpm)						
Baseline	976	69.1 (12.37)	68.0	60.0, 76.0	42.0	143.0
1° Endpoint Visit ⁵	650	70.1 (11.67)	69.0	62.0, 78.0	43.0	121.0
1° Endpoint Visit ⁵ -						
Baseline	635	0.7 (9.37)	1.0	-5.0, 6.0	-37.0	33.0
Final	358	71.7 (11.73)	71.0	63.0, 79.0	44.0	117.0
Final - Baseline	344	-0.5 (9.00)	0	-6.0, 5.0	-42.0	34.0
PR Interval (msec)						
Baseline	964	154.5 (24.65)	152.0	138.0, 168.0	72.0	250.0
1° Endpoint Visit ⁵	641	151.2 (21.75)	150.0	136.0, 165.0	97.0	238.0
1° Endpoint Visit ⁵ -	622	-0.3 (11.80)	0	-6.0, 6.0	-70.0	43.0
Baseline						
Final	348	151.9 (23.73)	149.5	134.0, 167.0	102.0	246.0
Final - Baseline	327	0.4 (11.34)	0	-5.0, 7.0	-70.0	45.0
QRS Interval (msec)						
Baseline	969	88.2 (11.43)	87.0	81.0, 94.0	40.0	156.0
1° Endpoint Visit ⁵	646	88.6 (11.33)	87.0	82.0, 94.0	59.0	164.0
1° Endpoint Visit ⁵ -	627	-0.3 (6.25)	0	-3.0, 2.0	-33.0	34.0
Baseline						
Final	354	90.6 (11.89)	89.0	83.0, 96.0	66.0	164.0
Final - Baseline	335	-0.1 (2.98)	0	-2.0, 2.0	-10.0	8.0
QT Interval (msec)						
Baseline	966	387.6 (34.90)	388.0	367.0, 410.0	130.0	556.0
1° Endpoint Visit ⁵	640	382.1 (30.42)	380.5	361.0, 401.0	283.0	507.0
1° Endpoint Visit ⁵ -						
Baseline	620	-3.4 (20.93)	-4.0	-16.0, 10.5	-75.0	67.0
Final	349	376.1 (29.38)	374.0	354.0, 394.0	305.0	477.0
Final - Baseline	329	0.2 (19.08)	1.0	-11.0, 13.0	-66.0	58.0
QTcB Interval (msec)						
Baseline	966	412.7 (29.17)	413.0	398.0, 429.0	142.0	625.0
1° Endpoint Visit ⁵	640	410.2 (23.48)	411.0	395.0, 426.0	331.0	473.0
1° Endpoint Visit ⁵ -						
Baseline	620	-1.3 (19.49) ¹	-1.5	-13.0, 11.0	-101.0	61.0
Final	349	408.0 (23.85)	409.0	388.0, 424.0	340.0	482.0
Final - Baseline	329	-0.5 (15.99) ²	-1.0	-11.0, 9.0	-70.0	66.0
QTcB Dispersion (msec)						
Baseline	377	25.3 (11.28)	21.0	20.0, 25.0	5.0	62.0
1° Endpoint Visit ⁵	363	23.6 (7.98)	21.0	20.0, 23.0	9.0	60.0
1° Endpoint Visit ⁵ -	363	-1.6 (12.99)	0	-2.0, 1.0	-41.0	45.0
Baseline						
Final	369	23.0 (6.34)	20.0	20.0, 23.0	9.0	60.0
Final - Baseline	368	-2.4 (11.6)	0	-3.0, 2.0	-41.0	30.0

Table continues

Table 5.3.5.3 - 27: Electrocardiogram Parameters in the Controlled Studies, NT 201 Treatment Group

	N	Mean (SD)	Median	25%, 75%	Min	Max
QTcF Interval (msec)						
Baseline	966	403.9 (26.95)	404.0	390.0, 419.0	138.0	571.0
1° Endpoint Visit ⁵	640	400.3 (21.29)	401.0	387.0, 413.0	335.0	475.0
1° Endpoint Visit ⁵ - Baseline		-2.1 (16.00) ⁵	-2.0	-12.0, 8.0	-76.0	54.0
Final	620					
Final	349	396.7 (21.26)	396.0	382.0, 409.0	348.0	480.0
Final - Baseline	329	-0.2 (13.08) ⁴	0	-9.0, 8.0	-40.0	50.0

Reviewer comment: In the table above, ECG parameters were essentially unchanged from baseline to final study visit in the pooled NT 201 patients. A prolongation of the QT interval was not observed, and the QT intervals for the final visits were minimally shorter than at baseline: for QTcB 410.2 msec baseline to 408.0 msec final visit, QTcF 403.9 msec baseline to 396.7 msec final visit).

The FDA requested additional information from Merz regarding the analysis of ECGs. The FDA’s question to the sponsor, and their response, are shown below:

FDA Request:

We acknowledge the response to the information request for QT interval data from the ECG. Please send the outlier analysis data for studies 0003 (BEB) and 0013 (CD) for QTcF. The text in the ISS 5.3.3 states that large changes of 60 msec were not present for the QTcF interval, but table 7.7.2.2.2.1.1 seems to indicate of maximum change of 105 from baseline to control.

Merz Response:

The response to the last FDA information request for QT interval data from the ECG, dated June 7, 2010 (see also “response-to-7jun2010-qt-interval-data-fda-info-request.pdf”) gives the tables of the QT analysis of all studies before a re-assessment of the ECGs of study 0003 (BEB) and study 0013 (CD). In these two studies ECGs were performed at baseline, during peak of effect (Control visit), and at the final visit. A central ECG assessment of an independent cardiologist took place at the time they were obtained. Nevertheless, a re-assessment was performed by an experienced CRO which was specialized on central ECG assessment for clinical studies. Nevertheless, the ISS text in section 5.5.3 (see also “integrated-summary-safety-120-day.pdf”, section 9.2.2) refers to the tables in section 11 of output tables given in “iss-appendix h.pdf”, i.e. after re-assessment of the ECGs of these studies by the CRO. The corresponding table of the analysis of the QTcF interval for all CD studies (i.e. studies 0013 and 0408) is given in

Table 11.11.6.2.1.1.1, for study 0013 (CD) alone in Table 11.11.6.2.1.2.1.1. For the BEB studies (i.e. 0003 and 0433) the corresponding table of the QTcF interval is given in Table 11.11.6.2.2.1.1, for study 0003 (BEB) alone in Table 11.11.6.2.2.2.1.1. Table 11.11.9 and 11.11.10 give the analysis of QTcF changes from baseline of >30 msec and >60 msec, respectively. These tables reveal that changes of 60 msec were not present for the QTcF interval as stated in the ISS on basis of the ECG data after re-assessment.

The case of maximum change in QTcF interval of 105 msec that you mentioned in your information request was measured in subject S003 in study 0003 (BEB). Table 1 below gives the QTcF intervals (values and changes from baseline) before and after re-assessment for this subject to demonstrate the differences.

Table 55: QTcF intervals (values and changes from baseline) of subject S003 of study 0003 (BEB)

(Adapted from Sponsor Table 1, Sequence 41, pg. 1)

Visit/Change	QTcF values before re-assessment [in msec]		QTcF values after re-assessment [in msec]	
	Value	Change from baseline	Value	Change from baseline
Baseline	332		419	
Control Visit	437	105	400	-19
Final Visit	438	106	379	-40

Unfortunately, the ECG data after re-assessment were erroneously not submitted in the initial BLA. Please find attached to this response the derived dataset A-ECGNEW.XPT with the corresponding dataset description ECGNEW.XLS and the raw dataset ECG3-13N.XPT which is the basis of the derived dataset. We apologize very much for any inconvenience that this missing dataset caused on your side (Merz response to FDA Information Request of June 14, 2010, Sequence 41).

Reviewer comment: The sponsor's response regarding the discrepancy between an ISS statement that one set of QTcF values were determined before re-assessment, whereas the second was after

re-assessment. It is notable that the differences before and after assessment are so large, as shown in the table above.

7.4.4.4 ECGs: BEB

Merz stated that serial electrocardiograms (ECGs) were performed in BEB Study 0003, and the results were assessed by the study Investigator and by an independent cardiologist. A brief summary of the results follows. The sponsor reported that the evaluated cardiac intervals (RR, PR, QRS, QT/QTc (F/B)) and heart rate did not show any significant changes between the baseline and respective post-baseline visits. Merz asserted that this was true for both the study drug NT 201 and the comparator drug Botox (BEB ISS, 120 Day Update, pg. 55).

The sponsor stated that “the outlier analysis did not yield a large incidence rate of changes greater than 30 ms in QT or QTcF(B) for either treatment in both studies. Large changes of 60 ms were not present for the QTcF interval. The cardiologist evaluated all ECGs with respect to rhythm, conduction, and morphological abnormalities. All but one clinically relevant finding noted during the control or follow-up visits were already present at baseline.”

Merz reported that one patient in the NT 201 group developed an Intermittent Left Bundle Branch Block. On the ECG printout for this subject (age 74 years), the blood pressure was also noted (170/90 mmHg). The sponsor hypothesized that this may be an indication of arterial hypertension with underlying hypertensive heart disease for which Left Bundle Branch Blocks (intermittent or persistent) are typical. Merz reported that T wave abnormalities (mostly inverted T waves) were equally distributed amongst the treatment groups and visits. The sponsor concluded that no effect of the study drugs on the QT and QTcF(B) intervals could be detected, and the heart rate, PR interval and QRS duration were not affected by either study drug (BEB ISS, 120 Day Update, pg. 55).

***Reviewer comment:** In placebo-controlled BEB Study 0433/1 study report, I was unable to find a summary table comparing ECG results in the NT 201 and placebo treatment group. Based on the text summary above, the sponsor has used primarily shift analyses and evaluation by an independent cardiologist to determine whether differences in the drug and placebo group are present. Although a summary table of values would be preferable, this is acceptable based on the preclinical and ECG results for the pooled and other indications.*

7.4.4.5 ECG: CD

In the CD indication, serial electrocardiograms (ECGs) were performed in Study 0013.

***Reviewer comment:** I reviewed Table 5.3.5.3-27 in the CD ISS which summarized changes in ECG parameters from baseline to final visit. As with the pooled data, the values were only minimally changed over the course of the study.*

7.4.4.6 ECGs: SP

Merz reported that serial electrocardiograms (ECGs) were performed only in Study (b) (4) which was discontinued prematurely due to slow enrollment. Therefore, only incomplete data are available from this study. During the FDA Meeting in March, 2005, it was agreed that in Study 0410 it would be sufficient to perform an ECG only at the Screening Visit, and that no additional ECG assessments were necessary [FDA Meeting Minutes 2005](SP ISS, pg. 43).

Reviewer comment: *I reviewed the meeting minutes referenced by the sponsor and confirmed that the DNP did state that additional ECGs were not required. As noted above, serial ECGs were performed only in the CD and BEB indications.*

7.4.5 Special Safety Studies/Clinical Trials

Reviewer comment: *Merz conducted several studies for the purpose of examining systemic spread of the NT 201. See Section 7.3.5.2 for details of studies conducted to measure systemic diffusion of NT 201.*

7.4.6 Immunogenicity

7.4.6.1 Immunogenicity: Pharmacology

(b) (4) (b) (4)



(b) (4)

Reviewer comment: (b) (4);

The sections below examine the immunology from the perspective of antibody formation.

7.4.6.2 Immunogenicity: Literature Review

A number of studies in the medical literature have examined the immunogenicity of botulinum toxin products. The primary of these studies are summarized here.

1. An early series, looking at 559 BoNT type A treated patients between 1984 and 1992, found 24 (4.3%) with antibodies by mouse assay. Some had had only one or two injection sessions. Eight of 76 patients with follow-up (10.5%) developed resistance to drug effect. As a rule, they had had been treated with larger doses and had injections at closer intervals, especially booster injections 2 to 3 weeks after the initial session.
2. Another study (by far the largest in the literature) looked at the correlation between the presence of neutralizing antibodies and non-responsiveness to treatment (Lange, et al. Clin Neuropharm 32(4)213-218, 2009). Serum samples were taken from 503 patients with a variety of diagnoses treated by BoNT-A (Dysport® or BOTOX®). The selected subjects were secondary nonresponders, i.e.: initially responded but then lost the responsiveness to therapy. Fewer than half of the subjects (n = 224, 44.5%) had neutralizing antibodies. The authors concluded that non-responsiveness is not well correlated with the presence of antibodies and that non responsiveness may not reliably be used as a surrogate for the presence of antibodies. They confirmed that the presence of antibodies in these non-responders was associated with higher doses and shorter intervals between injections (for example, only 6 of 38 subjects (16%) with blepharospasm, but 175 of 362 subjects (48%) with cervical dystonia).

The authors found the presence of antibodies to be unrelated to the commercial preparation used, but found that cumulative doses higher than 6000 units were associated with a higher proportion of patients with antibodies. Of note, the mean duration of therapy until secondary nonresponsive was 41 months (Dysport®) and 45 months (BOTOX®). This also suggests that formulation differences among BoNT agents may not be relevant to the formation of antibodies or the development of non-responsiveness. An alternative plausible explanation for the loss of efficacy to BoNT products could be that actual muscle fiber damage results from the use of toxin. This has been documented by biopsy in humans (Schroeder, et al. Mov Dis 24 (10)1494-1503, 2009).

3. In the NT 201 development program, antibodies were investigated (Goschel, et al Exp Neurol 147:96-102, 1997) and the Sponsor argues that antibodies were present in all non-responders, stating that non-responders who were not antibody positive subsequently responded to retreatment. However, in this paper, no study design specifications or clinical data are presented. The Sponsor demonstrated antibody development to high doses of BOTOX® but not NT 201 after biweekly injections for 12 weeks in rabbits. In a 33 week study comparing Dysport®, BOTOX® and NT 201, one animal did develop antibodies in the NT 201 group.

4. Well-documented cases of antibodies developing after a single injection or with low dose (as in the treatment of glabellar lines) exist.

7.4.6.3 Immunogenicity: Pooled Indications

During clinical development of NT 201, antibody assessments were performed using an ELISA (Enzyme-linked Immunosorbent Assay) or the improved FIA-AB (Fluorescence Immuno Assay for Antibodies) for screening. Positive samples were subsequently tested using the mouse *ex vivo* hemidiaphragm assay (HDA) for neutralizing antibodies. In the completed studies of NT 201, a total of 12 of 1080 subjects (1.1%) who were antibody negative at baseline developed neutralizing antibodies to Botulinum toxin during the course of their respective study (see Section 5.3.5.3, Table 4). Each of these 12 subjects had been treated with another Botulinum toxin prior to exposure to NT 201; no treatment-naïve subject developed antibodies to Botulinum toxin (120-Day Safety Update, pg. 76).

The sponsor's tally from all trials in the development program for all indications reveals that 0.7% of 1048 NT 201 patients and 0.8% of 354 BOTOX® patients developed anti BoNT antibodies (ISS, p. 84).

Reviewer comment: *It is notable that in the pooled active-controlled studies (NT 201 versus Botox®) the number of patients developing antibodies in the NT 201 and Botox treatment groups were similar (0.7% NT 201, 0.8% Botox).* (b) (4)

7.4.6.4 Immunogenicity: Safety – BEB

Merz reported that four NT 201-treated patients in the BEB studies who were antibody-negative at baseline developed borderline values of antibodies to Botulinum toxin, including two subjects in Study 0003 and two subjects in the Study 0433/1 Main Period. The sponsor added that none of these subjects experienced TEAEs suggestive of immune-mediated events (e.g., hypersensitivity reactions, anaphylactoid reactions, or anaphylaxis). Merz further noted that all of the patients who developed antibodies had received a Botulinum toxin other than NT 201 before study entry. The sponsor stated that no subjects in the Study 0433/2 OLEX Period developed antibodies to Botulinum toxin (BEB ISS, 120 Day Update, pg. 61).

Although the four patients did not experience AEs suggestive of a hypersensitivity reaction, the four subjects who developed anti-Botulinum antibodies did experience other AEs: two experienced TEAEs. Subject 2133 in Study 0433/1 experienced mild malaise which resolved. Subject 2153 in Study 0433/1 experienced the events worsening of hypertension, hemorrhoid pain, nasopharyngitis, and left ear infection; all of which resolved. (BEB ISS, 120 Day Update, pg. 61).

In Trial 0433/1 (placebo controlled) and Trial 0003 (active control with BOTOX®), the sponsor screened antibodies by ELISA and confirmed with the mouse hemidiaphragm bioassay. Antibody

titers > 3.58 mU/mL and hemidiaphragm paralysis times > 64 minutes were considered positive. In these two trials, 2 of 222 patients (1%) had antibodies at baseline (2 others were “borderline”). In Trial 0433/1 two subjects developed transient “borderline” antibodies which were not present at the final visit. In Trial 0003, one NT 201 subject became positive and another “borderline” at the final visit. In Trial 0003, two subjects developed antibodies in the BOTOX® arm; they had had 21 and 31 previous injection sessions, respectively. There were no clinical phenomena which could be attributed to this development.

7.4.6.5 Immunogenicity: Safety – CD

Four subjects who were antibody-negative at screening developed antibodies to Botulinum toxin during participation in the Study 0408/1 Main Period. Three of these subjects did not experience any TEAEs. The fourth subject, Subject 1257, experienced bilateral leg pain, bilateral leg weakness, bilateral arm pain and bilateral arm weakness approximately one week after treatment with NT 201.

During the Study 0408/2 Extension Period, four additional subjects developed antibodies to Botulinum toxin. Three of these subjects reported TEAEs (CD ISS, pg. 56).

1. **Subject 1053** had a positive FIA result at all assessments, a negative HDA result at baseline, a positive result before injection 3 on 25-Jun-2007, and a negative HDA result at the last study visit (August 2007). This subject experienced two TEAEs, mild torticollis and moderate neck pain, both of which occurred approximately two weeks after the antibody-positive sample was obtained (July 2007).
2. **Subject 1079** had a positive FIA result and a negative HDA result at baseline, and a positive (borderline) result at the 6th injection visit. This subject experienced the following TEAEs during the Extension Period (where the subject had multiple episodes of an event, the worst intensity and relationship are given): head titubation, haemoglobin decreased, gastric ulcer, neck pain (3 episode), headache, optic neuropathy and dysphagia (two episodes).
3. **Subject 1313** had a negative FIA and HDA result at baseline, and a positive (borderline) HDA result at the 4th injection visit. The subject experienced the TEAEs respiratory tract infection (moderate, not related) and pain in extremity (moderate, not related) during the Extension Period.

7.4.6.6 Immunogenicity: Safety – SP

In the Study 0410/1 Main Period and 0410/2 OLEX Period, antibody determination was performed at each visit before injection of NT 201, 4 weeks after the second injection with NT 201 during the Study 0410/2 (OLEX Period), and at the end of the trial. In these studies, Merz reported that 47 subjects received the first injection, 136 subjects received the second injection, 121 subjects received the third, 100 subjects received the fourth, 51 subjects received the fifth, and 7 subjects received the sixth injection.

Merz reported that no patient in these studies developed neutralizing antibodies to Botulinum toxin, despite receiving maximum doses of 500 U NT 201 (the median dose at each injection was 360 to 400 U), and up to 6 injections. Merz asserted that a high proportion of patients (73.6%) in this study had never been treated with a Botulinum toxin preparation prior to the study (120-Day ISS, pg. 57).

7.4.6.7 Immunogenicity: Reviewer Conclusions

Reviewer comment: *Only four of the 12 subjects who developed antibodies to Botulinum toxin experienced TEAEs. None of the TEAEs associated with anti-Botulinum antibodies were suggestive of immune-mediated events (e.g., hypersensitivity reactions, anaphylactoid reactions, or anaphylaxis). The sponsor asserted that most of the subjects who developed neutralizing antibodies showed a therapeutic response to treatment, and for many, the positive antibody titers were a transient finding or false positive because borderline results are measured. Although subjects in Study 0410 (SP) received up to six doses of NT 201 in a high dose of a maximum of 500 U, none of these subjects developed neutralizing antibodies. Finally, in studies comparing NT 201 and Botox®, the number of patients developing antibodies in the NT 201 and Botox treatment groups were essentially the same (0.7% NT 201, 0.8% Botox). NT 201 therefore does not demonstrate a strong signal for clinically significant immune responses, although cases of anaphylaxis have been reported during the postmarketing use of NT 201 outside of the United States.*

(b) (4)

7.5 Other Safety Explorations: AE Risk by Study Location

Reviewer comment: *A pattern has been observed in various drug development programs in which studies conducted in North America report higher rates of adverse events than similar studies conducted elsewhere. In some development program, this difference affected only common adverse events, but in others it has affected both serious and common adverse events. In some cases, the difference has been significant enough that the FDA has requested separate adverse event tables in labeling for North American and non-North American studies.*

I therefore examined the risk of serious and common adverse events in several North American and non-North American studies within the NT 201 development program. The results are shown in the table below. All of the SP studies were conducted outside North America, so SP could not be included in the analysis. In other development programs which have demonstrated higher AE rates in the North American studies, the effect is often more pronounced for AEs thought to be related to the drug, and less so for AEs not believed to be drug-related. In each indication I have selected AEs from each of these categories.

Table 56: Comparison of AEs in the BEB and CD Indications by Study Location (North American and non-North American)

Benign Essential Blepharospasm		
	North American Study: 0433/1 (North America) N=74 NT 201 Patients, 34 Placebo Patients	Non-North American Study: 0003 (Israel and Europe) N=152 NT 201 Patients, 148 Placebo Patients
Overall AEs	NT 201: 70% Placebo: 62%	NT 201: 40% Botox: 45%
Overall SAEs	NT 201: 0% Placebo: 2.8%	NT 201: 2% Botox: 3%
Ptosis	NT 201: 18.9% Placebo: 9%	NT 201: 6.1% Botox: 4.5%
Upper Respiratory Tract Infection	NT 201: 1.4% Placebo: 8.8%	NT 201: 0.7% Botox: 0.7%
Cervical Dystonia		
	North American Study: 0408/1 (United States) (N=159 NT 201 Patients, 74 Placebo Patients)	Non-North American Study: 0013 (Israel and Europe) (N= 231 NT 201 Patients, 232 Botox Patients)
Overall AEs	NT 201 = 56% Placebo = 42%	NT 201 = 28.1% Botox = 24.1%
Overall SAEs	NT 201= 3.7% Placebo = 0.0%	NT 201 = 1.7% Botox = 2.2%
Dysphagia	NT 201 =11.6% Placebo = 2.7%	NT 201 = 10.8% Botox = 8.2%
Muscular Weakness	NT 201 = 6.4% Placebo = 1.4%	NT 201 = 1.7% Botox = 0.4%
Injection Site Pain	NT 201 = 6.4% Placebo = 6.8%	NT 201 = 0.0% Botox = 1.9%

Reviewer comment: As observed in other drug development programs, the analysis above does show a higher number of reported adverse events in the North American studies compared to those outside of North America. In many instances the risk of the common adverse events (overall and for specific indications) was approximately two- to three-fold higher in the North American countries compared to the non-North American countries. Consistent with the pattern seen in other drug development programs, the effect is more pronounced for the common adverse

events than for serious adverse events. This difference in common adverse events should be considered in the selection of tables to be used in the US labeling.

7.5.1 Dose-Dependency for Adverse Events

Reviewer comment: *Because NT 201 is administered as an intermittent single injection, the examination of drug exposure in relation to adverse events should encompass both the dose of the injection and the total number of injections. The following sections therefore discuss both of these dose-related issues for the total NT 201 data and by indication (BEB, CD, and SP).*

7.5.1.1 Dose-Dependency for AEs: Pooled Indications

Reviewer comment: *The sponsor presented a table20showing common adverse events by dose group for all the pooled studies within the NT 201 development program. I do not include this table here as the adverse events are specific to the indications (for example, ptosis for BEB or dysphagia for CD) and pooling the groups dilutes the true risk in the relevant indication and providing misleading information within a dose-response analysis. In addition, the doses of NT 201 varied significantly by indications. For these reasons the dose-dependence of AEs should be examined by indication, as opposed to combined.*

7.5.1.2 Dose-Dependency for AEs: BEB

Dose: Merz stated that in the Study 0433/1 Main Period and 0433/2 OLEX Period, the incidence of SAEs was higher in subjects who received 10 to 40 U of NT 201, compared with those who received >40 U of NT 201. Six of 27 subjects in the 10 to 40 U group (22.2%), compared with 4 of 79 subjects in the >40 U group (5.1%), experienced SAEs. The sponsor noted that although it appears that the incidence of SAEs does not increase with higher NT 201 doses in the treatment of BEB, because of the small number of subjects with SAEs, it is not possible to draw reliable conclusions based on these data (BEB ISS – 120 Day Update, pg. 23).

Table 57: Very Common and Common Adverse Events in the BEB Development Program by Dose Categories

(Adapted from Sponsor Table 15, BEB ISS, pg. 17)

Table 15: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events in the NT 201 Treatment Group, Study 0433/1 Main Period

MedDRA System Organ Class	NT 201 Overall N=74	Placebo Overall N=34	NT 201 10-40 U N=13	NT 201 >40 U N=61
Subjects with TEAEs:	52 (70.3%)	21 (61.8%)	7 (53.9%)	45 (73.8%)
Eye disorders	28 (37.8%)	7 (20.6%)	5 (38.5%)	23 (37.7%)
Eyelid ptosis	14 (18.9%)	3 (8.8%)	2 (15.4%)	12 (19.7%)
Dry eye	12 (16.2%)	4 (11.8%)	3 (23.1%)	9 (14.8%)
Vision blurred	4 (5.4%)	2 (5.9%)	-	4 (6.6%)
Visual impairment	5 (6.8%)	-	-	5 (8.2%)
Lacrimation increased	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Gastrointestinal disorders	22 (29.7%)	5 (14.7%)	5 (38.5%)	17 (27.9%)
Dry mouth	12 (16.2%)	1 (2.9%)	4 (30.8%)	8 (13.1%)
Diarrhoea	6 (8.11%)	-	1 (7.7%)	5 (8.2%)
Dysphagia	3 (4.1%)	2 (5.9%)	1 (7.7%)	2 (3.3%)
Lip disorder	2 (2.7%)	-	-	2 (3.3%)
Infections and infestations	15 (20.3%)	5 (14.7%)	3 (23.1%)	12 (19.7%)
Nasopharyngitis	4 (5.4%)	1 (2.9%)	1 (7.7%)	3 (4.9%)
Respiratory tract infection	4 (5.4%)	1 (2.9%)	-	4 (6.6%)
Gastroenteritis viral	2 (2.7%)	-	-	2 (3.3%)
Urinary tract infection	2 (2.7%)	-	-	2 (3.3%)
Nervous system disorders	10 (13.5%)	3 (8.8%)	2 (15.4%)	8 (13.1%)
Headache	5 (6.8%)	1 (2.9%)	1 (7.7%)	4 (6.6%)
General disorders and administration site conditions	8 (10.8%)	3 (8.8%)	1 (7.7%)	7 (11.5%)
Asthenia	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Injection site haematoma	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Injection site pain	2 (2.7%)	-	-	2 (3.3%)
Musculoskeletal and connective tissue disorders	4 (5.4%)	7 (20.6%)	1 (7.7%)	3 (4.9%)
Respiratory, thoracic and mediastinal disorders	8 (10.8%)	1 (2.9%)	-	8 (13.1%)
Dyspnoea	4 (5.4%)	1 (2.9%)	-	4 (6.6%)
Injury, poisoning and procedural complications	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Muscle strain	2 (2.7%)	-	-	2 (3.3%)
Investigations	3 (4.1%)	1 (2.9%)	1 (7.7%)	2 (3.3%)
Metabolism and nutrition disorders	2 (2.7%)	1 (2.9%)	-	2 (3.3%)
Ear and labyrinth disorders	2 (2.7%)	-	-	2 (3.3%)
Reproductive and breast disorders	2 (2.7%)	-	-	2 (3.3%)

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: Treatment-emergent adverse event; U: units.

Source: Table 3.1.1.2.2.2.2.2 and Table 3.1.9.2.2.2.2.2, Section 5.3.5.3, Appendix H.

Reviewer comment: In the table above showing adverse events in the BEB by dose group, ptosis has a pattern suggesting a possible dose-response relationship (15.4 % for < 40 U, 19.7% for >40 U). However, the number of overall patients and the number of ptosis events is small, and a clear dose-response pattern is not demonstrated.

Number of Injections: When dose is assessed as the number of injections, the effect on common AEs are shown in the table below. Because of the number of injections and the small number of patients in each injection number group

Appears this way on original

Table 58: Common Adverse Events in the BEB Indication by Injection Number

(Adapted from Sponsor Table 16, BEB ISS, pg. 28)

Table 16: Common (Occurring in ≥1% of Subjects in Any Category) Adverse Events in the Study 0433 (BEB) Main and Extension Periods, by System Organ Class and Injection

MedDRA System Organ Class	Injection 1 NT 201 N=106	Injection 2 NT 201 N=98	Injection 3 NT 201 N=91	Injection 4 NT 201 N=86	Injection 5 NT 201 N=76	Injection 6 NT 201 N=36
Subjects with TEAEs	70 (66.0%)	42 (42.9%)	47 (51.7%)	32 (37.2%)	27 (35.5%)	14 (38.9%)
Eye disorders	36 (34.0%)	17 (17.4%)	21 (23.1%)	14 (16.3%)	12 (15.8%)	7 (19.4%)
Gastrointestinal disorders	27 (25.5%)	11 (11.2%)	7 (7.7%)	8 (9.3%)	3 (4.0%)	1 (2.8%)
Infections and infestations	18 (17.0%)	5 (5.1%)	12 (13.2%)	9 (10.5%)	9 (11.8%)	3 (8.3%)
Nervous system disorders	15 (14.2%)	7 (7.1%)	5 (5.5%)	3 (3.5%)	4 (5.3%)	2 (5.6%)
General disorders and administration site conditions	12 (11.3%)	3 (3.1%)	3 (3.3%)	2 (2.3%)	4 (5.3%)	-
Respiratory, thoracic and mediastinal disorders	9 (8.5%)	2 (2.0%)	2 (2.2%)	1 (1.2%)	2 (2.6%)	-
Investigations	8 (7.6%)	5 (5.1%)	3 (3.3%)	-	3 (4.0%)	2 (5.6%)
Musculoskeletal and connective tissue disorders	6 (5.7%)	9 (9.2%)	6 (6.6%)	2 (2.3%)	3 (4.0%)	1 (2.8%)
Injury, poisoning and procedural complications	5 (4.7%)	2 (2.0%)	-	3 (3.5%)	1 (1.3%)	-
Skin and subcutaneous tissue disorders	-	3 (3.1%)	1 (1.1%)	5 (5.8%)	2 (2.6%)	-
Metabolism and nutrition disorders	3 (2.8%)	2 (2.0%)	-	-	-	-
Reproductive system and breast disorders	2 (1.9%)	-	1 (1.1%)	-	1 (1.3%)	-
Ear and labyrinth disorders	2 (1.9%)	-	-	-	-	-
Neoplasms, benign, malignant and unspecified	2 (1.9%)	1 (1.0%)	1 (1.1%)	2 (2.3%)	-	-
Hepatobiliary disorders	1 (0.9%)	-	-	-	1 (1.3%)	-
Psychiatric disorders	1 (0.9%)	1 (1.0%)	2 (2.2%)	-	1 (1.3%)	-
Renal and urinary system disorders	1 (0.9%)	-	1 (1.1%)	1 (1.2%)	2 (2.6%)	1 (2.8%)
Immune system disorders	1 (0.9%)	1 (1.0%)	-	1 (1.2%)	1 (1.3%)	-
Vascular disorders	1 (0.9%)	2 (2.0%)	1 (1.1%)	-	1 (1.3%)	-
Cardiac disorders	-	-	-	1 (1.2%)	-	-
Surgical and medical procedures	-	-	-	1 (1.2%)	-	-

Table continues

Table 16: Common (Occurring in ≥1% of Subjects in Any Category) Adverse Events in the Study 0433 (BEB) Main and Extension Periods, by System Organ Class and Injection

MedDRA System Organ Class	Injection 1 NT 201 N=106	Injection 2 NT 201 N=98	Injection 3 NT 201 N=91	Injection 4 NT 201 N=86	Injection 5 NT 201 N=76	Injection 6 NT 201 N=36
Blood and lymphatic system disorders	-	-	-	-	1 (1.3%)	-

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject had a TEAE in that category.

BEB: benign essential blepharospasm; MedDRA: Medical Dictionary for Regulatory Activities; OLEX: open-label extension (period); TEAE: Treatment-emergent adverse event.

Source: Table 3.1.1.1, ISS Appendix J.

Reviewer comment: Based on the table above, Even when collapsed into SOC groupings, when stratified over six injections the number of patients in each sub-group is small, and a clear trend of AE risk change over time is not apparent.

7.5.1.3 Dose-Dependency for AEs: CD

Dose: For the placebo-controlled period of study 0408/1 alone, common and very common AEs by dose group are shown in the table below.

Table 59: Common and Very Common Adverse Events in the CD Study 0408/1 by Dose Group (Adapted from Sponsor Table 18, CD ISS, pg. 42)

Table 18: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events by NT 201 Dose Group, Study 0408/1 Main Period

MedDRA System Organ Class	NT 201 120 U ¹ N=77	NT 201 240 U ¹ N=82	Placebo N=74
Subjects with TEAEs	44 (37.1%)	45 (54.9%)	31 (41.9%)
Musculoskeletal and connective tissue disorders			
Neck pain	5 (6.5%)	12 (14.6%)	3 (4.1%)
Muscular weakness	5 (6.5%)	9 (11.0%)	1 (1.4%)
Musculoskeletal pain	5 (6.5%)	3 (3.7%)	1 (1.4%)
Muscle spasms	1 (1.3%)	3 (3.7%)	2 (2.7%)
Musculoskeletal stiffness	1 (1.3%)	4 (4.9%)	1 (1.4%)
Back pain	1 (1.3%)	1 (1.2%)	2 (2.7%)
Myalgia	1 (1.3%)	2 (2.5%)	-
Pain in extremity	-	3 (3.7%)	-
Table continues			
Gastrointestinal disorders			
Dysphagia	10 (13.0%)	15 (18.3%)	2 (2.7%)
Nausea	2 (2.6%)	4 (4.9%)	-
Dry mouth	1 (1.3%)	1 (1.2%)	-
Toothache	2 (2.6%)	-	-
Nervous system disorders			
Headache	2 (2.6%)	4 (4.9%)	3 (4.1%)
Dizziness	2 (2.6%)	2 (2.5%)	1 (1.4%)
Hypoaesthesia	2 (2.6%)	1 (1.2%)	-
Burning sensation	1 (1.3%)	1 (1.2%)	-
Head titubation	1 (1.3%)	1 (1.2%)	-
Somnolence	1 (1.3%)	1 (1.2%)	-
Head discomfort	-	2 (2.5%)	-
Paraesthesia	-	2 (2.5%)	-
Syncope vasovagal	-	2 (2.5%)	-
General disorders and administration site conditions			
Injection site pain	7 (9.1%)	3 (3.7%)	5 (6.8%)
Asthenia	1 (1.3%)	2 (2.5%)	-
Influenza like illness	1 (1.3%)	1 (1.2%)	-
Infections and infestations			
Sinusitis	2 (2.6%)	3 (3.7%)	2 (2.7%)
Nasopharyngitis	3 (3.9%)	-	5 (6.8%)

Table 18: Very Common (Occurring in ≥10% of Subjects) and Common (Occurring in ≥1% of Subjects and ≥1 Subject) Adverse Events by NT 201 Dose Group, Study 0408/1 Main Period

MedDRA System Organ Class Preferred Term	NT 201 120 U ¹ N=77	NT 201 240 U ¹ N=82	Placebo N=74
Upper respiratory tract infection	1 (1.3%)	1 (1.2%)	-
Respiratory, thoracic and mediastinal disorders	10 (13.0%)	8 (9.8%)	2 (2.7%)
Asthma	2 (2.6%)	2 (2.5%)	-
Oropharyngeal pain	2 (2.6%)	2 (2.5%)	-
Cough	2 (2.6%)	-	-
Dysphonia	2 (2.6%)	-	-
Dyspnoea	1 (1.3%)	1 (1.2%)	-
Rhinorrhoea	2 (2.6%)	-	-
Skin and subcutaneous tissue disorders	3 (3.9%)	3 (3.7%)	3 (4.1%)
Hyperhidrosis	1 (1.3%)	1 (1.2%)	-
Rash	-	2 (2.5%)	-

¹ Subjects in the 120 U column in this table are from the ≤120 U column in the source table. Subjects in the 240 U column are from the >120 to 240 U and >240 U columns in the source table, with the denominator and all percents adjusted accordingly.

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject experienced a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event; U: units.

Source: Table 3.1.9.2.1.2.2.2, Section 5.3.5.3, Appendix H.

Reviewer comment: Common TEAEs in the CD indication which demonstrated a higher risk in the 240 U group compared to the 120 U group were: neck pain (6.5% 120 U versus 14.6% 240 U), muscle weakness (6.5% 120 U versus 11.0% 240 U) and dysphagia (13% 120 U versus 18.3% 240 U.)

Number of Injections: The effect of repeated injections on the occurrence of adverse events (combined by SOC) are shown in the table below.

Table 60: Common AEs in Study 0408 Main and Extension Period by SOC and Number of Injections

(Adapted from Sponsor Table 17, CD ISS, pg. 38)

Table 17: Common (Occurring in ≥1% of Subjects in Any Injection Category) Adverse Events in Study 0408 Main Period and Extension Period Combined, by System Organ Class and Injection Number, as of 25-Jun-2009

MedDRA System Organ Class	Injecti on 1 NT 201 N=227	Injecti on 2 NT 201 N=207	Injecti on 3 NT 201 N=183	Injecti on 4 NT 201 N=161	Injecti on 5 NT 201 N=122	Injecti on 6 NT 201 N=61
Subjects with TEAEs	124 (54.6%))	109 (52.7%))	81 (44.3%))	71 (44.1%))	43 (35.3%))	24 (39.3%))
Musculoskeletal and connective tissue disorders	58 (25.6%)) 45 (19.8%))	32 (15.5%)) 28 (13.5%))	28 (15.3%)) 20 (10.9%))	20 (12.4%)) 15 (9.3%))	10 (8.2%)) 9 (7.4%))	3 (4.9%)) 5 (8.2%))
Gastrointestinal disorders	31 (13.7%))	19 (9.2%))	6 (3.3%))	16 (9.9%))	7 (5.7%))	4 (6.6%))

Table continues

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

General disorders and administration site conditions	26 (11.5%)	13 (6.3%)	12 (6.6%)	7 (4.4%)	5 (4.1%)	1 (1.6%)
Infections and infestations	25 (11.0%)	32 (15.5%)	22 (12.0%)	18 (11.2%)	12 (9.8%)	7 (11.5%)
Respiratory, thoracic and mediastinal disorders	20 (8.8%)	7 (3.4%)	4 (2.2%)	2 (1.2%)	4 (3.3%)	3 (4.9%)
Investigations	9 (4.0%)	8 (3.9%)	6 (3.3%)	4 (2.5%)	5 (4.1%)	3 (4.9%)
Skin and subcutaneous tissue disorders	8 (3.5%)	8 (3.9%)	5 (2.7%)	3 (1.9%)	2 (1.6%)	2 (3.3%)
Injury, poisoning and procedural complications	4 (1.8%)	8 (3.9%)	8 (4.4%)	6 (3.7%)	3 (2.5%)	3 (4.9%)
Psychiatric disorders	4 (1.8%)	7 (3.4%)	9 (4.9%)	7 (4.4%)	1 (0.8%)	1 (1.6%)
Ear and labyrinth disorders	3 (1.3%)	5 (2.4%)	-	-	-	-
Metabolism and nutrition disorders	3 (1.3%)	4 (1.9%)	-	2 (1.2%)	-	-
Eye disorders	2 (0.9%)	2 (1.0%)	5 (2.7%)	1 (0.6%)	2 (1.6%)	1 (1.6%)
Renal and urinary system disorders	-	2 (1.0%)	1 (0.6%)	-	-	-
Neoplasms, benign, malignant and unspecified	-	2 (1.0%)	-	1 (0.6%)	1 (0.8%)	1 (1.6%)
Vascular disorders	1 (0.4%)	7 (3.4%)	3 (1.6%)	-	2 (1.6%)	-
Reproductive system and breast disorders	1 (0.4%)	2 (1.0%)	-	-	1 (0.8%)	-
Endocrine disorders	-	-	-	-	-	1 (1.6%)

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; OLEX: open-label extension (period); TEAE: Treatment-emergent adverse event.

Source: Table 3.1.1.1, ISS Appendix J.

Table 61: Common Adverse Events by Injection Number in CD
(Adapted from Sponsor Table 17, CD ISS, pg. 23)

Table 17: Common (Occurring in ≥1% of Subjects in Any Injection Category) Adverse Events in Study 0408 Main Period and Extension Period Combined, by System Organ Class and Injection Number, as of 25-Jun-2009

MedDRA System Organ Class	Injecti on 1 NT 201 N=227	Injecti on 2 NT 201 N=207	Injecti on 3 NT 201 N=183	Injecti on 4 NT 201 N=161	Injecti on 5 NT 201 N=122	Injecti on 6 NT 201 N=61
Subjects with TEAEs	124 (54.6%)	109 (52.7%)	81 (44.3%)	71 (44.1%)	43 (35.3%)	24 (39.3%)
Musculoskeletal and connective tissue disorders	58 (25.6%)	32 (15.5%)	28 (15.3%)	20 (12.4%)	10 (8.2%)	3 (4.9%)
Gastrointestinal disorders	45 (19.8%)	28 (13.5%)	20 (10.9%)	15 (9.3%)	9 (7.4%)	5 (8.2%)
Nervous system disorders	31 (13.7%)	19 (9.2%)	6 (3.3%)	16 (9.9%)	7 (5.7%)	4 (6.6%)

Reviewer comment: In the SOCs in which there were the most number of patients receiving each injection (Musculoskeletal and Connective Tissue Disorders, Gastrointestinal Disorders, and General Disorders), the risk of adverse event decreases as the number of injection increases. As noted elsewhere in this review, one explanation for this trend is that patients who experienced bothersome adverse events withdrew from the study before they received additional injections, leaving the patients most resistant to adverse events to receive the most injections (survivor bias). This theory is supported by the decreasing number of patients with each subsequent injection.

7.5.1.4 Dose-Dependency for AEs: SP

Dose: Within the SP indication, AEs by dose group in the placebo-controlled Study 0410/1 were shown in the table below.

Table 62: Common Adverse Events in the NT 201 SP Study, 0410/1 by Dose Group
(Adapted from Sponsor Table 19, SP ISS, pg. 37)

Table 19: Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events in the NT 201 Treatment Group, Study 0410/1 Main Period, by Total Dose Group

MedDRA System Organ Class Preferred Term	NT 201 Overall N=73	Placebo Overall N=75	NT 201 >120-240 U N=17	NT 201 >240-360 U N=35	NT 201 >360 U N=21
Subjects with TEAEs	21 (28.8%)	20 (26.7%)	5 (29.4%)	9 (25.7%)	7 (33.3%)
Metabolism and nutrition disorders	6 (8.2%)	3 (4.0%)	2 (11.8%)	1 (2.9%)	3 (14.3%)
Hyperglycaemia	3 (4.1%)	-	1 (5.9%)	-	2 (9.5%)
Hypercholesterolaemia	2 (2.7%)	1 (1.3%)	1 (5.9%)	-	1 (4.8%)
Nervous system disorders	5 (6.9%)	7 (9.3%)	1 (5.9%)	3 (8.6%)	1 (4.8%)
Headache	2 (2.7%)	1 (1.3%)	-	1 (2.9%)	1 (4.8%)
Epilepsy	2 (2.7%)	-	1 (5.9%)	1 (2.9%)	-
Injury, poisoning and procedural complications	5 (6.9%)	2 (2.7%)	1 (5.9%)	3 (8.6%)	1 (4.8%)
Gastrointestinal disorders	3 (4.1%)	5 (6.7%)	1 (5.9%)	1 (2.9%)	1 (4.8%)
Diarrhoea	2 (2.7%)	2 (2.7%)	-	1 (2.9%)	1 (4.8%)
General disorders and administration site conditions	3 (4.1%)	3 (4.0%)	1 (5.9%)	2 (5.7%)	1 (4.8%)
Infections and infestations	2 (2.7%)	5 (6.7%)	2 (11.8%)	-	-
Investigations	2 (2.7%)	1 (1.3%)	1 (5.9%)	-	1 (4.8%)

Data are presented as number of subjects (percent of subjects).

"-" indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: Treatment-emergent adverse event; U: units.

Source: Table 3.1.1.2.3.2.1.2 and Table 3.1.9.2.3.2.1.2, Section 5.3.5.3, Appendix H.

Reviewer comment: As per the table above, although the total patients with adverse events increased across dose groups, for individual common AEs no strong dose response patterns were observed, which may be due to the instability in the analysis stemming from the small number of events in each dose strata.

7.5.2 Time Dependency for Adverse Events

7.5.2.1 Time Dependency for Adverse Events: Pooled Indications

Comparisons of the three Phase 3, randomized, double-blind, placebo-controlled studies (Study 0408/1 [CD], Study 0433/1 [BEB], and Study 0410/1 [SP]) indicate that NT 201 has a time to onset (mean of 6.0 – 7.7 days), time to waning (mean of 6.5 – 10.6 weeks), and duration of effect (mean of 73.9 – 97.7 days)(Clinical Overview, pg. 17).

Reviewer comment: Due to the small number of adverse events and the relatively wide range of therapeutic action of NT 201, although the pooled placebo-controlled studies did not find a difference in the NT 201 and placebo-treated patients with regard to the most frequent time category for reporting events (2 to 4 weeks) a complete time-dependency analysis was not possible.

7.5.3 Drug-Demographic Interactions

Reviewer comment: *For all the indications, including the pooled indications, there were too few non-Caucasian subjects to sub-analyze the adverse event data by race. Race is therefore not included in the discussion of the individual and pooled indications below.*

7.5.3.1 Drug-Demographic Interactions: Pooled Indications

For gender analysis, in the placebo-controlled studies of the three neurologic indications, Merz reported that “male subjects who received NT 201 had a slightly higher incidence of SAEs, compared with the male subjects who received placebo.” However, the sponsor noted that because the number of subjects in all groups who experienced SAEs was small, it is difficult to draw reliable conclusions based on these data (Pooled Neurologic Indications, 120 Day ISS, pg. 44).

For age and common AEs, Merz report that when the incidence rates of TEAEs in the three age groups are compared, subjects >65 years of age treated with NT 201 reported more events of dysphagia, dry mouth and eyelid ptosis, compared with subjects in the other age groups treated with NT 201. However, the number of subjects in each of the groups is small, making it difficult to draw reliable conclusions based on these data.

7.5.3.2 Drug-Demographics Interactions: BEB

For SAEs, there were too few events in the BEB placebo-controlled trials to construct an analysis based on gender. In the pooled BEB studies (the Study 0433/1 Main Period and Study 0003), 3 of 164 female subjects treated with NT 201 (1.8%), and 1 of 22 female subjects treated with placebo (4.6%), experienced an SAE. No male subjects treated with NT 201 in the pooled studies experienced serious events (BEB ISS – 120 Day Update, pg. 23).

For SAEs in the Study 0433/1 Main Period and 0433/2 OLEX Period, Merz reported that the incidence of SAEs in male and female subjects receiving NT 201 was similar. Four of 37 male subjects (10.8%) and 6 of 69 female subjects (8.7%) experienced SAEs (BEB ISS, 120 Day Update).

For SAEs, there were too few events to meaningfully examine the effect of age with NT 201 treatment. In the Study 0433/1 Main Period, the only subject who experienced an SAE was 75 years of age. In the Study 0433/1 Main Period and 0433/2 OLEX Period, in subjects who received NT 201, the incidence of SAEs was similar across age groups. One of 12 subjects ≤50 years of age (8.3%), 5 of 52 subjects >50 to 65 years of age (9.6%), and 4 of 42 subjects >65 years of age (9.5%) experienced SAEs (BEB 120 Day Update, pg. 23).

Reviewer comment: *The small number of AEs in the BEB indication precluded analysis by race.*

7.5.3.3 Drug-Demographics Interactions: CD

For SAEs, in the Study 0408/1 Main Period and Study 0408/2 Extension Period (analyzed together), Merz found that 15 of 227 subjects (6.6%) had experienced SAEs, including 8 of 79 male subjects (10.1%), and 7 of 148 female subjects (4.7%)(CD ISS, pg. 32).

For age, in the Study 0408/1 Main Period, the sponsor reported that 2 of 94 subjects (2.1%) in the NT 201 group who were ≤ 50 years of age, 2 of 110 subjects (1.8%) in the NT 201 group who were >50 65 years of age, no subject in NT 201 group who was >65 years of age, and no subject in the placebo group experienced an SAE.

Reviewer comment: *For age, gender and race, the number of patients and SAEs was too small to reliably detect any interaction.*

For common adverse events, in the Study 0408/1 Main Period, Merz stated that in male subjects, NT 201-treated subjects, compared with placebo-treated subjects, had a higher incidence of common or very common TEAEs (difference $\geq 3\%$) in every SOC, and most PTs (difference $\geq 2\%$). For female subjects, the PTs in which NT 201-treated subjects, compared with placebo-treated subjects, had a higher incidence (difference $\geq 2\%$) of common or very common events were, nausea, muscular weakness, neck pain, and musculoskeletal pain. Female patient treated with NT 201 appear to have greater incidence rates for the event dysphagia, compared with male subjects (CD ISS, pg 43).

Reviewer comment: *The sponsor prepared a table of common adverse event stratified by gender (Table 19, CD ISS), which I reviewed. Although there are a number of adverse events that are somewhat more common in one gender over the other, there are too few patients in each subgroup to support an analysis on the level of Preferred Term events. In addition, there is no biologic rationale to suspect that one gender would be affected differentially than another.*

In the pooled CD studies (the Study 0408/1 Main Period, and Studies 0013 and 9801), the sponsor reported that for subjects in the NT 201 group TEAE incidence was highest in the middle aged group (≤ 50 years of age: 64/212 subjects, 30.2%; >50 -65 years of age: 83/171 subjects, 48.5%; >65 years of age: 19/48 subjects, 39.6%). At the SOC level, subjects in the >50 -65 years of age group had a higher incidence of events in the Musculoskeletal and connective tissue disorders, Infections and infestations, and Respiratory, thoracic and mediastinal disorders SOCs, compared with the other age groups. At the PT level, Merz stated that the incidence of events in the NT 201 treatment group was similar across age groups, but the number of events was too small to allow for reliable assessment of the possible relationship between age and the incidence of adverse events in subjects receiving NT 201 (CD ISS, pg. 48).

Reviewer comment: *As with the analysis by gender, there were too few patients in each subgroup to support a reliable analysis. The number of patients in the over 65 age group was particularly small.*

Merz stated that there were too few non-Caucasian patients to perform any analyses by race (CD ISS, pg 22).

7.5.3.4 Drug-Demographic Interactions: SP

Overall, within the NT 201 and the placebo groups, more female subjects experienced TEAEs. For both male and female subjects in the Study 0410/1 Main Period, the incidence of TEAEs was similar in the placebo and NT 201 groups. At the PT level, the number of TEAEs was too small to permit a reliable assessment of the relationship between gender and the incidences of TEAEs with NT 201 administration.

When Studies 0410/1 Main Period and 0410/2 OLEX Period are analyzed together, female patients had a slightly higher overall incidence of TEAEs, compared with male subjects. Thirty-four of 52 female subjects (65.4%) and 56 of 95 male subjects (59.0%) experienced at least one TEAE. At the SOC level, a higher percent of female than male subjects (difference $\geq 5\%$) experienced events in the Investigations (10 subjects, 19.2% vs. 4 subjects, 4.2%), Infections and infestations 13 subjects, 25% vs. 16 subjects, 16.8%).

Merz stated that in the Study 0410 Main Period, TEAE risk did not increase with increasing age. No NT 201-treated subject over 65 years of age experienced a severe or a serious adverse event.

Reviewer comment: *I reviewed the source tables referenced by the sponsor for the statements above (SP ISS pgs. 38-40) and found the statements to be accurate.*

7.5.3.3.4 Drug-Demographics Interactions: Reviewer Conclusions

Reviewer comment: *In the various BEB, CD and SP studies within the NT 201 development program, analysis by age and gender showed minor variations in AE risk. However, due to the minimal change and the small number of patients in the subgroups, no demographic factor was demonstrated to be an effect modifier.*

7.5.4 Drug-Disease Interactions

7.5.4.1 Drug-Disease Interaction: Pooled Studies

Merz stated that in the pooled, controlled studies, the incidence of SAEs in NT 201-treated patients increased with greater baseline disease severity, with a similar pattern seen for Botox-treated subjects. The sponsor noted, however, that at the SOC and PT levels, the number of individual SAEs was low (most events occurred in only one subject), and Merz asserted that no pattern of increased incidence of certain events or types of events in subjects with severe disease at baseline is apparent (as shown in the table below).

Table 63: SAEs in the Total Pooled Indications (Including Non-Neurologic Indications) for SOC by Disease Severity

(Adapted from Sponsor Table 5.3.5.3-13, Pooled Neurologic Indications – 120 Day ISS, pg. 46)

Table 5.3.5.3 - 13: Serious Adverse Events Occurring in the NT 201 Treatment Group, by System Organ Class and Baseline Disease Severity – Pooled Studies, Overall and Placebo-Controlled, as of 17-Dec-2008

MedDRA System Organ Class	Overall NT 201	Overall NT 201 (Placebo-controlled Studies)	Overall Placebo	By Treatment and Baseline Disease Severity (Placebo-Controlled Studies)					
				Mild NT 201	Mild Placebo	Moderate NT 201	Moderate Placebo	Severe NT 201	Severe Placebo
	N=1313	N=618	N=346	N=61	N=34	N=241	N=147	N=316	N=0
Subjects with SAEs	38 (2.9%)	15 (2.4%)	2 (0.6%)	-	1 (2.9%)	7 (2.9%)	1 (0.7%)	8 (2.5%)	-
Nervous system disorders	8 (0.6%)	1 (0.2%)	1 (0.3%)	-	-	1 (0.4%)	1 (0.7%)	-	-
Gastrointestinal disorders	6 (0.5%)	1 (0.2%)	-	-	-	-	-	1 (0.3%)	-
Infections and infestations	6 (0.5%)	3 (0.5%)	-	-	-	2 (0.8%)	-	1 (0.3%)	-
Respiratory, thoracic and mediastinal disorders	3 (0.2%)	3 (0.5%)	1 (0.3%)	-	1 (2.9%)	2 (0.8%)	-	1 (0.3%)	-
Vascular disorders	3 (0.2%)	1 (0.2%)	-	-	-	-	-	1 (0.3%)	-
Ear and labyrinth disorders	2 (0.2%)	1 (0.2%)	-	-	-	-	-	1 (0.3%)	-
Injury, poisoning and procedural complications	2 (0.2%)	2 (0.3%)	-	-	-	1 (0.4%)	-	1 (0.3%)	-
Neoplasms malignant, benign, and unspecified	2 (0.2%)	-	-	-	-	-	-	-	-
Renal and urinary disorders	2 (0.2%)	1 (0.2%)	-	-	-	1 (0.4%)	-	-	-
Reproductive system and breast dis.	2 (0.2%)	1 (0.2%)	-	-	-	1 (0.4%)	-	-	-
Skin and subcutaneous tissue dis.	2 (0.2%)	-	-	-	-	-	-	-	-
Cardiac disorders	1 (0.1%)	-	-	-	-	-	-	-	-
Congenital, familial and genetic dis.	1 (0.1%)	1 (0.2%)	-	-	-	-	-	1 (0.3%)	-
Eye disorders	1 (0.1%)	-	-	-	-	-	-	-	-
General disorders and administration site conditions	1 (0.1%)	1 (0.2%)	-	-	-	-	-	1 (0.3%)	-
Psychiatric disorders	1 (0.1%)	-	-	-	-	-	-	-	-
Surgical and medical procedures	1 (0.1%)	1 (0.2%)	-	-	-	-	-	1 (0.3%)	-

"-" indicates that no subject had an event in that category. MedDRA: Medical Dictionary for Regulatory Activities. SAE: Serious Adverse Event. The controlled studies were: 0408/1 (CD) Main Period, 0013 (CD), 9801 (CD), 0410/1 (SP) Main Period, 0607 (SP), 0433/1 (BEB) Main Period, 0003 (BEB), 0520/1 (GFL) Main Period, 0527 (GFL), and 0617 (CF). The placebo-controlled studies were: 0408/1 (CD) Main Period, 0410/1 (SP) Main Period, 0433/1 (BEB) Main Period, 0520/1 (GFL) Main Period, 0527 (GFL). Source: Table 3.3.1.1.1 and Table 3.3.8.1.1, Section 5.3.5.3, Appendix H.

Merz explained that because the dose of NT 201 varied widely across indications, with the oldest (i.e., the BEB population) and sickest (i.e., the post-stroke SP population) patient represented primarily in the lowest and highest dose groups, it is difficult to assess the incidence of SAEs by total dose group in the pooled, controlled studies. However, when SAEs were examined by total NT 201 dose at the SOC and PT levels, the number of individual SAEs was low (most events occurred in only one patient), and the sponsor believes that no pattern of increased incidence of certain events is apparent (ISS, pg. 42).

Reviewer comment: I agree with the sponsor that examining SAEs in the pooled, NT 201 studies leads to indeterminate results. Common adverse events are presented by indication below.

7.5.4.2 Drug-Disease Interaction: BEB

In the Study 0433/1 Main Period, in the NT 201 treatment group, Merz reported that patients with mild disease at baseline had higher incidence rates of eyelid ptosis, compared with patients with moderate or severe disease at baseline. There was no clear pattern of increased incidences for TEAEs in any group of NT 201-treated patients; however, the number of subjects with

TEAEs in each group is small, making it difficult to draw reliable conclusions based on these data (BEB ISS, pg. 37).

Reviewer comment: I reviewed Table 19 within the BEB ISS which examined AEs by disease severity, and found no clinically meaningful pattern.

7.5.4.3 Drug-Disease Interaction: CD

For SAEs, in the Study 0408/1 placebo-controlled Main Period, in the NT 201 treatment group, Merz reported that no patient with mild disease at baseline, 2 of 81 subjects (2.5%) with moderate disease, and 2 of 39 subjects (5.1%) with severe disease experienced SAEs. The sponsor stated that no subject in the placebo group experienced a serious event. The sponsor added that a similar finding is noted in the Botox group, with 1 of 67 subjects (1.5%) with mild disease, 2 of 137 subjects (1.5%) with moderate disease, and 3 of 40 subjects (7.5%) with severe disease, experiencing SAEs. Merz asserted that when SAEs are examined by SOC and PT, however, no pattern of increased incidence of any particular event, with increased baseline disease severity, is noted (CD ISS, pg. 33).

For common adverse events, Merz stated that patients in the NT 201 group who had mild disease at baseline had a higher incidence of certain TEAEs (e.g., muscular weakness, musculoskeletal pain, headache, injection site pain, sinusitis, asthma) compared with the respective placebo group, than subjects in the NT 201 group with moderate or severe baseline disease. The sponsor hypothesized that the reason for the decreased incidence rates with increasing baseline severity may be due to the fact that moderate and severe CD often have substantial muscle hypertrophy due to the continuous muscle activity. Merz noted that botulinum neurotoxin administration usually targets these hypertrophic muscles (CD ISS, pg. 54).

Reviewer comment: One would expect the preceding explanation of the inverse relationship between common AEs and disease severity to have also applied to SAEs, which was not the case. Another explanation is that, as with other subgroup analyses, the small number of patients creates unstable results that can be heavily influenced by events, or lack thereof, only a few patients.

7.5.4.4 Drug-Disease Interaction: SP

Merz stated that the majority (78%) of subjects treated with NT 201 in the Main Period of the study had experienced an ischemic stroke, with a mean time since diagnosis of SP of approximately 5 years. In the Study 0410 Main Period, TEAE risk did not increase with baseline disease severity (0410/1 Final Safety Report, pg. 67).

Reviewer comment: I reviewed the tables referenced by the sponsor and did not a clinically meaningful trend of adverse events based on baseline disease severity measurements.

7.5.5 Drug-Drug Interactions

Merz stated that the effect of Botulinum toxin could “hypothetically” be potentiated by aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission, e.g., tubocurarine type muscle relaxants. The sponsor referenced three studies in support of this statement Santos 1981, Wang et al. 1984²¹ and Yamada et al. 1986²². Therefore, Merz cautioned that the concomitant use of NT 201 with aminoglycosides or spectinomycin requires special care, and peripheral muscle relaxants should be used with caution.

Reviewer comment: It was not possible to assess the effect of concomitant use of aminoglycosides, spectinomycin or muscle relaxants with respect to adverse event occurrence in the NT 201 development program. I reviewed the three studies referenced by the sponsor and concur that due to the theoretical risk a statement noting the potential interaction should be included in labeling.

7.6 Additional Safety Evaluations: Pre-Treatment with other Botulinum Toxin Products

Merz defined patients who had not been treated with Botulinum toxin for the study indication for at least one year before study entry as treatment-naïve, and patient who had been treated with Botulinum toxin for the study indication within one year as pre-treated, as agreed at the pre-BLA meeting with FDA (FDA meeting minutes, July, 2007). These definitions were somewhat different for studies examining botulinum antibodies, with “pre-treated” defined as treatment with a Botulinum toxin of any serotype, for *any* indication, at any time before study entry, and “treatment-naïve” defined as no treatment with a Botulinum toxin for *any* indication at any time before study entry (CD ISS, pg. 15).

7.6.1 Botulinum Toxin Pre-Treatment

7.6.1.1 Botulinum Toxin Pre-Treatment: BEB

Merz stated that there were very few patients who were Botulinum toxin naïve in the BEB studies, thus no assessment of the relationship between treatment status and the incidence of AEs could be performed (BEB ISS, 120-Day Update, pg. 23).

7.6.1.2 Botulinum Toxin Pre-Treatment: CD

The percent of patients with prior treatment with other botulinum toxin products varied by study protocol. In the Study 0408/1 (CD) Main Period, Merz stated that 87 of 159 subjects (54.7%)

²¹ Wang YC, Burr DH, Korthals GJ, Sugiyama H. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. *Appl Environ Microbiol* 1984; 48(5): 951- 955. (49) Ward AB, Aguilar M, De Beyl Z, Gedlin 22 *Neuropharmacol* 2007; 30(2): 86-94. (55) Yamada S, Kuno Y, Iwanaga H. Effects of aminoglycoside antibiotics on the neuromuscular junction: Part I. *Int J Clin Pharmacol Ther Toxicol* 1986; 24(3): 130- 138.

were pre-treated and 72 of 159 subjects (45.3%) were treatment-naïve. The percent of pre-treated and treatment-naïve subjects in the placebo group was similar to the NT 201 group. As per protocol, in Study 9801 Merz reported that 100% of subjects were treatment-naïve (not treated with any Botulinum toxin one year prior to trial entry) and in Study 0013, 100% of subjects were pre-treated with Botulinum toxin (CD ISS, pg. 15).

Among the CD studies, Merz stated that only Study 0408 enrolled both Botulinum toxin pre-treated and treatment-naïve subjects. In the Main Period of this study, the four subjects who experienced SAEs were pre-treated. In the study 0408/2 Extension Period, 11 additional patients experienced common AEs. These include 8 of 11 subjects (72.7%) who were pre-treated and 3 of 11 subjects (27.3%) who were treatment-naïve at the beginning of the study 0408/1 Main Period (CD ISS, pg. 32).

Reviewer comment: *Although pre-treated patients in the CD indication seem to be over-represented among patients who experienced AEs (100% of patients in the SAEs, 73% of patients with common AEs and 55% within the general study population), the number of patients is small and the comparison is not controlled for dose or disease severity.*

7.6.1.3 Botulinum Toxin Pre-Treatment: SP

The effect of botulinum pre-treatment on AEs in the SP indication is shown in the following table.

Table 64 Common AEs by Botulinum-Toxin Pre-Treatment Status in the SP Indication of the Program

(Adapted from Sponsor Table 23, SP ISS, pg. 41)

Table 23: Common (Occurring in ≥1% of Subjects and >1 Subject) Adverse Events in the NT 201 Treatment Group, Study 0410/1 Main Period, by Botulinum Toxin Pre-Treatment Status

MedDRA System Organ Class Preferred Term	Treatment-Naive NT 201 N=61	Treatment-Naive Placebo N=65	Pre-Treated NT 201 N=11	Pre-Treated Placebo N=10
Subjects with TEAEs	21 (34.4%)	16 (24.6%)	0	4 (40.0%)
Metabolism and nutrition disorders				
Hyperglycaemia	6 (9.8%)	2 (3.1%)	-	1 (10.0%)
Hypercholesterolaemia	3 (4.9%)	-	-	-
Hypercholesterolaemia	2 (3.3%)	-	-	1 (10.0%)
Nervous system disorders				
Headache	5 (8.2%)	7 (10.8%)	-	-
Headache	2 (3.3%)	1 (1.5%)	-	-
Epilepsy	2 (3.3%)	-	-	-
Injury, poisoning and procedural complications				
Gastrointestinal disorders	5 (8.2%)	2 (3.1%)	-	-
Gastrointestinal disorders	3 (4.9%)	5 (7.7%)	-	-
Diarrhoea	2 (3.3%)	2 (3.1%)	-	-
General disorders and administration site conditions				
Infections and infestations	3 (4.9%)	2 (3.1%)	-	1 (10.0%)
Infections and infestations	2 (3.3%)	4 (6.2%)	-	1 (10.0%)
Investigations	2 (3.3%)	1 (1.5%)	-	-

Data are presented as number of subjects (percent of subjects).

“-” indicates that no subject had a TEAE in that category.

MedDRA: Medical Dictionary for Regulatory Activities; TEAE: Treatment-emergent adverse event; U: units.

Source: Table 3.1.10.2.3.2.1.2, Section 5.3.5.3, Appendix H.

In the Study 0410/1 Main Period, only treatment-naïve subjects receiving NT 201 experienced TEAEs; none of the subjects pre-treated with Botulinum toxin in the NT 201 group had a TEAE. At the PT level, treatment-naïve subjects receiving NT 201 had a higher incidence of the events hyperglycaemia, hypercholesterolaemia, and epilepsy (difference ≥3%). However, due to the low incidence of subjects with TEAEs, it is very difficult to make reliable comparisons of events (SP ISS, pg. 42).

Reviewer conclusions: *In the NT 201 development program, in the CD indication AEs were more frequent in patients with previous treatment with botulinum toxin, whereas the reverse was true in the SP indication (There were two few events in the BEB indication to evaluate events by treatment status). Due to the small number of events and probably confounding by disease severity and dose, no evidence of a difference in AE risk by treatment status is apparent.*

7.6.2 Human Carcinogenicity

The proposed NT 201 labeling states that “No genotoxicity, carcinogenicity or pre- and postnatal development studies have been conducted with Xeomin.”

In the “Nonclinical Overview” (pg. 35), the sponsor elaborated on their rationale for not performing carcinogenicity studies.

No carcinogenicity studies have been conducted with NT (b) (4) 201, in accordance with the guidance in (ICH S6 1997): “Standard carcinogenicity bioassays are generally

inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed depending on duration of clinical dosing, patient population and/or biological activity of the product (e.g. growth factors, immunosuppressive agents, etc.). When there is a concern about carcinogenic potential a variety of approaches may be considered to evaluate risk.”

Merz asserted “there is no scientific cause for concern regarding a carcinogenic potential of BoNT/A and NT (b) (4)201.”

Reviewer comment: *Dr. Lois Freed within the DNP was consulted regarding the sponsor’s assertion that carcinogenicity studies were not required. Dr. Freed confirmed that such studies are difficult to perform for botulinum toxin products and the sponsor was indeed exempt from performing them.*

According to the integrated summary of safety, in the pooled, placebo-controlled trials, treatment-emergent adverse events in the “Neoplasms benign, malignant and unspecified” SOC occurred in 5 of 701 subjects (0.7%) in the NT 201 group, compared with 4 of 346 subjects (1.2%) in the placebo group. The events that occurred in the NT 201 group were melanocytic naevus, dysplastic naevus syndrome, haemangioma, lentigo maligna stage unspecified, and skin cancer (1 subject, 0.1%, each). The events in the placebo group were melanocytic naevus (2 subjects, 0.6%), basal cell carcinoma, and skin papilloma (1 subject, 0.3%, each).

Reviewer Comment: *In the pooled, placebo-controlled trials, the risk of neoplasm was higher in the placebo group (1.2%) compared to NT 201 group (0.7%). The cancers occurring in the placebo-controlled trials were largely skin cancers or precancerous lesions, which are also the most common form of cancer observed within the general population.*

System Organ Class Preferred Term	Treatment			
	NT 201		Placebo	
	No. of Pat. N (%)	Occ. of AEs N (%)	No. of Pat. N (%)	Occ. of AEs N (%)
VASCULAR DISORDERS				
Hypertension	7 (1.00)	7 (0.81)	2 (0.58)	2 (0.74)
Haematoma	1 (0.14)	1 (0.12)	2 (0.58)	2 (0.74)
Flushing	1 (0.14)	1 (0.12)	-	-
Hypertensive crisis	1 (0.14)	3 (0.35)	-	-
Hypotension	1 (0.14)	1 (0.12)	-	-
Hot flush	-	-	1 (0.29)	1 (0.37)
Ischaemic limb pain	-	-	1 (0.29)	1 (0.37)
PSYCHIATRIC DISORDERS	12 (1.71)	15 (1.73)	2 (0.58)	2 (0.74)
Insomnia	7 (1.00)	8 (0.92)	-	-
Anxiety	1 (0.14)	1 (0.12)	2 (0.58)	2 (0.74)
Depression	3 (0.43)	3 (0.35)	-	-
Anxiety disorder	1 (0.14)	1 (0.12)	-	-
Depressed mood	1 (0.14)	1 (0.12)	-	-
Panic attack	1 (0.14)	1 (0.12)	-	-
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	5 (0.71)	5 (0.58)	4 (1.16)	4 (1.49)
Melanocytic naevus	1 (0.14)	1 (0.12)	2 (0.58)	2 (0.74)
Dysplastic naevus syndrome	1 (0.14)	1 (0.12)	-	-
Haemangioma	1 (0.14)	1 (0.12)	-	-
Lentigo maligna stage unspecified	1 (0.14)	1 (0.12)	-	-
Skin cancer	1 (0.14)	1 (0.12)	-	-
Basal cell carcinoma	-	-	1 (0.29)	1 (0.37)
Skin papilloma	-	-	1 (0.29)	1 (0.37)

7.6.3 Human Reproduction and Pregnancy Data

Merz performed several preclinical studies examining the effect of prenatal NT 201 exposure. These were performed in rabbits and rats and did not reveal any adverse reproductive toxicity finding up to dose levels exhibiting maternal toxicity. Maternal NOAEL was 30 LDU/kg and embryotoxicity NOAEL was 90 LDU/kg.

(b) (4)

This was also their rationale for not performing any peri- and post-natal toxicology studies for NT 201.

Merz noted that there was limited clinical experience of NT 201 use during pregnancy. The sponsor stated that one patient in the ongoing Extension Period of Study 0408/2 (CD), one patient in Study 0013 (CD), and one patient in Study 0520/2 (GFL) became pregnant following exposure to NT 201. The subject in Study 0013 had an elective abortion “for personal reasons.” Brief narratives for the other two pregnancies follow (ISS, pg. 71).

- Subject 1232:** This 35-year-old female with CD was enrolled in the Study 0408/2 Extension Period. She received a single dose of NT 201 120 U in the Main Period of the study, and

received three injections of NT 201 during the Extension Period. The last injection was on November 16, 2007. The patient stopped taking birth control pills between the last week of November and the first week of December, 2007. She did not inform the study Investigator of this change. She had her last menstrual period on (b) (6). On February 26, 2008, the patient's participation in the study was discontinued because of pregnancy. On (b) (6), the subject gave birth at (b) (6) gestation to a healthy boy weighing 8 lbs (3.63 kg). Mother and child "were doing well."

- Subject 2117:** This 43-year-old female with GFL was enrolled in the Study 0520/2 Extension Period. She received the first dose of NT 201 20 U in the Main Period of the study on November 20, 2006, and the most recent dose of NT 201 20 U on July 9, 2007. At Visit 10 of the Main Period (August 30, 2007), the patient's pregnancy test was positive. The subject was not treated further in the study. The pregnancy was followed to outcome. A healthy baby was born on (b) (6); and "the mother and child were doing well."

The sponsor stated that in the pooled, placebo-controlled studies, no TEAEs in the Pregnancy, puerperium and perinatal conditions SOC occurred in any treatment group. (b) (4)

Reviewer comment: *In the Dysport® development program, there were more cases of pregnancy during treatment. The following is exempted from Dr. Stone's²³ safety review of Dysport®:*

"There were 37 cases detailing possible exposure during pregnancy, 11 in clinical trials and 26 spontaneous. No cases of exposure during pregnancy or lactation were reported from Category 1, 2 or 3 studies. Eleven cases were received from Category 4 studies. Of these, 7 subjects were known to have received Dysport and four cases occurred in ongoing studies which had not been unblinded at data cutoff. These eleven pregnancies are summarized in Table 7.1.1.14-1. Women with unfavorable outcomes were older and had slightly higher average total exposure to Dysport."

Clearly, although no bad outcomes were reported in the NT 201 development program, the number of pregnancies was too small to make conclusions about the effect of prenatal NT 201 exposure. Given that the indications for NT 201 use are not life-threatening, known to affect pregnancies in themselves or progressive, from a risk-benefit standpoint I would recommend that patients known to be pregnant be advised not to receive NT 201. For reference, Dysport® is labeled as Pregnancy Category C.

Reviewer comment: *The meeting minutes for the Type B Pre-BLA of December 12, 2008 stated that "Discussion of the administrative, quality, preclinical and clinical questions related to the BLA for the proposed indications cervical dystonia (b) (4) FDA emphasized the need to conduct pre and post natal development studies and stated that the Sponsor*

should provide written justification if they are unable to provide these studies.” The FDA’s Dr. Barbara Wilcox reported that the sponsor had not completed a pre- and post-natal development study as requested at the meeting, and that their justification was not adequate. She noted that a PMR to address the deficiency was planned.

7.6.4 Pediatrics and Assessment of Effects on Growth

Merz noted that the indications for which NT 201 was studied, and particularly BEB, CD and SP, occur almost exclusively in older patients. For example, post-stroke spasticity and cervical dystonia (which has a typical onset age between 40 and 50 years) are rare in the pediatric population. Blepharospasm essentially does not occur in pediatric patients. Merz stated they are requesting a waiver of the Pediatric Research Equity Act (PREA) requirement for pediatric studies in CD (ISS, pg. 87). However, the meeting minutes from December 12, 2008 has the following comment from FDA: “Post-marketing safety data from approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The risk for this is probably greatest in children treated for spasticity but can also occur in adults treated for spasticity. Therefore, we will be requesting a placebo controlled clinical trial in children with lower-limb spasticity, and a placebo controlled clinical trial in adults with lower limb spasticity as post-marketing requirements.”

7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.6.5.1 Overdose

The sponsor explained that the signs and symptoms of overdose of NT 201 are not evident immediately after injection. A consensus statement published in 2001 by the Working Group on Civilian Biodefense [Arnon et al. 2001] notes that persons potentially exposed to Botulinum toxin should be closely supervised for up to several weeks, and those with symptoms of overdose should be treated promptly with anti-toxin and supportive care which may include mechanical ventilation for weeks or months (ISS, pg. 99).

Merz summarized the symptoms of botulinum toxin overdose as severe neuromuscular paralysis manifesting as may generalized weakness, ptosis, diplopia, swallowing and speech difficulties, and/or paralysis of the respiratory muscles, resulting in aspiration pneumonia (Clinical Overview, pg. 33).

By the time overdose symptoms occur, Merz stated that treatment with anti-toxin is no longer be effective because the neurotoxin has already irreversibly blocked the transmitter release. Compounds releasing acetylcholine (e.g., physostigmine, guanidine, 3,4-diaminopyridine) might be effective. The sponsor noted, however, that there is no specific antidote to Botulinum toxin.

Merz stated that the lethal amount of crystalline BoNT/A for a 70 kilogram human is estimated at 0.09 µg intravenous (IV) or IM, or 70 µg applied orally. For comparison, a vial with 100 U of NT 201 contains 0.6 ng of BoNT/A, or less than 1/100 of the estimated human lethal dose following IV or IM administration [Arnon et al. 2001](ISS, pg. 98).

Reviewer comment: *Although there were no cases of systemic spread within the Xeomin development program, there have been cases of systemic spread with other botulinum toxins when administered at high doses. The Dysport® label carries a “Black Box” warning noting that Dysport® “and all botulinum toxins products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects.” Although no cases of systemic spread were observed in the NT 201 development program, I recommend that this boxed warning be included in the NT 201 labeling as well.*

7.6.5.2 Abuse

The sponsor stated that there were no reports of drug abuse of Botulinum toxin type A preparations. They further added that based on the mode of action, there is no reason to assume a potential for abuse or dependence (ISS, pg. 98).

Reviewer comment: *I agree that based both on the post-marketing results of other botulinum toxins and the apparent lack of overlap between botulinum toxin’s mechanism of action and known abuse mechanisms, I agree that there is little evidence of an abuse potential for NT 201.*

7.6.5.3 Withdrawal and Rebound

Merz stated that there were no cases of withdrawal symptoms reported within the NT 201 development program, and that the nature of action of botulinum toxin was inconsistent with drugs which cause a withdrawal syndrome.

Reviewer comment: *Although its effects last for weeks, NT 201 is administered as a single intermittent injection, so withdrawal seems unlikely. In addition, although the patient’s pre-treatment symptoms will return as the effect of NT 201 decreases with time, there is no evidence to expect the symptoms will increase in a rebound fashion, and I found no evidence of this during the safety review.*

7.7 Additional Submissions / Safety Issues

7.7.1 NT 201- Botox® Comparison Studies

Merz performed Studies 0013 and 9801 within the CD indication to compare the safety profile of NT 201 in comparison with Botox®. In both of these studies, the sponsor concluded that NT 201 and Botox were shown to have a similar safety profile (CD ISS, pg. 58).

In Study 0013, Merz stated that 231 subjects were treated with NT 201 and 232 subjects with Botox®. SAEs were observed in 4 of 231 (1.7%) subjects in the NT 201 group, and in 5 of 232 (2.2%) subjects in the Botox group. The most common TEAE in both treatment groups was dysphagia. Only one patient (in the Botox® group) discontinued due to an adverse event (pathological fracture of ankle)(CD ISS, pg. 58).

In Study 9801, the sponsor stated that 41 subjects were randomized to receive one of three doses of NT 201, and 12 subjects received Botox®. The sponsor reported that 2 of 41 subjects receiving NT 201, and 1 of 12 subjects receiving Botox®, experienced SAEs. The patient in the Botox group died (of metastatic colon cancer). Merz stated that the incidence of TEAEs was higher in the Botox® group than in the NT 201 groups. Dysphagia was reported by three subjects in the NT 201 treatment groups (7.3%), and no subject in the Botox® group (0%). Merz asserted that no clinically significant changes in laboratory values were observed at Day 14 and Day 120 in the NT 201 dose groups or the Botox group (CD ISS, pg. 58).

8 Postmarket Experience

At the time of the BLA filing, NT 201 was approved in Argentina, Canada, Mexico, Uruguay, and several European countries for the indications BEB and CD in adults. It was first approved in Germany in 2005. In Canada, NT 201 is also approved for the indication post-stroke SP of the upper limb. In Argentina, NT 201 is additionally approved for a variety of other indications including focal spasticities, strabismus, and the temporary improvement of glabellar frown lines (ISS, pg. 99).

The sponsor submitted a Periodic Safety Update Report (PSUR#6) encompassing the time period until July 1, 2009. During the year covered by this PSUR, (b) (4) vials of Xeomin® were sold. Assuming 1 vial per patient and injections every 3 to 4 months, the Sponsor estimates (b) (4) patients exposed. An additional 1031 subjects in clinical trials were also exposed to NT 201. Cumulative exposure in clinical trials and since the first marketed use of Xeomin® on May 31, 2005 is estimated at (b) (4) vials and about (b) (4) patients. No marketing authorizations have been withdrawn or suspended.²⁴

Merz reported that they searched the NT 201 pharmacovigilance database for all safety data from marketed use of NT 201 and other Botulinum neurotoxin products through January 29, 2009. The sponsor's pharmacovigilance data consisted of spontaneous reports or reports from the literature (Merz noted that no consumer reports had been received as of January 2009). (ISS, pg. 99-100).

Merz found that the following adverse events were reported to the database during post-approval use of NT 201: eye swelling, eyelid edema, dysphagia, nausea, injection site pain, injection site reaction, hypersensitivity including allergic dermatitis, skin rash, erythema, drug eruptions,

²⁴ This paragraph adapted from the NT 201 BEB Efficacy Review prepared by Dr. Ken Bergman, pg. 109.

herpes zoster, muscular weakness, muscle spasm, dysarthria, and myalgia. The sponsor specified that events were selected for inclusion in this document based on either frequency (i.e., events occurring in ≥ 2 subjects) or medical importance (ISS, pg. 100).

***Reviewer comment:** The majority of the events above, such as injection site reaction and pain, dysphagia, and muscular weakness/spasm, are those expected with use of a botulinum toxin product.*

In addition, Merz found the following adverse reactions have been identified for subjects receiving other Botulinum toxin type A complex preparations (i.e., not NT 201) during post-approval period of NT 201: “madarosis,” blurred vision, dry eye, optic neuropathy, angle closure glaucoma, mydriasis, ptosis, ophthalmoplegia, oculomotor weakness, palatal palsy, dyspepsia, dysgeusia, dry mouth, hoarseness, necrotizing fasciitis, fibrous histiocytoma, muscular weakness, asthenia, facial paresis, stridor, dizziness, headache, and overdose (ISS, pg 101).

9 APPENDICES

9.1 Literature Review/References

Literature references are contained within the specific sections of the safety review.

As detailed in Section 8 of this review, NT 201 has been previously approved in a number of countries outside of the United States. A search of the literature for reports yielded the following:

- A search for the key word “Xeomin:” returned only 24 publications. These were summaries of safety and efficacy for various indications, and did not contain any adverse event case reports.
- A search for the key word “NT 201” returned only 9 publications. These were of the same nature as the publications for the key word “Xeomin” and there were no safety-related case reports.

9.2 Labeling Recommendations

The sponsor’s proposed labeling was insufficient in a number of respects, including lack of class labeling regarding spread of toxin effect that includes a Boxed Warning, inadequate discussion of overdose that is class labeling, and inadequate presentation of adverse events.

9.3 Advisory Committee Meeting

There will be no advisory committee meeting regarding NT 201.

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

9.4 FDA Meeting Minutes (February 2, 2009) with Pre-BLA Exposure Specifications

Question 8: Does the Division share the applicant's view that the proposed safety database is adequate to support an application for the indications cervical dystonia (b) (4) [redacted] ?

Preliminary FDA Response:

The briefing document suggests that there were extension periods for the pivotal efficacy trials in each indication. However, it is not clear how many subjects were in the extension period for each of these indications, or how many doses were administered to each subject and for how long the observation period was continued. In particular, your long term safety data (i.e. up to 1 year of exposure) must cover the full range of doses recommended for each indication (i.e. up to 400U per treatment). Please clarify the extent of data available by duration (e.g. up to 6 months, up to 12 months) and by dose (e.g. up to 200U, up to 300U, up to 400U).

Please provide analyses of the effects on blood glucose and bicarbonate by dose and duration in your NDA.

Meeting Discussion:

The sponsor noted that at the time of the BLA filing they will only have single dose data, which they believe is sufficient because NT-201 is not the first in its class and botulinum toxins are as a class well studied. The Division noted that even though NT-201 is not the first in its class, it is clearly not identical to other botulinum toxin products, and safety related to multiple dosing, injection location, different doses and immunogenicity may not adequately be extrapolated from single-dose data. The Division stated that the lack of chronic use data in the BLA submission is a problem in the context of the typical requirements of six months of exposure to at least 300 patients and one year exposure to at least 100 patients; and further, (b) (4) that chronic use data from the ongoing openlabel studies can be included in the BLA. The sponsor agreed to (b) (4) include the data from the open-label extension of the spasticity study (MRZ- 0410) that will provide data from 60 patients exposed for 1 year at 400 units, 30 patients exposed for 1 year at 300-400 units and 30 patients exposed for one year at 200-300 units. In addition, 85 patients with cervical dystonia will have been treated for one year at 240 units but the data will still be blinded at the filing, which the Division found acceptable as long as long term safety data from the indication with the highest dose and duration was included in the BLA. The Division noted that the BLA should be sufficient with respect to the full data package at the time of filing.

The sponsor agreed to provide the above requested analysis of the effects on blood glucose, but not on bicarbonate as this data was not collected.

9.5 Tabular Summary of all Serious Adverse Events

Summary of all SAEs within the NT 201 development program (Adapted from Sponsor Table 1, 120-Day ISS, Appendix D, pg. 5)

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose Botulinum Toxin Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Cervical Dystonia					
Study 0408/1 (CD) Main Period					
1016 50, male	NT 201 240 U <i>Pre-Treated</i>	Appendicitis	Not related	Severe	Resolved
1044 51, male	NT 201 240 U <i>Pre-Treated</i>	Asthma	Not related	Severe	Resolved
1128 58, male	NT 201 240 U <i>Pre-Treated</i>	Chronic obstructive pulmonary disease	Not related	Severe	Resolved
1235 38, male	NT 201 240 U <i>Pre-Treated</i>	Staphylococcal infection	Not related	Severe	Resolved
Study 0408/2 (CD) Extension Period (Treatment given for Main Period/Extension Period; Extension Period dose remains blinded for some subjects)					
1032 69, male	NT 201 1080 U <i>Treatment-Naïve</i>	Cholecystitis Pancreatitis	Not related Not related	Severe Severe	Resolved Resolved
1046 43, female	NT 201 240 U / NT 201 <i>Treatment-Naïve</i>	Suicidal ideation	Not related	Moderate	Resolved
1077 61, female	NT 201 840 U <i>Pre-Treated</i>	Accidental overdose Basal cell carcinoma	Not related Not related	Severe Mild	Resolved Resolved
1095 51, male	NT 201 1320 U <i>Pre-Treated</i>	Non-cardiac chest pain	Not related	Mild	Resolved
1116 66, male	Placebo/ NT 201 480 U <i>Pre-Treated</i>	Colonic polyp Appendiceal abscess Respiratory failure	Not related Not related Not related	Severe Mild Moderate	Resolved Resolved Resolved
1122 49, female	NT 201 660 U <i>Pre-Treated</i>	Herpes zoster	Not related	Moderate	Resolved

Table continues

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Bomlinum Toxin</i> Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0408/2 (CD) Extension Period (Treatment given for Main Period/Extension Period; For some subjects, Extension Period remains blinded) (continued)					
1155 59, female	NT 201 600 U <i>Pre-Treated</i>	Chest injury	Not related	Moderate	Resolved
1162 57, male	NT 201 480 U <i>Pre-Treated</i>	Pancreatitis	Not related	Severe	Resolved
1241 67, female	NT 201 600 U <i>Treatment-Naïve</i>	Compression fracture	Not related	Moderate	Resolved
		Lung neoplasm malignant	Not related	Severe	Resolved
1271 66, female	NT 201 600 U <i>Treatment-Naïve</i>	Small intestinal obstruction	Not related	Severe	Resolved
1316 72, female	NT 201 240 U / NT 201 <i>Pre-Treated</i>	Hip fracture	Not related	Moderate	Resolved
Study 0013 (CD)					
003 50, male	NT 201 120 U <i>Pre-Treated</i>	Vertigo	Not related	Mild	Resolved w/ sequelae
		Cerebral disorder ¹	Not related	Mild	Resolved w/ sequelae
		Haematoma	Not related	Mild	Resolved w/ sequelae
011 40, male	Botox 100 U <i>Pre-Treated</i>	Anxiety	Not related	Moderate	Resolved
051 73, female	NT 201 200 U <i>Pre-Treated</i>	Neoplasm (ovarian tumor)	Unlikely related	Mild	Resolved
170 50, male	NT 201 100 U <i>Pre-Treated</i>	Eczema	Not related	Moderate	Resolved
207 51, female	Botox 60 U <i>Pre-Treated</i>	Transient ischaemic attack	Not related	Mild	Resolved
		Aphasia	Not related	Mild	Resolved
309 50, female	NT 201 100 U <i>Pre-Treated</i>	Metrorrhagia	Not related	Moderate	Resolved
347 52, female	Botox 200 U <i>Pre-Treated</i>	Leukaemia	Not related	Severe	Resolved w/ sequelae
444 34, female	Botox 100 U <i>Pre-Treated</i>	Cerebral ischaemia ²	Not related	Moderate	Resolved
549 46, female	Botox 150 U <i>Pre-Treated</i>	Agitation	Not related	Moderate	Resolved

Table continues

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Bonulinum Toxin</i> Pre-treatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0605/1 (CD) Main Period					
1082 58, female	NT 201 220 U <i>Treatment-Naive</i>	Renal abscess	Not related	Severe	Resolved
1088 60, male	NT 201 100 U <i>Treatment-Naive</i>	Foot fracture	Not related	Moderate	Resolving
Study 0605/2 (CD) OLEX Period					
1007 66, male	NT 201 460 U <i>Pre-Treated</i>	Myocardial infarction	Not related	Severe	Resolved
1012 55, female	NT 201 663 U <i>Treatment-naive</i>	Retinal detachment Eye haemorrhage	Not related Not related	Severe Severe	Resolved w/ sequelae
1020 65, male	NT 201 825 U <i>Pre-Treated</i>	Myocardial infarction Arrhythmia	Not related Not related	Severe Severe	Resolved Resolved
1037 52, female	NT 201 320 U <i>Treatment-naive</i>	Femoral neck fracture	Not related	Severe	Resolved
1047 59, male	NT 201 410 U <i>Pre-Treated</i>	Mood disorder due to a general medical condition	Not related	Moderate	Resolving
1048 60, male	NT 201 580 U <i>Pre-treated</i>	Squamous cell carcinoma	Not related	Moderate	Not resolved
1079 52, female	NT 201 400 U <i>Pre-treated</i>	Alcoholism	Not related	Mild	Resolving
1091 69, female	NT 201 490 U <i>Pre-Treated</i>	Radius fracture	Unlikely related	Not reported	Resolved
1094 61, female	NT 201 575 U <i>Pre-Treated</i>	Pneumonia Hodgkin's disease	Not related Not related	Moderate Severe	Resolving Not resolved
Study 9801 (CD)					
0602 59, female	Botox, 180 U ³ <i>Treatment-naive</i>	Jaundice Colon cancer	Not related Not related	Severe Severe	Not resolved Death
0608 61, female	NT 201, 120 U ³ <i>Treatment-naive</i>	Nephrolithiasis	Not related	Moderate	Resolved
0801 47, male	NT 201, 180 U ³ <i>Treatment-naive</i>	Neoplasm (<i>Malignant neoplasm of the pharynx</i>)	Not related	Severe	Not resolved

Table continues

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Bonlinum Toxin</i> <i>Pre-treatment Status</i>	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Benign Essential Blepharospasm					
Study 0433/1 (BEB) Main Period					
2122 75, female	Placebo <i>Pre-Treated</i>	Dyspnoea	Not related	Moderate	Resolved
Study 0433/2 (BEB) OLEX Period					
2001 75, male	NT 201 600 U <i>Pre-Treated</i>	Colon cancer	Not related	Severe	Resolved w/ sequelae
		Streptococcal bacteraemia	Not related	Moderate	Resolved
2045 60, male	Placebo+NT 201 280 U <i>Pre-Treated</i>	Pancreatitis	Not related	Severe	Resolved
2064 78, male	Placebo+NT 201 160 U <i>Pre-Treated</i>	Gastroenteritis	Not related	Severe	Resolved
		Atrial fibrillation	Not related	Moderate	Resolved
		Cardiomyopathy ⁴	Not related	Moderate	Resolved
		Cardiac failure congestive ⁴	Not related	Moderate	Resolved
2108 65, female	NT 201 350 U <i>Pre-Treated</i>	Staphylococcal infection	Not related	Severe	Resolved
		Chest pain	Not related	Moderate	Resolved
2122 75, female	Placebo+NT 201 250 U <i>Pre-Treated</i>	Pharyngoesophageal diverticulum	Not related	Moderate	Resolved
2146 59, female	NT 201 340 U <i>Pre-Treated</i>	Thyroid neoplasm	Not related	Moderate	Resolved
2162 63, male	Placebo+NT 201 270 U <i>Pre-Treated</i>	Diverticulitis	Not related	Moderate	Resolved
2174 22, female	NT 201 40 U <i>Pre-Treated</i>	Convulsion	Not related	Severe	Resolved
2179 72, female	Placebo+NT 201 30 U <i>Pre-Treated</i>	Spinal compression fracture	Not related	Severe	Resolved
2223 52, female	Placebo+NT 201 300 U <i>Pre-Treated</i>	Bronchitis	Not related	Severe	Resolved

Table continues

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Bonlinum Toxin</i> Pre-treatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0003 (BEB)					
203/011 37, female	Botox <i>Pre-Treated</i>	Depression	Not related	Moderate	Resolved
015/534 46, female	NT 201 25 U <i>Pre-Treated</i>	Abdominal pain	Not related	Moderate	Resolved
175/677 76, male	Botox <i>Pre-Treated</i>	Aortic aneurysm	Not related	Moderate	Resolved
145/744 72, female	NT 201 40 U <i>Pre-Treated</i>	Enterocolitis	Not related	Moderate	Resolved
253/819 61, female	Botox <i>Pre-Treated</i>	Blepharospasm	Not related	Moderate	Resolved
309/843 67, male	Botox <i>Pre-Treated</i>	Diabetes mellitus	Unlikely related	Mild	Resolved
		Hypertension	Unlikely related	Mild	Resolved
354/872 74, female	NT 201 48 U <i>Pre-Treated</i>	Diverticulum intestinal haemorrhagic	Not related	Moderate	Resolved
402/895 73, male	Botox <i>Pre-Treated</i>	Acute myocardial infarction	Not related	Severe	Resolved
Spasticity					
Study 0410/1 (SP) Main Period					
1008 56, male	NT 201 380 U <i>Treatment-Naïve</i>	Bronchitis chronic	Not related	Mild	Resolved
1036 62, male	NT 201 170 U <i>Treatment-Naïve</i>	Cellulitis	Not related	Moderate	Resolved
1088 71, female	Placebo <i>Treatment-Naïve</i>	Intracranial haematoma	Not related	Severe	Death
1119 49, male	NT 201 170 U <i>Treatment-Naïve</i>	Epilepsy	Not related	Moderate	Not resolved
		Paraparesis	Not related	Moderate	Resolved
		Status epilepticus	Not related	Severe	Resolved
1140 34, male	NT 201 310 U <i>Treatment-Naïve</i>	Hypertension	Not related	Mild	Resolved
		Vertigo	Not related	Mild	Resolved

Table continues

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Bonlinum Toxin</i> Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0410/2 (SP) OLEX Period					
1002 32, female	Placebo + NT 201 1600 U <i>Treatment-Naïve</i>	Hydrocephalus	Not related	Moderate	Resolved
1007 49, male	Placebo + NT 201 1200 U <i>Treatment-Naïve</i>	Hemiparesis Coronary artery bypass	Not related Not related	Moderate Moderate	Resolved Resolved
1009 65, female	Placebo + NT 201 1600 U <i>Treatment-Naïve</i>	Diabetes mellitus inadequate control	Not related	Moderate	Resolved
1027 55, female	1800 U <i>Treatment-Naïve</i>	Tracheobronchitis	Not related	Moderate	Resolved
1028 55, male	Placebo + NT 201 1470 U <i>Treatment-Naïve</i>	Rehabilitation therapy Anaemia	Not related Not related	Mild Moderate	Resolved Resolved
1029 45, male	NT 201 1425 U <i>Treatment-Naïve</i>	Extradural hematoma Epilepsy	Not related Not related	Severe Moderate	Resolved w/ sequelae Resolved
1033 45, male	Placebo + NT 201 1895 U <i>Pre-Treated</i>	Epilepsy	Not related	Severe	Resolved
1054 72, male	NT 201 685 U <i>Pre-Treated</i>	Death Pulmonary embolism Transient ischaemic attack	Not related Not related Not related	Severe Moderate Severe	Death Resolved Not resolved
1058 67, male	NT 201 800 U <i>Treatment-naïve</i>	Cardiac arrest	Not related	Severe	Death
1076 50, male	Placebo + NT 201 1165 U <i>Treatment-Naïve</i>	Calculus ureteric	Not related	Moderate	Resolved
1079 52, male	Placebo + NT 201 1500 U <i>Treatment-Naïve</i>	Subileus	Not related	Moderate	Resolved
1100 60, male	NT 201 600 U <i>Treatment-Naïve</i>	Renal cell carcinoma stage I Prostate cancer	Not related Not related	Severe Severe	Resolved Resolving

Table continues

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose Bomlinum Toxin Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0410/2 (SP) OLEX Period (continued)					
1116 61, male	Placebo + NT 201 1600 U <i>Treatment-Naïve</i>	Cardiovascular insufficiency	Not related	Moderate	Resolving
		Cardiomyopathy	Not related	Moderate	Resolving
1121 45, male	NT 201 710 U <i>Treatment-Naïve</i>	Dizziness	Not related	Moderate	Resolved
		Headache	Not related	Moderate	Resolved
1124 51, male	Placebo+ NT 201 1195 U <i>Treatment-Naïve</i>	Intervertebral disc protrusion	Not related	Severe	Not resolved
1131 61, female	NT 201 1500 U <i>Treatment-Naïve</i>	Colonoscopy	Not related	Mild	Resolved
1136 65, female	NT 201 1085 U <i>Treatment-Naïve</i>	Hyperparathyroidism	Not related	Mild	Not resolved
		Rehabilitation therapy	Not related	Mild	Resolved
1139 55, male	Placebo + NT 201 730 U <i>Treatment-Naïve</i>	Muscle spasticity	Not related	Mild	Resolved
1140 34, male	NT 201 740 U <i>Treatment-Naïve</i>	Hemiparesis	Not related	Mild	Resolved
1160 47, female	Placebo + NT 201 800 U <i>Treatment-Naïve</i>	Femur fracture	Not related	Moderate	Resolved
1162 28, male	Placebo + NT 201 1305 U <i>Treatment-Naïve</i>	Epilepsy	Not related	Moderate	Resolved
		Muscle spasticity	Not related	Mild	Resolved
1165 58, female	Placebo + NT 201 1080 U <i>Treatment-Naïve</i>	Muscle spasticity	Not related	Mild	Resolved w/ sequelae
1169 70, male	NT 201 1920 U <i>Pre-Treated</i>	Cerebrovascular Accident	Not related	Severe	Death
1176 59, male	Placebo + NT 201 1600 U <i>Treatment-Naïve</i>	Rectal cancer	Not related	Severe	Resolving
1196 61, male	Placebo + NT 201 1600 U <i>Treatment-Naïve</i>	Pneumonia	Not related	Moderate	Resolved
1197 64, female	NT 201 670 U <i>Pre-Treated</i>	Colon cancer	Not related	Severe	Resolved w/ sequelae
		Peritonitis	Not related	Severe	
		Pretermatural anus ⁵	Not related	Severe	

Table continues

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Boulinum Toxin</i> Pre-treatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
(b) (4)					
161 47, male	NT 201 330 U <i>Pre-Treated</i>	Symptomatic epilepsy Symptomatic epilepsy	Not related Not related	Mild Mild	Resolved Resolved
165 71, male	Placebo <i>Pre-Treated</i>	Chronic obstructive pulmonary disease	Not related	Severe	Resolved
Study 0607 (SP)					
1002 73, male	NT 201 350 U <i>Pre-Treated</i>	Transient ischaemic attack	Not related	Mild	Resolved
1004 56, male	NT 201 305 U <i>Treatment-Naïve</i>	Epilepsy	Not related	Mild	Resolved
1006 82, female	NT 201 250 U <i>Treatment-Naïve</i>	Decubitus ulcer	Not related	Moderate	Resolving
1025 69, male	NT 201 250 U <i>Pre-Treated</i>	Cerebral haemorrhage	Not related	Moderate	Resolved w/ sequelae
		Transient ischaemic attack	Not related	Mild	Resolved
1037 25, male	NT 201 390 U <i>Pre-Treated</i>	Implant site infection	Not related	Severe	Not resolved
1099 70, female	NT 201 340 U <i>Pre-Treated</i>	Acarodermatitis	Not related	Moderate	Resolving
1116 53, male	NT 201 400 U <i>Pre-Treated</i>	Epilepsy	Not related	Moderate	Resolved
1120 80, male	NT 201 400 U <i>Pre-Treated</i>	Faecaloma	Not related	Moderate	Resolved
1129 64, male	NT 201 320 U <i>Pre-Treated</i>	Loss of consciousness	Not related	Moderate	Resolved
1138 35, male	NT 201 90 U <i>Treatment-Naïve</i>	Visual impairment	Not related	Moderate	Resolved
		Convulsion	Not related	Moderate	Resolved
		Epileptic aura	Not related	Moderate	Resolved
		Appendicitis	Not related	Severe	Resolved
1172 59, male	NT 201 375 U <i>Pre-Treated</i>	Impaired gastric emptying	Not related	Moderate	Resolved
1182 79, female	NT 201 130 U <i>Treatment-Naïve</i>	Myocardial infarction	Not related	Mild	Resolved

Table continues

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Boulinum Toxin</i> Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
(b) (4)					
135	NT 201 400 U	Bradycardia	Not related	Moderate	Resolved
59, male	<i>Treatment-Naïve</i>	Pneumothorax	Not related	Moderate	Resolved
101	Placebo	Myocardial infarction	Not related	Severe	Death
85, male	<i>Treatment-Naïve</i>				
114	Placebo	Carotid artery stenosis	Not related	Moderate	Resolved
74, female	<i>Treatment-Naïve</i>				
Crow's Feet					
Study 0617 (CF)					
1161	NT 201 24 U	Depression	Not related	Moderate	Not resolved
52, female	<i>Pre-Treated</i>				
1066	NT 201 24 U	Hypertensive crisis	Not related	Moderate	Resolved
54, female	<i>Treatment-Naïve</i>	Hypertensive crisis	Not related	Moderate	Resolved
Glabellar Frown Lines					
(b) (4)					
1089	NT 201 20 U	Fibroadenoma of breast	Not related	Moderate	Resolved
34, female	<i>Treatment-Naïve</i>				
(b) (4)					
1229	NT 201 24 U	Tibia Fracture	Not related	Severe	Resolved
46, female	<i>Treatment-Naïve</i>	Joint injury	Not related	Severe	Resolved
1398	Vistabel 24 U	Encephalitis viral	Not related	Moderate	Resolved
38, female	<i>Treatment-Naïve</i>				
Study 0520/1 (GFL) Main Period					
2090	NT 201 20 U	Lumbar vertebral fracture	Not related	Severe	Not resolved
42, male	<i>Treatment-Naïve</i> ⁶				
2050	NT 201 20 U	Bunion operation	Not related	Moderate	Resolved
45, female	<i>Treatment-Naïve</i> ⁶				
2366	NT 201 20 U	Hip dysplasia	Not related	Moderate	Resolved
49, female	<i>Treatment-Naïve</i> ⁶				
2404	NT 201 20 U	Lower limb fracture	Not related	Moderate	Resolved w/ sequelae
55, female	<i>Treatment-Naïve</i> ⁶				
Study 0520/2 (GFL) OLEX Period					
2256	NT 201 20 U	Myocardial infarction	Not related	Moderate	Resolved w/ sequelae
52, female	<i>Pre-Treated</i>				
2296	NT 201 20 U	Pulmonary edema	Not related	Severe	Resolved
66, female	<i>Pre-Treated</i>				
2326	NT 201 20 U	Nephrolithiasis	Not related	Severe	Resolved
47, female	<i>Pre-Treated</i>	Nephrolithiasis	Not related	Severe	Resolved

Table continues

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Bonlinum Toxin</i> Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0520/2 (GFL) OLEX Period (continued)					
2338 61, female	NT 201 20 U <i>Pre-Treated</i>	Foot deformity	Not related	Severe	Resolved
2348 45, female	NT 201 20 U <i>Pre-Treated</i>	Limb injury	Not related	Severe	Resolved
Study 0527 (GFL)					
1193 44, female	NT 201 10 U <i>Treatment-Naïve⁶</i>	Urinary incontinence Pelvic floor muscle weakness	Not related Not related	Moderate Moderate	Resolved Resolved
1265 42, female	NT 201 10 U <i>Treatment-Naïve⁶</i>	Appendicitis perforated	Not related	Severe	Resolved
1291 50, female	NT 201 10 U <i>Treatment-Naïve⁶</i>	Pyrexia	Not related	Moderate	Resolved
Study 0609 (GFL)					
1001 59, male	NT 201 80 U <i>Pre-Treated</i>	Arterial stenosis	Not related	Mild	Resolved
1158 53, female	NT 201 100 U <i>Pre-Treated</i>	Tibia fracture	Not related	Moderate	Resolved w/ sequelae
1164 36, male	NT 201 80 U <i>Pre-Treated</i>	Spinal osteoarthritis	Not related	Severe	Resolved
1201 37, female	NT 201 80 U <i>Pre-Treated</i>	Blighted ovum	Not related	Severe	Resolved
1221 39, female	NT 201 100 U <i>Pre-Treated</i>	Migraine	Not related	Severe	Resolved
1250 38, female	NT 201 80 U <i>Pre-Treated</i>	Uterine leiomyoma	Not related	Moderate	Resolved
1266 39, female	NT 201 100 U <i>Pre-Treated</i>	Salivary gland neoplasm (<i>benign</i>)	Not related	Severe	Resolved
1268 38, female	NT 201 100 U <i>Pre-Treated</i>	Cerebral artery embolism	Not related	Not reported	Resolved
		Cerebrovascular accident	Not related	Severe	Resolved
		Atrial septal defect	Not related	Moderate	Resolved
1274 38, female	NT 201 60 U <i>Pre-Treated</i>	Uterine prolapse	Not related	Severe	Resolved
		Cystopexy	Not related	Severe	Resolved
		Hysterectomy	Not related	Moderate	Resolved

Table continues

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose Botulinum Toxin Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0609 (GFL) (continued)					
2025 40, male	NT 201 80 U <i>Pre-Treated</i>	Appendicitis	Not related	Moderate	Resolved
2033 57, female	NT 201 80 U <i>Pre-Treated</i>	Bile duct stone	Not related	Moderate	Resolved
2071 48, female	NT 201 120 U <i>Pre-Treated</i>	Polymenorrhea	Not related	Moderate	Resolved
2074 68, female	NT 201 100 U <i>Pre-Treated</i>	Colonic polyp	Not related	Moderate	Resolved
2078 45, female	NT 201 100 U <i>Pre-Treated</i>	Polypectomy	Not related	Moderate	Resolved
2086 55, female	NT 201 100 U <i>Pre-Treated</i>	Breast cancer	Not related	Severe	Resolved
2119 52, male	NT 201 100 U <i>Pre-Treated</i>	Facial paresis	Not related	Severe	Resolved
2144 57, female	NT 201 80 U <i>Pre-Treated</i>	Herpes zoster oticus	Not related	Severe	Resolved
2205 36, female	NT 201 100 U <i>Pre-Treated</i>	Cholelithiasis	Not related	Moderate	Resolved
2212 56, female	NT 201 20 U <i>Pre-Treated</i>	Cholecystectomy	Not related	Moderate	Resolved
2216 55, female	NT 201 80 U <i>Pre-Treated</i>	Haemorrhoids	Not related	Moderate	Resolved
2277 58, male	NT 201 60 U <i>Pre-Treated</i>	Abortion missed	Not related	Severe	Resolved
2284 42, female	NT 201 80 U <i>Pre-Treated</i>	Drug exposure before pregnancy	Not related	Severe	Resolved
2376 42, female	NT 201 20 U <i>Pre-Treated</i>	Cervical polyp	Not related	Moderate	Resolved
3095 70, female	NT 201 40 U <i>Pre-Treated</i>	Uterine polyp	Not related	Moderate	Resolved
		Suicide attempt	Not related	Severe	Resolved
		Depression suicidal	Not related	Severe	Not resolved
		Joint dislocation	Not related	Severe	Resolved
		Ligament rupture	Not related	Severe	Resolved
		Radius fracture	Not related	Severe	Resolved
		Haematoma	Not related	Severe	Resolved
		Mammoplasty	Not related	Moderate	Resolved
		Cerebral infarction	Not related	Mild	Resolved
		Cerebrovascular accident	Not related	Mild	Resolved
		Lipoma	Not related	Moderate	Resolved

Table continues

Table 1: Summary of Treatment-Emergent Serious Adverse Events in the NT 201 Studies

Subject # Age (years), Gender	Cumulative Dose <i>Botulinum Toxin</i> Pretreatment Status	Event as MedDRA Preferred Term	Relationship to Treatment	Intensity	Outcome
Study 0724 (GFL)					
3176 38, female	Still blinded (NT 201 or placebo)	Abortion spontaneous	Not related	Unknown (lost to fu)	Unknown (lost to fu)
3248 54, female	Still blinded (NT 201 or placebo)	Tibia fracture Fibula fracture	Not related Not related	Severe Severe	Resolving Resolving
Study 0741 (GFL)					
4054 39, female	Still blinded (NT 201 or placebo)	Renal cell carcinoma	Not related	Moderate	Resolved
Healthy Volunteer Studies					
Study 0113 (HV)					
9 25, male	NT 201 2 U/Botox 2 U <i>Treatment-Naive</i>	Intervertebral disc disorder	Not related	Moderate	Resolved

¹ Subject 003 experienced a concussion, which was mis-coded to cerebral disorder (and is shown as cerebral disorder in the summaries).

² Subject 444 experienced cervicocranial syndrome, which was mis-coded to cerebral ischemia (and is shown as cerebral ischemia in the summaries).

³ In Study 9801, subjects received two treatments. Each dose of study medication was divided as follows: 1/3 of the total dose (in units) into the splenius capitis, and 2/3 into the sternocleidomastoid.

⁴ Subject 2064: The events cardiomyopathy and cardiac failure congestive are not in the current clinical database because, although a report of these events has been received, they were not yet coded at the time of the cutoff for the summary tables.

⁵ Subject 1197 had a colostomy, but the event was mis-coded to "pretermatural anus" (and is shown as pretermatural anus in the SAE summaries).

⁶ In Studies 0520 (GFL) and 0527 (GFL), "treatment-naïve" is defined as not having received Botulinum toxin in the 12 months before study entry.

For sites of administration in each study, see ISS Table 1, Table 2, and Table 3.

No SAEs occurred in Studies 0703 (BEB), 9901 (HV), and 0709 (HV).

fu: follow-up; MedDRA: Medical Dictionary for Regulatory Activities; OLEX: open-label extension (period); U: units; w/: with.

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

9.6 Anaphylaxis Post-Marketing Report

**5 pages withheld
immediately after this
page as B4 (TS/CCI)**

9.8 Full Narratives for BEB Patients who experienced Dyspnea or Dry Mouth in Study 0433/1

Merz Pharmaceuticals
BLA 125360

FDA Information Request for doses and reports/narratives for NT201 for the patients who had dyspnea and dry mouth, dated June 14, 2010

FDA Request:

In BEB study 0433/1 Main period, please provide the doses of NT 201 for the patients who had dyspnea and dry mouth. Please also send those case reports/narratives for those events.

Merz Response:
(see next page)

Merz Pharmaceuticals
BLA 125360

Country: US; **Center:** 1028; **Scr:** S2001; **RandomNumber:** 5704; **Initials:** (b) (6)
AE Preferred Term: Dry mouth

This 75-year-old male subject (white, weight 239 lb, height 70.5 in) was a non-smoker. His medical history was significant for cholecystectomy in 1986, haemorrhoid operation in 1986, right shoulder injury in 1996, prostate cancer from JUN-2000 until NOV-2000, surgical removal of prostate cancer in (b) (6) and skin cancer removed from right side of face on (b) (6) (b) (6). Concomitant diseases included hypothyroidism since 1976, blurred vision due to macular degeneration since 1998, seasonal allergies since 25-MAY-1999, gastroesophageal reflux disease since 2001, corneal dystrophy since 26-MAR-2001, macular degeneration since 21-APR-2003, cataract since 19-JUL-2005, hypertension since February 2006, atrial fibrillation since 12-OCT-2006, and dry eyes since 28-NOV-2006. Concomitant medications were levothyroxine sodium 0.1µg/day [sic] for hypothyroidism, omeprazole 20 mg/days for gastroesophageal reflux disease, cyproheptadine hydrochloride 1.2 mg/day for blepharospasm, OcuVite vitamins (daily dose unknown) as dietary supplement, hydrochlorothiazide (daily dose unknown) and metoprolol succinate 100 mg/day for hypertension. Blepharospasm was first diagnosed in May 1990. Estimated duration of BEB was 16 years and five months. Before entering the study the subject had been treated for almost 16 years with 100 U Botox®. The last injection prior to study entry was on 13-JUN-2006 with Botox® 100 U. The subject signed informed consent on 12-OCT-2006 and received a total dose of 100 U of NT 201 on 24-OCT-2006. On 06-NOV-2006 the subject experienced dry mouth, which was rated as mild in intensity and not related to treatment by the investigator. This event resolved on 05-DEC-2006, no action was taken regarding the adverse event. The subject did not experience any other adverse events in the Main Period and continued in the Open Label Extension Period.

Country: US; **Center:** 1022; **Scr:** S2020; **RandomNumber:** 5875; **Initials:** (b) (6)
AE Preferred Term: Dry mouth

This 60-year-old male subject (hispanic or latino, weight 127.20 lb, height 58. in) was a non-smoker. His medical history was significant for blepharoplasty left eye in 2002 and May 2004. Concomitant diseases included intermittent insomnia since 1997, lactose intolerance since 1977, intermittent dry eyes since 1993, intermittent bilateral eyes light sensitivity since 1999, bilateral ptosis since 2002, difficulty articulating since 2002, intermittent right hand joint pain since 2002, benign prostate hyperplasia since 2004, intermittent indigestion since 2004, intermittent abdominal pain since 2004 and blurred vision since 2006. Concomitant medications were tamsulosin hydrochloride 0.4 mg/day for benign prostate hyperplasia. During the Main Period the subject was started on esomeprazole magnesium 40 mg/day for indigestion, and chlorphenamine with dextromethorphan for common cold.

Blepharospasm was first diagnosed in 2002. Estimated duration of BEB was 14 years. Before entering the study the subject had been treated for almost 5 years with 75 U Botox®. The last injection prior to study entry was on 04-SEP-2007 with Botox® 70 U. The subject signed informed consent on 08-JAN-2008 and received 63 U of NT 201 on 15-JAN-2008. On 07-FEB-2008 the subject experienced dry mouth, which was rated as mild in intensity and not related to treatment by the investigator. This event resolved on 11-APR-2009, no action was taken regarding the adverse event. Furthermore, the subject experienced four other adverse events during the Main Period. On 16-JAN-2008 the subject experienced right upper lip droop, which

was rated as mild in intensity and related to treatment by the investigator. This event was ongoing and stable at the end of the trial, no action was taken regarding the adverse event. On 07-Feb-2008 the subject experienced common cold, which was rated as mild in intensity and not related to treatment by the investigator. This event was treated with chlorphenamine w/dextromethorphan and resolved on 24-Feb-2008. On 20-JAN-2008 the subject experienced worsening of bilateral intermittent eyes light sensitivity, which was rated as mild in intensity and not related to treatment by the investigator. The event resolved on 22-Jan-2008, no action was taken regarding the adverse event. On 14-FEB-2008 the subject experienced worsening of eyelid ptosis, which was rated as moderate in intensity and not related to treatment by the investigator. The event resolved on 29-JUN-2008 during Open Label Extension Period, no action was taken regarding the adverse event. The subject continued in the Open Label Extension Period.

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Country: US; Center: 1039; Scr: S2026; RandomNumber: 5710; Initials: (b) (6)
AE Preferred Term: Dry mouth

This 73-year-old female subject (white, weight 181 lb, height 62 in) was a non-smoker. Her medical history was significant for tonsillectomy in 1939, appendectomy in 1942, hysterectomy in 1966, spinal fusion surgery in 1978, intestinal operation in 1980, gastric ulcer surgery in 1984, benign breast lump removal in 1985, benign tumor excision (leg) in 1990, shoulder operation on (b) (6), spinal fusion surgery in 1973, and cataract operation on (b) (6)

(b) (6) Concomitant diseases at study start included insomnia since 2004, eyelid ptosis (following Botox® injections) from 16-AUG-2004 until 08-MAY-2007, stomatitis since March 2005, multiple drug allergies since September 2005, back pain since March 2006, dyskinesia oesophageal since Februar 2000, depression since Februar 1992, hypothyroidism since March 2001, myalgia since April 1997, gastrooesophageal reflux disease since March 1997, and hypertension since July 2006. Concomitant medications were bupropion 150 mg/day for depression, lansoprazole 30 mg/days for gastrooesophageal reflux disease, ibuprofen 200 mg prn for myalgia, nifedipine 90 mg/day for oesophageal dyskinesia, levothyroxine sodium 76 mg [sic]/day for hypothyroidism, calcium 600 mg/day as mineral supplementation, Echinacea purpurea 500 mg/day for phytotherapy, zolpidem tartrate 0.125 mg[sic]/day for insomnia, herbal preparation 100 mg/day for myalgia, cyanocobalamin 100 µg/ml PRN for vitamin supplementaion, lysine 500 mg/mg for stomatitis, hydrochlorothiazide 25 mg/day for hypertension.

Blepharospasm was first diagnosed on 30-JUL-2004. Estimated duration of BEB was three years and one month. Before entering the study the subject had been treated for almost 2 ½ years with 60-70 U Botox®. The last injection prior to study entry was on 07-FEB-2006 with a total dose of 49.5 U.

The subject signed informed consent on 08-MAY-2007 and received a total dose of 50 U of NT 201 on 15-MAY-2007. On 04-JUN-2007 the subject experienced dry mouth, which was rated as mild in intensity and related to treatment by the investigator. This event resolved on 01-AUG-2007 during Open Label Extension Period, no action was taken regarding the adverse event. Furthermore, the subject experienced two other adverse events during the Main Period. On 15-MAY-2007 the subject experienced pain at injection site for 20 minutes which was rated as mild and related to treatment by the investigator. No action was taken regarding the adverse event. On 25-MAY-2007 the subject experienced eyelid ptosis which was rated as mild and related to treatment by the investigator. This event was resolved on 27-MAY-2007; no action was taken regarding the adverse event. The subject continued in the Open Label Extension Period.

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Country: US; **Center:** 1039; **Scr:** S2027; **RandomNumber:** 5711; **Initials:** (b) (6)
AE Preferred Term: Dry mouth

This 77-year-old female subject (white, weight 150 lb, height 63 in) was a non-smoker. Her medical history was significant for surgically sterilization in 1978. Concomitant diseases included hypoparathyroidism since 10-JUN-1988, dry mouth since April 1995, eyelid ptosis since APR-1995, hypertension since 04-APR-1995, cervical dystonia since 21-JUL-2001 (treated with Botox 170-225 U from 21-JUL-2001 to 03-May-2003), hyperlipidemia since 2003, Meige's syndrome since 30-MAR-2006 (treated with 40 U Botox® from 30-MAR-2006 to 09-JUN-2007) and insomnia SEP-2007. Concomitant medications were levothyroxine sodium 12.5 µg/day for hypothyroidism, metoprolol 100 mg/day for hypertension, simvastatin 20 mg/day for hyperlipidemia and quetiapine 100 mg/day for insomnia. Blepharospasm was first diagnosed in 1980. Estimated duration of BEB was 27 years. Before entering the study the subject had been treated for almost 22 years with 50-60 U Botox®. The last injection prior to study entry was on 21-SEP-2007. The subject signed informed consent on 26-NOV-2007 and received 60 U of NT 201 on 03-DEC-2007. On 10-DEC-2007 the subject experienced worsening of dry mouth, which was rated as mild in intensity and related to treatment by the investigator. This event resolved on 17-DEC-2007, no action was taken regarding the adverse event. Furthermore, the subject experienced two other adverse events during the Main Period. On 25-DEC-2007 the subject experienced respiratory infection which was rated as mild and not related to treatment by the investigator. The event resolved on 08-JAN-2008, no action was taken regarding the adverse event. On 04-JAN-2008 the subject experienced exacerbation of segmental crania-brachial dystonia which was rated as moderate and not related to treatment by the investigator. This event was ongoing and stable at the end of the trial; no action was taken regarding the adverse event. The subject continued in the Open Label Extension Period.

Country: US; **Center:** 1039; **Scr:** S2029; **RandomNumber:** 5884; **Initials:** (b) (6)
AE Preferred Term: Dry mouth

This 73-year-old female subject (white, weight 262 lb, height 67 in) was a non-smoker. Her medical history was significant for hysterectomy in 1974. Concomitant diseases at study start included insomnia since 1957, anxiety since 1972, depression since 1972, hypertension since 1988, hyperlipidemia since 1998, drug hypersensitivity since 1998, gastroesophageal reflux disease since 2004, diabetes mellitus since 2005, and dry mouth since 24-JAN-2008. Concomitant medications were buspirone hydrochloride 15 mg/day for anxiety, sertraline hydrochloride 100 mg/day for depression, clonidine 0.1 mg/day for hypertension, triamterene 37.5 mg/day for hypertension, atorvastatin calcium 20 mg/day for hyperlipidemia, omeprazole 20 mg/days for gastroesophageal reflux disease, glipizide 2.5 mg/day and metformin hydrochloride 850 mg for diabetes mellitus, and quetiapine 100 mg/day for insomnia. Blepharospasm was first diagnosed 1998. Estimated duration of BEB was 10 years. Before entering the study the subject had been treated for approximately 10 years with up to 65 U Botox®. The last injection prior to study entry was on 09-NOV-2007 with a total dose of 32.5U. The subject signed informed consent on 24-JAN-2008 and received a total dose of 32.5U of NT 201 on 31-JAN-2008. On 07-FEB-2008 the subject experienced worsening of dry mouth, which was rated as moderate in intensity and related to treatment by the investigator. This event was resolved on August 2008 during Open Label Extension Period. On the same day the subject also experienced another non-serious adverse event of dry eyes which was mild in intensity and

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

assessed as related to study treatment. This event resolved on 28-FEB-2008. One day later, on 29-FEB-2008 the subject experienced mild dysphagia which was also considered treatment-related and which resolved on 27-MAR-2008. The subject continued in the Open Label Extension Period.

Country: US; **Center:** 1077; **Scr:** S2031; **RandomNumber:** 5872; **Initials:** (b) (6)
AE Preferred Term: Dyspnea

This 68-year-old female subject (white, weight 204 lb, height 63 in) was an ex-smoker. Her medical history was significant for eczema on ears in 2000, ptosis of right eyelid from August 2004 until 31-MAR-2005, blepharoplasty of right eye on (b) (6) torn meniscus in 2007. Concomitant diseases included depression since 1981, dry eyes since 1988, blurred vision due to cataracts since 1990 [sic], dry mouth since 1990, cataracts since June 1998, diplopia since June 1998, dry skin since 2000, eczema on both legs since 2000 (resolved on 31-MAR-2008), increased blood cholesterol since 2003, hypothyroidism since 2003, hypertension since 2005, eyelid ptosis since 2007, gastroesophageal reflux disease since September 2007. Concomitant medications were artificial tears for dry eyes, citalopram hydrobromide 10 mg and risperidone 0.5 mg for depression, levothyroxine 50 mg for hypothyroidism, pravastatin 60 mg for blood cholesterol increased, lisinopril 20 mg for hypertension, etodolac 200 mg for meniscus lesion, omeprazole 20 mg for gastroesophageal reflux disease, diphenhydramine hydrochloride 50 mg and betamethasone dose unknown for eczema.

Blepharospasm was first diagnosed in January 1987. Estimated duration of BEB was 21 years. Before entering the study the subjects had been treated for almost 20 years with 40-97.5 U Botox®. The last injection prior to study entry was on 31-OCT-2007 with 55.5 U Botox®. The subject signed informed consent on 11-JAN-2008 and received 55.5 U of NT 201 on 16-JAN-2008. On 11-FEB-2008 the subject experienced dyspnea, which was rated mild in intensity and not related to treatment by the investigator. The event resolved on 17-FEB-2008, no action was taken regarding the adverse event. Furthermore, the subject experienced another adverse event during the Main Period. On 11-FEB-2008 the subject experienced nasopharyngitis which was rated as mild and not related to treatment by the investigator. The event resolved on 17-FEB-2008, no action was taken regarding the adverse event. The subject continued in the Open Label Extension Period.

Country: US; **Center:** 1019; **Scr:** S2061; **RandomNumber:** 5733; **Initials:** (b) (6)
AE Preferred Term: Dry mouth

This 56-year-old female subject (white, weight 174.20 lb, height 66 in) was a non-smoker. Her medical history was significant for tubal ligation in 1980. Concomitant diseases at study start included facial spasms since 2001, heart burn since 2002, hyperlipidemia since 2005, thyroid polyp since 2006. Concomitant medications were rabeprazole 20 mg prn for dyspepsia and rosuvastatin 10 mg/day for hyperlipidemia, as well as multiple dietary supplements. During the Main Period the subject was started on systane, daily dose unknown (as needed) for dry eyes. Blepharospasm was first diagnosed in JUN-2001. Estimated duration of BEB was 8 years. Before entering the study the subject had been treated for almost 6 years with 40 U Botox®. The last injection prior to study entry was on 14-MAR-2007 with Botox® 40 U. The subject signed informed consent on 19-JUN-2007 and received a total dose of 40U of NT 201 on 26-JUN-2007. On 11-JUL-2007 the subject experienced dry mouth, which was rated as

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

moderate in intensity and related to treatment by the investigator. This event was ongoing at the end of the Main Period and resolved on 24-JAN-2008 when the subject was already enrolled in the Open Label Extension Period. No action was taken regarding this event. On 01-AUG-2007 the subject experienced another non-serious adverse event of dry eyes which was mild in intensity and assessed as related to study treatment. This event was treated with Systane eyedrops and resolved on 09-OCT-2007. The subject continued in the Open Label Extension Period.

Country: US; **Center:** 1033; **Scr:** S2067; **RandomNumber:** 5737; **Initials:** (b) (6);
AE Preferred Term: Dry mouth

This 60-year-old female subject (white, weight 133 lb, height 59 in) was a smoker. Her medical history was significant for tuberculosis in 1990-1991. Concomitant diseases included asthma since unknown time period, emphysema since 1991, menopausal symptoms since January 1996, deafness in right ear since 2003, deafness since 2004, eyelid ptosis since 2004, and peptic ulcer since 2006. Concomitant medications were theophylline 5 mg/day and salbutamol (PRN) for asthma and omeprazol 20 mg/day for peptic ulcer. During the Main Period the subject was started on erythromycin (dose unknown) and cough syrup (dose unknown, PRN) for nasopharyngitis.

Blepharospasm was first diagnosed in 12-APR-2004. Estimated duration of BEB was 2 years and 9 months. Before entering the study the subject had been treated for almost 2 ½ years with Botox®. The last injection prior to study was on 19-OCT-2006 with Botox® 40 U. The subject signed informed consent on 17-JAN-2007, and received 40 U of NT 201 on 31-JAN-2007.

On 28-FEB-2007 the subject experienced dry mouth, which was rated as mild in intensity and related to treatment by the investigator. This event resolved on 21-MAR-2007. Furthermore, the subject experienced three other adverse events during the Main Period. On 20-FEB-2007 the subject experienced gastrointestinal disorder, which was rated as mild and not related to treatment by the investigator. The event resolved on 26-Feb-2007, no action was taken regarding the adverse event. On 20-FEB-2007 the subject experienced worsening of mild ptosis, which was rated as moderate in intensity and related to treatment by the investigator. The event resolved on 09-MAY-2007, no action was taken regarding the adverse event. On 20-FEB-2007 the subject experienced hepatitis C, which was rated as moderate in intensity and not related to treatment by the investigator. The event was ongoing and stable at the end of the trial; no action was taken regarding the adverse event. The subject continued in the Open Label Extension Period.

Country: US; **Center:** 1002; **Scr:** S2072; **RandomNumber:** 5741; **Initials:** (b) (6);
AE Preferred Terms: Dry mouth, Dyspnoea

This 59-year-old female subject (white, weight 180.08 lb, height 64 in) was a non-smoker. Her medical history was significant for thyroid nodule removal in 1972, tonsillectomy in 1975, hysterectomy in 1980, breast lump removal in 2000 and blepharoplasty in 2001. Concomitant diseases at study start included eyelid ptosis since 2001, thyroid neoplasm since 2002, headache since 27-NOV-2002, gastroesophageal reflux disease since 2003, hypercholesterolaemia since January 2005, and not clinically significant ECG abnormalities since 03-JAN-2007. Concomitant medications were pantoprazole 40 mg/day for gastroesophageal reflux disease and pravastatin sodium 20 mg/day for hypercholesterolaemia. During the Main Period the subject was started on antibiotics (details unknown) and levofloxacin 750 mg for epiglottitis and promethaxacine (dose unknown) for prophylaxis of nausea and vomiting

Blepharospasm was first diagnosed on 27-NOV-2002. Estimated duration of BEB was four years and two months. Since first diagnosis of BEB the subject had been treated with 80-100 U Botox®. The last injection prior to study entry was on 22-AUG-2006 with a total dose of 90 U of Botox®.

The subject signed informed consent on 31-JAN-2007 and received a total dose of 90 U of NT 201 on 08-FEB-2007. Seven days later, on 15-FEB-2007, the subject experienced the non-serious adverse events visual disturbance, dysphagia, dry eye, and worsening eyelid ptosis. All were rated as mild in intensity, with the exception of eyelid ptosis, all were assessed as not related to study treatment. No action was taken regarding these events, the outcome for dysphagia was reported as resolved on 08-MAR-2007, visual disturbance, dry eye, and? worsening ptosis resolved on 11-MAR-2007. On 20-FEB-2007 the subject experienced severe epiglottitis which was considered not related to study treatment. This event was treated with levofloxacin 750 mg/day for six days, a single intravenous injection of an unknown antibiotic, and a single intramuscular injection of promethazine for the prevention of nausea, both on 22-FEB-2007. Epiglottitis resolved on 27-FEB-2007. On 22-FEB-2007, two days after the onset on epiglottitis, the subject experienced dyspnea and dry mouth, both mild in intensity and not related to study treatment. Dyspnea resolved on 27-FEB-2007, dry mouth on 08-MAR-2007, both without intervention. The subject experienced one additional non-serious adverse event, general body weakness, during the Main Period. Event onset was on 23-FEB-2007, the event resolved on 27-FEB-2007 without intervention. Also this event was assessed as mild and not related to study treatment. The subject continued in the Open Label Extension Period.

Country: US; **Center:** 1084; **Scr:** S2259; **RandomNumber:** 5852; **Initials:** (b) (6)
AE Preferred Term: Dry mouth

This 63-year-old female subject (white, weight 175 lb, height 60.00 in) was a non-smoker. Her medical history was significant for hysterectomy in 1990. Concomitant diseases included hypertonic bladder since 1992, urinary tract infection since 1992, vision blurred since 1999, eyelid ptosis since 2000, hypertension since 2003, headache since September 2007, gastroesophageal reflux disease since 2006, dry eye and speech disorder, both since March 2007. Concomitant medications at study start were valsartan 320 mg/day and hydrochlorothiazide 22 mg/day for hypotension, omeprazole (daily dose unknown) 1 capsule INR for gastroesophageal reflux disease, solifenacin 10 mg/day for hypertonic bladder, nitrofurantoin 50 mg for urinary tract infection acetylsalicylic acid 325 mg/day for cardiovascular event prophylaxis, multivitamins (daily dose unknown) as vitamin supplement, calcium 1000 mg/day as mineral supplementation, fish oil (daily dose unknown) as medical diet. During the Main Period the subject was started on amlodipine 2.5 mg/day for hypertension and twice ibuprofen 600 mg/day for headache.

Blepharospasm was first diagnosed in 2000. Estimated duration of BEB was 8 years and three months. Before entering the study the subject had been treated for nearly 5 months with up to 100 U Botox ®. The last injection prior to study entry was on 05-DEC-2007 including a total dose of 100 U Botox ®.

The subject signed informed consent on 27-FEB-2008 and was treated with 100 U of NT 201 in total on 03-MAR-2008. On 01-APR-2008 the subject experienced dry mouth, which was rated as mild in intensity and related to treatment by the investigator. This event was ongoing and stable at the end of the trial, no action was taken regarding the adverse event. The subject did not

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

experience any other adverse events in the Main Period and continued in the Open Label Extension Period.

Country: US; **Center:** 1089; **Scr:** S2245; **RandomNumber:** 5863; **Initials:** (b) (6)
AE Preferred Term: Dyspnoea

This 60-year-old male subject (white, weight 146 lb, height 67.00 in) was an ex-smoker. His medical history was significant for a shoulder operation in November 2001 for pin in left shoulder. Concomitant diseases included seasonal allergy since 2000, rotor cuff syndrome since April 2001, joint range (left shoulder) of motion decreased since November 2001, visual disturbance since 2002, eyelid ptosis since 2002, facial dystonia since 26-AUG-2002, dry mouth since January 2003, intervertebral disc (cervical) protrusion since September 2003, cardiac valve prosthesis user since 2005 and musculoskeletal (back) discomfort since August 2006. Concomitant medications at study start were cetirizine (daily dose unknown) INR for seasonal allergy and acetylsalicylic acid 81 mg/day as cardiovascular event prophylaxis, and w/pseudoephedrine hydrochloride (daily dose unknown) for upper respiratory tract infection. During the Main Period the subject was started on naproxen sodium w/pseudoephedrine hydrochloride (dose unknown) for upper respiratory tract infection.

Blepharospasm was first diagnosed on 26-AUG-2002. Estimated duration of BEB was 6 years and two months. Before entering the study the subject had been treated for nearly 5 years with up to 100 U Botox®. The last injection prior to study entry was on 31-AUG-2007 including a total dose of 100 U Botox®.

The subject signed informed consent on 07-DEC-2007 and was treated with 80 U of NT 201 in total on 14-DEC-2007. On 07-MAR-2008 the subject experienced dyspnoea, rated as mild in intensity and not related to treatment by the investigator. This event was resolved on 04-AUG-2008 during the Open Label Extension Period, no action was taken regarding the adverse event. In addition the subject experienced headache (23-DEC-2007, mild, not drug related, resolved on 24-DEC-2007), dry eyes (January 2008, mild, not drug related, resolved on 14-AUG-2008) and International Normalised Ratio (INR) increased (28-MAR-2008, moderate, not drug related, resolved during the Open Label Extension Period on 20-JUN-2008).

Country: US; **Center:** 1061; **Scr:** S2102; **RandomNumber:** 5770; **Initials:** (b) (6)
AE Preferred Term: Dyspnoea

This 67-year-old female subject (white, weight 142 lb, height 63.00 in) was a non-smoker. Her medical history was significant for a tonsillectomy in 1949, appendicitis in 1974, menopausal symptoms in 1974, carpal tunnel syndrome in 1980, and cataract operation on (b) (6). Concomitant diseases blurred vision since October 1947, osteoporosis since 1980, haemorrhoids since 1984, anxiety since 1997, increased blood cholesterol since 1997, bilateral hand tremor, chin tremor and gait disturbance since 15-OCT-1999; eyelid ptosis, dry eye and dry mouth all since 15-OCT-1999; myalgia since 2000, eyelid disorder since 2005, hypersensitivity since 2005, insomnia since 2005, arthritis since 2006 and cardiac murmur since 10-MAY-2007. Concomitant medications at study start were pravastatin sodium 8 mg/day for blood cholesterol increased, celecoxib 200 mg/day for myalgia, clonazepam 0.5 mg/day for blepharospasm, zolpidem tartrate 10 mg/day for insomnia, bupropion 300 mg/day for anxiety, alendronate sodium 10 mg for osteoporosis and ceterizine hydrochloride 10 mg/day for hypersensitivity; cyanocobalamin 500

mg/day, tocopherol 1000 IU/day and multivitamin (daily dose unknown) all three for vitamin supplementation; fish oil (daily dose unknown) and glucosamine w/chondroitin sulfate 750/600 mg/day both for medical diet. During the Main Period the patient was started on propacet (daily dose unknown, PRN) for arthritis.

Blepharospasm was first diagnosed in 1995. Estimated duration of BEB was 12 years. Before entering the study the subject had been treated for nearly 10 years with Botox®. The last injection prior to study entry was on 01-FEB-2007 including a total dose of 50 U Botox®.

The subject signed informed consent on 10-MAY-2007 and was treated with 50 U of NT 201 in total on 17-MAY-2007. On 04-JUN-2007 the subject experienced dyspnoea, rated as mild in intensity and not related to treatment by the investigator. This event was resolved on 09-AUG-2007 during the Open Label Extension Period, no action was taken regarding the adverse event. In addition the subject experienced facial weakness (17-MAY-2007, mild, not drug related, ongoing and stable at trial termination), nausea (18-MAY-2007, mild, drug related, resolved on 22-MAY-2007) and asthenia (04-JUN-2007, moderate, not drug related, resolved on 09-AUG-2007). No action was taken regarding all three adverse events and the subject continued in the Open Label Extension Period.

Country: US; **Center:** 1006; **Scr:** S2083; **RandomNumber:** 5751; **Initials:** (b) (6)

AE Preferred Term: Dry mouth

This 71-year-old female subject (white, weight 151 lb, height 66.00 in) was an ex-smoker. Her medical history was significant for appendectomy in 1944 and cataract operation with lens implant in 2000. Concomitant diseases included allergic sinusitis since 1970, osteoarthritis since 2000, dyskinesia since 2001, dry eye since 2003, dysphagia since 2003 and eyelid ptosis since 2006. Concomitant medications at study start were acetylsalicylic acid 81 mg/day for cardiovascular event prophylaxis, multivitamin (daily dose unknown) for vitamin supplementation, oscal 1200 mg/day for mineral supplementation and fish oil 1200 mg/day for medical diet.

Blepharospasm was first diagnosed in 1982. Estimated duration of BEB was 25 years. Before entering the study the subject had been treated for nearly 3 years with 64 U Botox®. The last injection prior to study entry was on 21-FEB-2007 including a total dose of 69 U Botox®.

The subject signed informed consent on 09-MAY-2007 and was treated with 69 U of NT 201 in total on 21-MAY-2007. On 01-AUG-2007 the subject experienced dry mouth, which was rated as mild in intensity and not related to treatment by the investigator. This event was resolved on 29-SEP-2008 during Open Label Extension Period, no action was taken regarding the adverse event. No further adverse events occurred during the Main Period and the subject continued in the Open Label Extension Period.

Country: US; **Center:** 1002; **Scr:** S2080; **RandomNumber:** 5766; **Initials:** (b) (6)

AE Preferred Term: Dry mouth

This 68-year-old female subject (white, weight 166 lb, height 68.00 in) was a non-smoker. No significant medical history was indicated at study start. Concomitant medication and reported diseases at study start included omeprazole (0.4 mg/day) for gastroesophageal reflux disease and alprazolam (0.5 mg/day) for anxiety, both since 2000.

Clinical Safety Review
M. Lisa Jones, MD MPH
BLA 125360
Xeomin®, NT 201 (Incobotulinumtoxin A)

Blepharospasm was first diagnosed in 1984. Estimated duration of BEB was 23 years. Before entering the study the subject had been treated for nearly 20 years with 100 U Botox®. The last injection prior to study entry was on 22-MAY-2007 including a total dose of 100 U Botox®. The subject signed informed consent on 23-AUG-2007 and was treated with 100 U of NT 201 in total on 30-AUG-2007. On 10-OCT-2007 the subject experienced dry mouth, which was rated as mild in intensity and related to treatment by the investigator. This event was resolved at the end of the Main Period, and no action was taken regarding the adverse event. Further reported adverse event was ptosis on 07-SEP-2007, rated as mild in intensity and assessed related to treatment. The event resolved during the Main Period and the subject continued in the Open Label Extension Period.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 MRZ 60201-0433/1 Main Period: Prospective, double-blind, placebo-controlled, randomized, multi-center trial with open-label extension period to investigate efficacy and safety of NT 201 in the treatment of Blepharospasm MRZ 0433/2 OLEX (Extension Period): open-label extension period to investigate continued efficacy and safety of NT 201 in the treatment of blepharospasm	X			Single injection session of NT 201 compared to placebo. Subjects were previously treated successfully with Botox. N=109 in ITT (75 NT 201, 34 PBO) from 34 centers in US and Canada. Primary efficacy variable: change from baseline in the JRS Severity subscore at six weeks. Open label extension period: investigate safety and efficacy of repeated injections of NT 201 in subjects with BEB over a 1 yr period = OLEX period.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			There is only one pivotal study. In previous meeting minutes (pre Phase 3) the division stated the need for a proportion of treatment naïve subjects as well (defined as no BoNT for 1 year).
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			They appear to conform to discussion in regulatory meetings
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	US and Canada trial sites
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			But whether numbers of subjects and exposure data is adequate is a matter for review.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Past PSUR submitted
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			Subject to review
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 11.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric waiver, birth to 16 years, low incidence of blepharospasm.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Sponsor states that there have been no reports of abuse or dependence with botulinum toxin type A. 2.5.5.8
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See Item 17 comment.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		Datasets not SDTM compliant with regard to subject identifiers, format, file content, dataset filenames, and absence of any xml dataset backbone or field definitions with hyperlinked field names.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		Requests will be made of the sponsor for tables of adequate structure and information.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		
34.	Are all datasets to support the critical safety analyses available and complete?		X		
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			No deaths. One SAE with narrative included.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

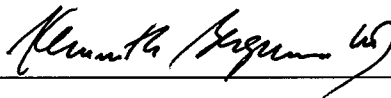
If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewer's Note: A separate list is being compiled with regard to clinical requests for adequate data tables to be forwarded to the sponsor separately.

Kenneth Bergmann, MD
 Reviewing Medical Officer



August 31, 2009
 Date

 Clinical Team Leader

 Date