CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review

Date	7/28/2010
From	Gerald D. Podskalny, DO
Subject	Cross Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 125360
Applicant	Merz
Date of Submission	July 2, 2009
PDUFA Goal Date	August 4, 2010 (extended)
Proprietary Name / Established (USAN) names	Xeomin/ incobotulinumtoxinA
Dosage forms / Strength	50 Unit and 100 Unit Vials for IM injection
Proposed Indication(s)	1. Cervical Dystonia 2. Blepharospasm
Recommended:	***Approval***

Cross Discipline Team Leader Review

1. Introduction

Merz submitted a BLA for Xeomin (incobotulinumtoxinA) to the agency seeking approval for the treatment for Benign Essential Blepharospasm (BSP) and Cervical Dystonia (CD). IncobotulinumtoxinA (Xeomin) is also a new botulinum toxin type A product and if approved it would be the third type A product marketed in the U.S. There are 2 botulinum toxin type A products and 1 type B product approved for the U.S. market. All of the botulinum toxin products are approved to treat cervical dystonia but only onabotulinumtoxinA (Botox®) is approved in the U.S. for the treatment of Blepharospasm. (b) (4)

(b) (4)

(b) (4)

All botulinum toxins are considered symptomatic therapy for conditions that cause increased muscle tone that is severe enough to cause pain and disability (i.e., dystonia or spasticity). All of the botulinum toxins share a similar mechanism of action to reduce muscle tone by interfering with the release of acetylcholine at the neuromuscular junction, thereby causing incomplete and temporary neuromuscular paralysis, which relaxes treated muscle groups. Both cervical dystonia and blepharospasm are forms of focal dystonia.

The review will focus on the following issues:

- Is there sufficient evidence that Xeomin the safe and effective in accordance with CFR and agency practice?

- Is there sufficient information to providers to guide appropriate dosing and safe use for Blepharospasm (BSP) and Cervical Dystonia (CD)?

Benign essential blepharospasm and blepharospasm are two different syndromes. Although, the sponsor defined BSP as the target population for their pivotal trial the patients enrolled in the trials had other forms of dystonia in conjunction with blepharospasm. Dr. Bergmann covers this issue in greater detail in his review of the Blepharospasm indication. The inclusion of other BSP does not affect the finding of safety and effectiveness but will affect the specific wording of the indication.

2. Background

CD is characterized by involuntary, inappropriate neuromuscular hyperactivity in muscles of the neck and shoulder, which leads to abnormal head movements and postures, and may cause significant disability and pain. CD is a chronic condition that affects more women than men, with a female to male ratio of approximately 2:1 [Marras et al. 2007]. The prevalence of CD has been estimated to be between 5.7 and 18.1 per 100,000 [Butler et al. 2004].

BSP is a progressive disease characterized by spontaneous, spasmodic, bilateral, intermittent or persistent involuntary contractions of the orbicularis oculi muscles. BSP primarily affects women in their fifties and sixties, with a female to male ratio of 2-3:1. Earlier treatments for BSP were granted orphan designation (Botox).

Botulinum toxin type A blocks cholinergic transmission at the neuromuscular junction, and at certain sympathetic nerve terminals, by inhibiting the release of acetylcholine stored in vesicles within the nerve terminal (chemical denervation). The nerve terminals of the neuromuscular junction no longer respond to nerve impulses. With time, the impulse transmission is reestablished by the formation of new nerve terminals and motor endplates, or by recovery of the previous ones.

Botulinum Toxin binds to the cholinergic nerve terminals with high selectivity and affinity. Following binding to the receptor, the steps leading to inactivation of neuromuscular transmissions are as follows:

a) internalization of Botulinum toxin type A into the nerve terminal.

b) translocation of the light-chain part of the molecule into the cytosol of the nerve terminal

c) enzymatic cleavage of a presynaptic target protein, SNAP 25 (botulinum toxin A) that is essential for the release of acetylcholine, resulting in inhibition of acetylcholine release

Preparations of Botulinum toxin type A, Botox (Allergan) and Dysport (Ipsen), and Botulinum toxin type B, Neurobloc (Solstice Neuroscience Inc.), have been approved for clinical use in

Europe for several years. To date NT 201 (Xeomin) is approved in Argentina, Canada, Mexico, Uruguay, and several European countries for the symptomatic management of BSP and CD of a predominantly rotational form (spasmodic torticollis) in adults. In Canada, Xeomin is also approved for the treatment of post-stroke spasticity of the upper limb. In Argentina, Xeomin is also approved for a variety of other indications covering focal spasticity, strabismus, and the temporary improvement of glabellar frown lines. The Botulinum toxin preparations available in the United States (US) are Botox and Myobloc. Botox is approved in the US for the treatment of CD, BSP, strabismus, hyperhidrosis, and glabellar lines. Myobloc is approved in the US for the treatment of CD and Dysport is approved for cervical dystonia and glabellar frown lines.

3. CMC/Device

Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, **recommends approval of BLA #125360 for Xeomin manufactured by Merz, Pharmaceuticals GMbH. (From the OBP/DTP review)**

"The data submitted in this application support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A (BONT/A, uncomplexed) naturally secreted by *C. botulinum*, is well controlled, and leads to a product that is potent and safe, when used according to the label. The product is free from endogenous or adventitious infectious agents. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs.

This product will be on lot release per 21CFR 610. It is recommended that this product be approved for human use under the conditions specified in the package insert".

Structure

The active pharmaceutical ingredient of Xeomin is purified type A neurotoxin with molecular weight of 150 kDa, free of complex proteins, which is produced by the anaerobic fermentation of the bacterium Clostridium botulinum, Hall strain ATCC 3502. The neurotoxin moiety is a 1296 amino acid dichain molecule consisting of a heavy chain (Hc,100 kDa) and a light chain (Lc, 50 kDa) linked by a disulfide bond. The final product is a lyophilized material containing type A toxin complex, human albumin and sucrose.

Biological activity

The full activity of botulinum toxin requires both the heavy (Hc) and light (Lc) chains. The Hc is needed for neuronal binding, up-take by receptor and transport of Lc into the cytosol. In the cytosol the Lc, hydrolyzes a member of the SNARE protein complex, which blocks vesicle exocytosis. The target for type A toxin is a 25-kD synaptosomal associated protein (SNAP-25). SNAP-25 is cleaved at the C-terminus (Q_{197}-R) by BoNT/A, generating truncated SNAP-25 that can't participate in formation of the SNARE core complex. When injected IM. at therapeutic doses, Xeomin induces partial chemical denervation of the muscle resulting in a localized reduction in muscle contraction.

Potency Assays to Measure Activity

The mouse lethal dose assay is used to assess product activity. The assay is conducted by administering pre-established dilutions of Xeomin into groups of mice. The potency of botulinum toxin therapeutic preparations is expressed in LD_{50} units, with one unit of activity defined as the amount of drug required to kill 50% of the animals. The assay is a good indicator of both light and heavy chain function since both are required for activity *in vivo*. Despite problems with a high level of inter-laboratory variability, the LD50 assay is still used to assess potency for release of all botulinum toxin products currently on the market in the US and Europe.

DS Manufacture:

Xeomin drug substance is produced as a secreted protein by (b) (4) anaerobic fermentation of *Clostridium botulinum* type A, Hall strain (ATCC3562). It is purified from the culture solution (b) (4) to a purified neurotoxin without accessory proteins. The process is validated and well-controlled through defined operating and performance parameters. The manufacturing site, Merz Group Services GmbH, Am Pharmpark 15A, D-06861 Dessau-Rosslau, Germany was inspected Nov 5 -13, 2009. A number of 483 observations were issued. Some of the issues were resolved prior to taking an action on the Xeomin application and the others can be addressed as PMCs.

DS Purity

Xeomin DS is produced from bacterial fermentation. Drug substance is highly pure and does not contain process-related impurities.

DS Release Tests

The tests for release of DS include appearance (b) (4), protein (b) (4), , Western blot (immunological identity: HC and LC), ELISA (immunological identity: presence of BoNT/A), reduced SDS-PAGE (identity: Single chain, HC and LD), reduced SDS-PAGE Coomassie stain (purity) and (product related impurities), bioburden (b) (4), and endotoxin (b) (4) and SE-HPLC (b) (4) Drug product is formulated with an excess of HSA and DS is present in nanogram quantities. Therefore, it is not possible to test DP for aggregates.

Drug Product Presentation

Xeomin is supplied as a sterile single use vial. Each vial 100 or 50 Unit vial contains dried *C.botulinum* toxin type A, sucrose (b) (4) and human albumin (b) (4) As each vial is intended for single patient use, no anti-microbial preservatives are included in the formulation.

Excipients

The product is formulated with sucrose and human albumin. Sucrose is a natural disaccharide obtained from plant. Human albumin is manufactured by CSL Behring and is a FDA approved medicinal product in the US (BLA-1-2366). Human plasma was received from selected donation centers in the US, authorized by FDA.

Stability

Increased protein concentration and loss of potency are observed when drug substance is stored at temperatures of 2-8 ^{0}C. Real time stability data indicate that drug substance is stable when stored frozen (b) (4) for at least 36 months.

The proposed drug substance shelf life of 36 months when stored at (b) (4) is supported by data submitted by the Sponsor.

Item	Responsibility
Merz Group Services GmbH Site Dessau Am Pharmapark 15A D-06861 Dessau-Rosslau Germany FEI 3006896175	Drug substance and drug product manufacturing site
(b) (4)	Microbiological testing of drug substance and general analytical and stability testing site for drug product
Merz Pharmaceuticals GmbH Hermannswerder Haus 15 D-14473 Potsdam Germany FEI 3007501745	Analytical testing site of drug substance and ELISA testing site for drug product
(b) (4)	LD50 assay testing of drug substance and drug product
	Stability testing of drug substance
Merz Pharmaceuticals LLC 4215 Tudor Lane Greensboro, NC 27410 FEI 3004335969	Product release

Establishment Assessment: (From the OBP/DTP review)

All sites listed in the BLA are acceptable from a CGMP perspective. The Merz Groups Services GmbH, Site Dessau, in Dessau-Rosslau, Germany is the manufacturing site for the drug substance and the drug product. The site was inspected November 5-13, 2009 by CDER/OC/BMT and CDER/OBP/DTP and the establishment was classified as VAI and was found to be acceptable. The analytical testing site, (b) (4) was inspected November 9-13, 2009 by BMT and DTP and was classified as VAI and is acceptable from a CGMP perspective. The potency assay test site, (b) (4) was inspected on November 2-3, 2009 by BMT and DTP, was classified as VAI, and is acceptable from a CGMP perspective.

CMC Post-Marketing Commitments

1. To characterize the specificity of the antibody used in the abnormal toxicity test to evaluate whether this antibody recognizes only type A toxin and not other serotypes. Results of this validation study together with the proposed specifications for use in drug product release and in the lot release protocol will be submitted in a Prior Approval Supplement (PAS) by [SPONSOR PROPOSE DATE].

2. To characterize the ability of the SE-HPLC assay to accurately assess the aggregate content of the drug substance at release and on stability. This may be established by demonstrating that SE-HPLC provides similar results in aggregate content evaluations as compared to an orthogonal method that is quantitative and does not disrupt weak protein- protein interactions (e.g., AUC or FFF). Results of this validation study will be submitted in a Prior Approval Supplement (PAS) by [SPONSOR PROPOSE DATE].

3. To investigate the development and implementation of a non-animal based potency assay for drug substance, drug product release and stability testing. A summary report together with any proposed modifications to the release and stability specifications should be submitted in a prior Approval Supplement to the Agency by [SPONSOR PROPOSE DATE].

Environmental Analysis(From the OBP/DTP review)

Merz requested a categorical exclusion for an Environmental Analysis, as stated in 21 CFR 25.31 (c) based on the following:

- Xeomin is administered by a small local injection in the infected muscle(s) once every 3 months
- The diseases treated are rare diseases and therefore only limited amounts will be used.

Therefore the approval of Xeomin is not expected to significantly alter the concentration or distribution of botulinum neurotoxin A (BoNT/A) or its metabolites or degradation products in the environment.

- The Agency concurs that a categorical exclusion based on 21 CFR 25.31 (c) is appropriate for this product.

Per FDA guidance environmental assessments provided to the Agency do not need to include production and disposal sites since laws and regulations require deactivation. Appropriate deactivation of waste was found to occur during the inspection. **Therefore, an environmental assessment of the production site not necessary.**

4. Nonclinical Pharmacology/Toxicology

Pharmacology Toxicology (PT) Reviewer Recommendation for Regulatory Action

Based on the nonclinical data provided, BLA STN# 125360/0 is approvable for the proposed indications. The toxicities of NT201 demonstrated in the nonclinical studies were consistent with the expected effects of the known pharmacologic activity of the product. The clinical patient population can be selected and/or monitored appropriately to avoid unreasonable risk.

Overview

The sponsor conducted nonclinical studies in rats, mice, rabbits and nonhuman primates. The pivotal general toxicology studies included single and repeat-dose toxicology studies, the longest of which lasted 9 months in non-human primates (Study #AA41667). In addition, fertility, and embryo-fetal developmental toxicology studies were performed in rats and rabbits, and local tolerance for eye irritation (rabbits).

General Toxicology

Single Dose Lethality Study

A single dose mouse lethality study (compliant with EU GLP) evaluated the lethality of 6 doses of NT 201 delivered by a single IP injection. The LD_{50} for this lot of NT 201, as calculated by probit analysis, was 6.9690 pg/animal. Therefore, for the lot tested, one LD_{50} Unit equals approximately 7 pg.

Single dose Toxicology

The sponsor submitted results from two comparative single dose toxicity studies conducted in mice. In the first Study #11252/1/98 animals received a single intravenous administration of one of 5 dose level of NT 201, Botox or Dysport. In Study #16464/03, Mice received a single dose of 0, 5, 50 or 150 U/kg (0.1U, 1U or 3 U total per mouse) of NT 201 or Botox by intramuscular injection. The results of both studies were reviewed by the agency's Pharmacology/Toxicology reviewer who concluded the findings (including histopathology) was consistent with the expected toxicity associated with botulinum toxin products.

Repeat Dose Toxicology

Study 422/016 was a13-week repeat dose toxicity study of NT 201 or Botox administered intramuscularly (a single gastrocnemius) in cynomolgus monkeys. The study was a GLP compliant study of male and female animals (3 per sex per group) that received 0. 4, 8 or 16 units of NT 201 or Botox IM once every 4 weeks for a total of 4 doses.

No NOEL was established due to the limping and weakness of the injected muscle at all dose levels. The NOAEL level was determined to be 4 U/kg due to loss of appetite and body weight in the 8 and 16 U/kg groups for NT201. The animals were found to have a dose related reductions in size and weight of the contralateral gastrocnemius (not injected) muscle. The sponsor attributes this finding to alteration of the animal pattern of locomotion caused by weakening of the injected muscle. The PT reviewer considered the possibility this may finding may be caused by distant spread of the toxin to the contralateral limb.

Cardiovascular Toxicology

hERG Study

A hERG study was conducted using (b) (4) (active moiety is the same as NT 201) and 10, 000 units were reported to have no effect on hERG currents. The PT reviewer concluded that it is unlikely that NT 201 would inhibit hERG currents.

Study 442/015 was a comparative combined efficacy and cardiovascular risk assessment of NT201 and BOTOX. A single intramuscular administration of 16 U/kg, was delivered into the (gluteus medius) in the conscious cynomolgus monkey monitored via telemetry. This was a GLP compliant study. There were small variation in heart rate and ECG parameters reported but no significant changes in ECG were reported. The PT reviewer noted the study provided limited information because of the single dose design of the study. In addition, the comparison of NT 201 with Botox can not be interpreted because equivalence has not been established between the potency units for the two products, therefore it is not possible to know if the two products are comparable...

Genetic toxicology

The sponsor did not conduct mutagenicity studies with NT (b) (4) 201 citing information provided in ICH S6, 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. Moreover, the administration of large quantities of peptides/proteins may yield unpredictable results. It is not expected that these substances would interact directly with DNA or other chromosomal material."
Based on the chemical structure and mode of action of NT 201, there is no reason to suspect any possible mutagenic potential.

Carcinogenicity

The sponsor did not conduct carcinogenicity studies involving NT 201 in accordance with the guidance in ICH S6, Module 4, Section 4.3 "Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. The sponsor stated their belief that there is no reason to expect that NT 201 is associated with risk for carcinogenic potential.

Reproductive toxicology

Study # (b) (4) 442/019 examined fertility male and female rabbits who received intramuscular injections into back muscles of NT 201 every 2 weeks. The doses studied included 0, 1.25, 2.5 3.5 units/kg (males received 5 doses females received 3 doses). The results of this non-GLP compliant study showed a possible increase in failure to mate for the male animals (1, 2, 3, 2 for the control, low, intermediate and high dose groups, respectively). Otherwise, there was no significant histopathology finding outside injected skeletal muscle.

Embryonic Fetal Development

Study AA62003 was a non-GLP compliant dose range-finding study that administered intramuscular NT 201 in the pregnant rat.

Pharmacology Toxicology Reviewer's Conclusion:

"Under the conditions of this pilot study, exposure to NT201 by intramuscular injection of the pregnant female on GD6, 12 and 19 resulted in a small increase in early resorption in the high dose group (30 U/kg) relative to control and the lower dose groups. The sponsor does not consider this finding biologically relevant because the early resorption occurred in only 2 females in that group. However, with only 5 animals available for evaluation, 2 animals represent a large proportion of the group. Furthermore, early resorption was observed in embryo-fetal studies with similar products and systemic exposure is suspected in other repeat-dose studies with NT201. Therefore, a relationship to systemic exposure of NT201 should be suspected. Under the conditions of this study, the developmental NOAEL is 10 U/kg".

Study MDS 442/018 was a GLP compliant segment II embryo toxicity study of NT 201 administered by the intramuscular route in the rabbit.

Pharmacology Toxicology Reviewer's Conclusion:

"The dams exhibited the expected dose-related effects of NT201, including reduced weight gain and food intake. The high dose group showed significant maternal toxicity. Five abortions were noted for this group. The middle dose level of 2.5 U/kg was determined to be the MTD for this study due to weight loss and reduced food intake.

There were no indications of embryo-toxicity, fetal external or visceral malformations or variations attributable to test article in groups receiving 2.5 U/kg or less. A slight increase in incidence of vertebral incomplete ossification was noted in all treated groups, relative to control. The incidence was small and within the range of recent historical controls, but is similar to the effects of other botulinum toxin products in similar studies. The NOAEL was determined to be 1.25 U/kg".

Special toxicology studies:

Study (b) (4) 11373/98 examined the effect of (b) (4) on hemolytic properties in human blood *(in vitro)*. The PT reviewer concluded, "Under the conditions of this study, (b) (4) did not show hemolytic potential when mixed with normal human erythrocytes".

Local Tolerance Studies

Study (b) (4) 21110 was a study that examined the potential for acute eye irritation/corrosion caused by NT201 in rabbits. The PT reviewer concluded that Under the conditions of this study, instillation of 100 U of NT201 (to conjunctival sac OD) appeared to be non-irritating.

Antigenicity

The sponsor conducted two studies (10929/97 and (b) (4) 12444/99) in the rabbit that administered NT 201 injected intracutaneously for repeated administrations. Both studies were judged to be inadequate with no useful information regarding immunogenicity reported.

Labeling Recommendations
Nonclinical studies to evaluate the potential adverse effects of NT201 treatment on fertility (rabbit) and embryonic (rat and rabbit) development were conducted. The results showed a tendency toward pre-implantation loss, early embryonic resorption in rats and rabbits and a trend toward reduced fetal weight in rats. In the pivotal embryo-fetal study in rabbits, abortions were observed at the highest dose. Pregnancy Category C is recommended.

CDTL Comment:
Although, a number of the preclinical development program were not GLP compliant or the studies did not sufficiently address the question they were designed to answer, there is no new preclinical findings that suggest a new or increased risk to patients who may receive Xeomin for cervical dystonia or blepharospasm. I agree with classification of Xeomin as category C in pregnancy. PT has requested two postmarketing studies (PMR) to obtain the necessary animal data to support the safe use on incobotulinumtoxinA in the pediatric postmarketing studies (PMR/PMCs) that are requested by the agency.

Postmarketing Requirements

1. A prenatal and postnatal development (including maternal function) study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on stages of development and endpoints not evaluated in an embryo-fetal development study, in accordance with guidance set forth in ICH S5(R2): *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005).

2. A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Xeomin (incobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology studies submitted in this application. Clinical Pharmacology (CP) recommended changes to the proposed product label based on published reports or on label language that is common to all botulinum toxin products.

The recommended changes were communicated to the sponsor and agreement was reached early in labeling discussions. The label changes were made as tracked changes to distinguish the edits from CP reviewer from the sponsor's original language.

(b) (4)

(b) (4)

Concomitant treatment of XEOMIN and amino

6. Clinical Microbiology

General Considerations (excerpts from the CMC-Microbiology Review)
One batch of drug substance is derived from (b) (4) Each (b) (4) after purification yields (b) (4) of purified drug substance. The drug substance is a highly potent toxic substance and is manufactured in a dedicated facility using (b) (4). (b) (4)

(b) (4)

Drug Substance Microbiology Review
An assessment of the CMC drug substance section of the application from a microbiology product quality perspective is provided in the CMC Microbiology review.

Recommendation for Approvability

The **drug substance portion of the BLA, as amended, is recommended for approval** from a microbiology product quality perspective with the following post marketing commitments:

(b) (4)

(b) (4)

Microbiology Reviewer comments: (b) (4). The cycle should not be referred to as a (b) (4) and additional information on the (b) (4) cycle was requested (see below in this review).

Microbiology Product Reviewer comments: (PMC1-4) The (b) (4) The (b) (4) cycles were validated using biological indicator spores of Geobacilus stearothermophilus. (b) (4)

CDTL Comment
The sponsor has agreed to submit the validation data requested in PMC (b) (4).

Drug product is manufactured using (b) (4) The sponsor has committed to qualifying the crimping machine with media filled vials and a re-validated microbial ingress test (PMC (b) (4)

The initial BLA did not contain any shipping validation data or information. A protocol for the transport validation study for vials throughout Europe and to USA was submitted and will be executed post-approval (PMC (b) (4)).

The stability program includes sampling for sterility (b) (4) The sterility test will be replaced with a container closure dye ingress test under development (PMC (b) (4)

CMC Microbiology Product Quality Assessment:

The BLA, as amended, is recommended for approval from a microbiology product quality perspective. It is recommended that the following post-marketing commitments (PMCs) be communicated to the sponsor. The PMCs are as follows:

1. Conduct studies to determine the resistance of Clostridium botulinum spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be revalidated in the event the Clostridium spores are determined to be more resistance to (b) (4) inactivation than the Geobacilus stearothermophilus biological indicator spores. Submit results of the study in a CBE-O by August 2010.

2. Include a culture purity test at the end of the (b) (4) step capable of detecting contaminating anaerobes. Submit assay qualification data and information in a CBE-O by December 2010. .

3. Re-validate the drug substance release bioburden assay to include the use of (b) (4) of sample volume without dilution and submit results in a CBE-O by December 2010.

4. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Submit summary data in a CBE-O by December 2010.

5. Revalidate the microbial ingress test (container closure integrity test) to demonstrate the integrity of the drug product container closure. Determine the sensitivity (minimum detectable leak size) of the test. Information and summary data will be submitted in a CBE-O by 2/1/2011.

6. Re-qualify the crimping machine with media filled vials and the revalidated microbial ingress test. Summary data will be submitted in a CBE-O supplement by 2/1/201 1.

7. Complete shipping validation studies for the drug product vials using the worst shipping temperature and duration. Validation information and summary data should be submitted in CBE-30 by 10/31/2011.

8. Develop a container closure integrity test to replace the sterility test in the stability program. Information and summary validation data fro the container closure integrity test will be submitted in a PAS by 12/31/201 1.

CDTL Comment
The sponsor has committed to conduct all of the CMC and CMC Microbiology PMCs and has provided milestone dates, which are included in the approval letter.

9. Clinical/Statistical- Efficacy

Cervical Dystonia-Trial 408/1
The sponsor's pivotal efficacy trial is study 408/1 and study 0013 is an active control study that supports study 408/1. Study 0013 is designed as a non-inferiority trial, which was submitted as a supportive study to the CD application. Study 0013 lacks important design elements (a justification for the M1, M2 or placebo group) that would make the study a true non-inferiority trial or a trial that can support a claim for effectiveness.

Study 0408/1 (CD) was a randomized, double-blind, placebo-controlled single dose trial comparing 120 units and 240 units (total dose) of NT 201 to placebo. 222 patients with CD were enrolled in this Phase 3 study that lasted 20 weeks. The trial enrolled both previously treated and toxin naïve patients (N=87≈40%) with CD. The primary efficacy endpoint was the change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score from Baseline to Week 4 (Visit 3) post-injection. The primary analysis population is the intent-to-treat (ITT) population, with missing values replaced by the subject's Baseline value. Upon completion of study 408/1 participants were offered the chance to enroll in the long-term extension trial 408/2. Patient data from 408/1 (Main Phase) was unblinded and all patients were re-randomized to double blind treatment with 120 units or 240 units of NT 201 for the next year. Patients could receive follow up injections with the blinded fixed dose NT 201 when they met criteria. The protocol was amended to permit a dose adjustment if the site investigator believed it was necessary. The requirements for re-injection were that patients felt the need for repeat injection and the site investigator confirmed that their TWSTRS-Total score was ≥ 20 and least 6 weeks had passed since their last injection. The blind was supported by the creation of a matching placebo vial that contained sucrose and 1 mg of human albumen that was identical to the NT 201 (Xeomin) vials. The solution properties of the placebo vials were similar to vials containing NT 201.

Patient Population and Demographics

Women and men between the ages of 18-75 years were recruited into the study. All patients had primarily rotational CD and the subjective need for injection a minimum TWSTRS total and subscale scores as follows:

TWSTRS-Total score > 20
TWSTRS-Severity score > 10
TWSTRS-Disability score > 3
TWSTRS-Pain score > 1

Pretreated patients enrolled in to the study must have a history of a stable response to botulinum toxin injections, with their last treatment with a botulinum toxin product at least 10 weeks prior to enrollment. Pretreated patients were excluded if the dose of botulinum toxin required to produce a stable response in the past (Types A or B) exceeded reasonable limits.

Text Table 11: Second-Last and Last Injection of Botulinum toxin before Baseline (Pre-Treated Subjects of ITT Population)

Variable	240 U group N=50	120 U group N=47	Placebo group N=46	Total N=143
Duration Since Second-Last Injection in months (Mean (SD) [Median]) [a]	14.4 (24.82) [7.5]	10.2 (7.74) [7.7]	13.5 (20.05) [7.7]	12.7 (19.04) [7.6]
Duration Since Last Injection in months (Mean (SD) [Median])	9.0 (19.55) [4.0]	5.6 (6.58) [3.6]	8.1 (18.18) [3.9]	7.6 (15.90) [3.9]

The demographic composition of the trial participants was typical for clinical trials in CD. The disease is more prevalent in Caucasian women in their 40's and 50's. The trial population was 66% female with a mean age of approximately 53 years. There were few minority patients of either gender enrolled in the trial. The only significant difference between the

treatment groups was that the 120 unit group had a significantly higher median weight 179 lbs (27.7 median BMI) compared to the 240 unit and placebo groups who had a median body mass of 160 lbs (24.4 median BMI) and 165 lbs (26.9 median BMI) respectively. The lower median body mass reported in the 240 unit group could provide a slight advantage in the efficacy determination with the assumption that patients with a lower body mass have smaller muscles resulting in more pronounced weakening (treatment effect) associated with NT-201. However, the results in men who would be expected to have a higher mean BMI and body mass did not demonstrate an added benefit of the 240 unit dose over the 120 unit dose.

CDTL Comment:

The trial entry criteria appeared to be reasonable resulting in a patient population that is consistent with the population likely to use the Xeomin in clinical practice. The requirement that patients not be treated within the last 10 weeks seems too short on face. The concern may be that patients who received a botulinum toxin product 10-12 week earlier may still be receiving a benefit from their previous botulinum toxin treatment when they entered the trial. I do not believe that this would significantly impact the efficacy measures because patients were required to meet a pre-specified severity score at trial entry. In addition, the mean duration since the last toxin injection at trial entry for pre-treated patients was 3.1 months (4 months median) for the 240 unit group and 2.8 (3.6 months median) for the 120 unit group. The time since the last botulinum toxin injection was sufficient to expect that the effect from the previous injection would have worn off prior to receiving the first NT 201 (Xeomin) injections as part of the clinical trial.

14.1.3.5: Study Subjects
Demographic Data and Other Baseline Characteristics
Most Recent Injection Session Prior to Trial Entry - ITT Population (Pre-Treated Subjects)

Pooled Study Center - Total

	NT 201 (240U) N=50	NT 201 (120U) N=47	Placebo N=46	Total N=143
Duration Since Most Recent Injection (months)				
N	50	47	46	143
Mean (SD)	9.03 (19.548)	5.61 (6.578)	8.07 (18.177)	7.60 (15.896)
Q1	3.10	2.80	3.30	3.10
Median	4.00	3.60	3.90	3.90
Q3	6.50	4.90	5.40	5.70
Min/Max	2.2/134.2	2.1/43.9	2.1/124.9	2.1/134.2
Nmiss	0	0	0	0
Botulinum Toxin Type of Most Recent Injection (n, %)				
BOTOX	43 (86.0)	41 (87.2)	40 (87.0)	124 (86.7)
Myobloc	4 (8.0)	4 (8.5)	6 (13.0)	14 (9.8)
Other - DYSPORT	3 (6.0)	2 (4.3)	0	5 (3.5)
Onset of Effect of Most Recent Injection (days)				
N	47	45	42	134
Mean (SD)	8.0 (5.02)	7.4 (5.38)	7.9 (3.27)	7.8 (4.65)
Q1	4.0	4.0	7.0	5.0
Median	7.0	7.0	7.0	7.0
Q3	10.0	9.0	10.0	10.0
Min/Max	2/28	1/30	3/14	1/30
Nmiss	3	2	4	9
Duration of Effect of Most Recent Injection (weeks)				
N	48	45	42	135
Mean (SD)	10.9 (3.84)	10.6 (3.82)	11.3 (3.95)	10.9 (3.85)
Q1	9.0	9.0	8.0	9.0
Median	11.0	10.0	11.0	11.0
Q3	12.0	12.0	13.0	12.0
Min/Max	2/20	4/24	3/20	2/24
Nmiss	2	2	4	8
Stable Therapeutic Response to This and the Prior Injection Sessions (n, %)				
Yes	50 (100.0)	47 (100.0)	46 (100.0)	143 (100.0)
No	0	0	0	0

[a] Unknown muscles were excluded from this analysis.
[b] Muscles not treated for Cervical Dystonia or unknown muscles were excluded from this analysis.
Source Data: Listing 16.2.1.3.5
Data Extraction: 20MAY2008
Table Generation: 19NOV2008 11:06

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Primary Endpoint Analysis

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 (ITT population).

The sponsor used an ANCOVA for the primary endpoint analysis using a fixed-sequence step downward testing procedure to avoid the need for multiplicity adjustment. The first comparison was the 240 U versus placebo group. If the difference was statically significant ($p \leq 0.05$) in favor of the 240 U treated group then the second comparison of the 120 U versus placebo was performed. The final comparison was between the 120 U and 240 U groups.

The primary method for assessment of the differences between the treatment groups used the sponsor's full ANCOVA model with missing values replaced by the baseline value (equals "No effect"). There was no adjustment for multiple comparisons for the secondary and tertiary endpoints since the sponsor considered these exploratory analyses.

Primary Endpoint Analysis 240 Unit Dose-Placebo Using Different ANCOVA Models (Sponsor's Table)

14.2.1.2.1.1: Efficacy Data
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) - Total Score
Analysis of Covariance - Change From Baseline in Total Score
Control Visit 3 (Week 4)
ITT Population

Comparison Sequence: NT 201 (240U) - Placebo

Population	Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference LS-Mean (SE) (95% CI) NT 201 (240U)	Treatment Difference LS-Mean (SE) (95% CI) Placebo	LS-Mean Treatment Difference (95% CI)
Total	Missings Replaced by Baseline Value	Full Model	Treatment	<0.001	-7.3 (2.18) (-11.6,-3.0)	1.6 (2.28) (-2.9,6.2)	-9.0 (-12.0,-5.9)
			Gender	0.043			
			Age	0.800			
			Pre-Treatment	0.562			
			Baseline TWSTRS-Total Score	0.017			
			Pooled Center	0.351			
		Final Model	Treatment	<0.001	-10.3 (1.09) (-12.5,-8.1)	-1.7 (1.14) (-4.0,0.5)	-8.6 (-11.6,-5.6)
			Gender	0.040			
			Baseline TWSTRS-Total Score	0.008			
		Simple Model	Treatment	<0.001	-10.9 (1.10) (-13.1,-8.7)	-2.2 (1.15) (-4.5,0.1)	-8.7 (-11.8,-5.6)
	Observed Cases	Full Model	Treatment	<0.001	-7.4 (2.19) (-11.8,-3.1)	1.7 (2.29) (-2.8,6.2)	-9.1 (-12.2,-6.0)
			Gender	0.024			
			Age	0.803			
			Pre-Treatment	0.465			
			Baseline TWSTRS-Total Score	0.016			
			Pooled Center	0.365			
		Final Model	Treatment	<0.001	-10.5 (1.10) (-12.7,-8.4)	-1.8 (1.15) (-4.0,0.5)	-8.8 (-11.8,-5.7)
			Gender	0.026			
			Baseline TWSTRS-Total Score	0.007			

Comparison Sequence: NT 201 (240U) - Placebo

Population	Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (240U)	Treatment Difference: LS-Mean (SE) (95% CI) Placebo	Treatment Difference: LS-Mean Treatment Difference (95% CI)
Total	Observed Cases	Simple Model	Treatment	<0.001	-11.2 (1.11) (-13.4,-9.0)	-2.3 (1.17) (-4.6,0.0)	-8.9 (-12.1,-5.7)

[a] Missings Replaced by Baseline Value = Missing value was set to a zero effect (change=0);
Observed Cases = No replacement for missing values;
Missings Replaced by Treatment Group Mean Value = Missing value replaced by mean of the corresponding treatment group.
[b] Full Model = Included all adjusting variables (used for confirmatory testing);
Final Model = Included adjusting variables with an influence of p <= 0.2 in the full model (backward selection);
Simple Model = Included only the treatment effect (used as sensitivity analyses).
Source Data: Listing 16.2.2.3.3.2
Data Extraction: 20MAY2008

Table Generation: 19NOV2008 11:18

Primary Endpoint Analysis 120 Unit Dose-Placebo Using Different ANCOVA Models (Sponsor's Table)

14.2.1.2.1.1: Efficacy Data
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) - Total Score
Analysis of Covariance - Change From Baseline in Total Score
Control Visit 3 (Week 4)
ITT Population

Comparison Sequence: NT 201 (120U) - Placebo

Population	Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (120U)	Treatment Difference: LS-Mean (SE) (95% CI) Placebo	Treatment Difference: LS-Mean Treatment Difference (95% CI)
Total	Missings Replaced by Baseline Value	Full Model	Treatment	<0.001	-10.8 (2.11) (-15.0,-6.6)	-3.3 (2.20) (-7.6,1.1)	-7.5 (-10.4,-4.6)
			Gender	0.449			
			Age	0.408			
			Pre-Treatment	0.345			
			Baseline TWSTRS-Total Score	0.125			
			Pooled Center	0.656			
		Final Model	Treatment	<0.001	-9.8 (1.01) (-11.8,-7.8)	-2.3 (1.04) (-4.3,-0.2)	-7.5 (-10.4,-4.7)
			Baseline TWSTRS-Total Score	0.085			
		Simple Model	Treatment	<0.001	-9.9 (1.02) (-11.9,-7.9)	-2.2 (1.05) (-4.3,-0.1)	-7.7 (-10.6,-4.8)
	Observed Cases	Full Model	Treatment	<0.001	-10.7 (2.13) (-15.0,-6.5)	-3.2 (2.22) (-7.5,1.2)	-7.6 (-10.5,-4.6)
			Gender	0.397			
			Age	0.384			
			Pre-Treatment	0.405			
			Baseline TWSTRS-Total Score	0.120			
			Pooled Center	0.700			
		Final Model	Treatment	<0.001	-9.9 (1.02) (-12.0,-7.9)	-2.3 (1.06) (-4.4,-0.2)	-7.6 (-10.5,-4.7)
			Baseline TWSTRS-Total Score	0.082			
		Simple Model	Treatment	<0.001	-10.0 (1.03) (-12.0,-8.0)	-2.3 (1.07) (-4.4,-0.2)	-7.7 (-10.7,-4.8)

[a] Missings Replaced by Baseline Value = Missing value was set to a zero effect (change=0);
Observed Cases = No replacement for missing values;
Missings Replaced by Treatment Group Mean Value = Missing value replaced by mean of the corresponding treatment group.
[b] Full Model = Included all adjusting variables (used for confirmatory testing);
Final Model = Included adjusting variables with an influence of p <= 0.2 in the full model (backward selection);
Simple Model = Included only the treatment effect (used as sensitivity analyses).
Source Data: Listing 16.2.2.3.3.2
Data Extraction: 20MAY2008

Table Generation: 19NOV2008 11:18

14.2.1.2.1.1: Efficacy Data
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) - Total Score
Analysis of Covariance - Change From Baseline in Total Score
Control Visit 3 (Week 4)
ITT Population

Comparison Sequence: NT 201 (120U) - Placebo

Population	Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (120U)	Treatment Difference: LS-Mean (SE) (95% CI) Placebo	Treatment Difference: LS-Mean Treatment Difference (95% CI)
Total	Missings Replaced by Treatment Group Mean Values	Full Model	Treatment	<0.001	-10.7 (2.11) (-14.9,-6.5)	-3.2 (2.19) (-7.5,1.2)	-7.5 (-10.4,-4.6)
			Gender	0.353			
			Age	0.391			
			Pre-Treatment	0.422			
			Baseline TWSTRS-Total Score	0.109			
			Pooled Center	0.697			
		Final Model	Treatment	<0.001	-10.0 (1.01) (-12.0,-8.0)	-2.4 (1.04) (-4.5,-0.4)	-7.5 (-10.4,-4.7)
			Baseline TWSTRS-Total Score	0.073			
		Simple Model	Treatment	<0.001	-10.0 (1.02) (-12.0,-8.0)	-2.3 (1.04) (-4.4,-0.3)	-7.7 (-10.5,-4.8)

[a] Missings Replaced by Baseline Value = Missing value was set to a zero effect (change=0);
Observed Cases = No replacement for missing values;
Missings Replaced by Treatment Group Mean Value = Missing value replaced by mean of the corresponding treatment group.
[b] Full Model = Included all adjusting variables (used for confirmatory testing);
Final Model = Included adjusting variables with an influence of p <= 0.2 in the full model (backward selection);
Simple Model = Included only the treatment effect (used as sensitivity analyses).
Source Data: Listing 16.2.2.3.3.2
Data Extraction: 20MAY2008
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Primary Endpoint Analysis 120-240 Unit Using Different ANCOVA Models (Sponsor's Table).

14.2.1.2.1.1: Efficacy Data
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) - Total Score
Analysis of Covariance - Change From Baseline in Total Score
Control Visit 3 (Week 4)
ITT Population

Comparison Sequence: NT 201 (120U) - NT 201 (240U)

Population	Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (120U)	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (240U)	Treatment Difference: LS-Mean Treatment Difference (95% CI)
Total	Missings Replaced by Baseline Value	Full Model	Treatment	0.447	-9.2 (2.27) (-13.7,-4.7)	-10.5 (2.25) (-14.9,-6.0)	1.3 (-2.1,4.6)
			Gender	0.128			
			Age	0.222			
			Pre-Treatment	0.747			
			Baseline TWSTRS-Total Score	0.021			
			Pooled Center	0.093			
		Final Model	Treatment	0.449	-8.3 (1.41) (-11.1,-5.5)	-9.6 (1.37) (-12.3,-6.8)	1.3 (-2.1,4.6)
			Gender	0.125			
			Baseline TWSTRS-Total Score	0.033			
			Pooled Center	0.097			
		Simple Model	Treatment	0.563	-9.9 (1.25) (-12.4,-7.4)	-10.9 (1.23) (-13.3,-8.5)	1.0 (-2.5,4.5)
	Observed Cases	Full Model	Treatment	0.425	-9.3 (2.28) (-13.8,-4.8)	-10.7 (2.27) (-15.2,-6.2)	1.4 (-2.0,4.8)
			Gender	0.097			
			Age	0.182			
			Pre-Treatment	0.784			
			Baseline TWSTRS-Total Score	0.018			
			Pooled Center	0.138			

[a] Missings Replaced by Baseline Value = Missing value was set to a zero effect (change=0);
Observed Cases = No replacement for missing values;
Missings Replaced by Treatment Group Mean Value = Missing value replaced by mean of the corresponding treatment group.
[b] Full Model = Included all adjusting variables (used for confirmatory testing);
Final Model = Included adjusting variables with an influence of p <= 0.2 in the full model (backward selection);
Simple Model = Included only the treatment effect (used as sensitivity analyses).
Source Data: Listing 16.2.2.3.3.2
Data Extraction: 20MAY2008
Table Generation: 19NOV2008 11:18

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14.2.1.2.1.1: Efficacy Data
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) - Total Score
Analysis of Covariance - Change From Baseline in Total Score
Control Visit 3 (Week 4)
ITT Population

Comparison Sequence: NT 201 (120U) - NT 201 (240U)

Population	Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (120U)	Treatment Difference: LS-Mean (SE) (95% CI) NT 201 (240U)	LS-Mean Treatment Difference (95% CI)
Total	Observed Cases	Final Model	Treatment	0.425	-8.2 (1.42) (-11.1,-5.4)	-9.6 (1.39) (-12.4,-6.9)	1.4 (-2.0,4.7)
			Gender	0.087			
			Age	0.197			
			Baseline TWSTRS-Total Score	0.022			
			Pooled Center	0.110			
		Simple Model	Treatment	0.512	-10.0 (1.26) (-12.5,-7.5)	-11.2 (1.25) (-13.6,-8.7)	1.2 (-2.3,4.7)
	Missings Replaced by Treatment Group Mean Values	Full Model	Treatment	0.426	-9.4 (2.26) (-13.9,-5.0)	-10.8 (2.24) (-15.2,-6.3)	1.3 (-2.0,4.7)
			Gender	0.095			
			Age	0.143			
			Pre-Treatment	0.763			
			Baseline TWSTRS-Total Score	0.011			
			Pooled Center	0.136			
		Final Model	Treatment	0.427	-8.3 (1.41) (-11.1,-5.5)	-9.7 (1.37) (-12.4,-6.9)	1.3 (-2.0,4.7)
			Gender	0.086			
			Age	0.155			
			Baseline TWSTRS-Total Score	0.014			
			Pooled Center	0.108			
		Simple Model	Treatment	0.515	-10.0 (1.25) (-12.5,-7.5)	-11.2 (1.23) (-13.6,-8.7)	1.1 (-2.3,4.6)

[a] Missings Replaced by Baseline Value = Missing value was set to a zero effect (change=0);
Observed Cases = No replacement for missing values;
Missings Replaced by Treatment Group Mean Value = Missing value replaced by mean of the corresponding treatment group.
[b] Full Model = Included all adjusting variables (used for confirmatory testing);
Final Model = Included adjusting variables with an influence of p <= 0.2 in the full model (backward selection);
Simple Model = Included only the treatment effect (used as sensitivity analyses).
Source Data: Listing 16.2.2.3.3.2
Data Extraction: 20MAY2008
Table Generation: 19NOV2008 11:18

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CDTL Comment

The sponsor chose a backwards selection approach for model building with the significant p-value level for covariate selection set at p=0.2. The criteria for selecting variables for inclusion in the model are too lenient. The alpha level for selecting variables for inclusion in the model should have been set at ≤ 0.1 for exploration and 0.05 for the final inclusion criteria. In addition, most of the covariates did not have a strong biological justification for inclusion in the model. Although, gender meets criteria for model inclusion based on p-value, there is no biological reason to expect Xeomin works differently in women compared to men. CD preferentially affects women and more women were enrolled into study 408/1, which could account for the significant p value in the model selection criteria. The only two covariates that should be included in the model are in the final model are treatment group and baseline TWSTRS total score. The results for the simple model containing treatment as a variable is the most conservative (baseline total TWSTRS score could be included) analysis, which still demonstrates a statistically significant effect compared to placebo for the primary endpoint, using the pre-specified method of replacement of missing data (impute baseline value). The results for the 120 unit group demonstrated a similar statically significant difference compared to placebo (p=≤ 0.001). regardless of the variables included in the model or the method for replacing missing data the difference between the 120 Unit and 240 Units groups with respect to the primary endpoint was not statistically significant (p= 0.425 observed full model to p= 0.563 simple model, missing replaced by baseline value).

Subgroup Analysis-Gender

Text Table 22: 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 by Group Mean Value)

(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

Pre-treated Versus Naïve Patients

Text Table 20: Mean Change from Baseline to Visit 3 in TWSTRS-Total Score in Total ITT Population, Treatment-naïve and Pre-treated Subjects (Missing Values Replaced by the Subject's Baseline Value)

(Sub)Group	240 U group	120 U group	Placebo group
Total ITT population	-10.9 (11.72) (N=81)	-9.9 (10.35) (N=78)	-2.2 (7.30) (N=74)
Treatment-Naïve Subjects	-10.0 (9.16) (N=31)	-11.9 (11.12) (N=31)	-2.0 (5.97) (N=28)
Pre-Treated Subjects	-11.44 (13.12) (N=50)	-8.53 (9.71) (N=47)	-2.4 (8.07) (N=46)

Source: Tables 14.2.1.1.6.1
U=Units

CDTL Comment:

The sponsor presented data that suggests the influence of gender on the ANCOVA analysis of the primary outcome regardless of the method of imputation favors a gender specific effect supporting the superiority of the 240 unit dose over the 120 unit dose. Although, the pretreated female group appears to have a significantly greater response to the 240 unit dose compared to the 120 unit dose. The opposite is true for pretreated men in the 240 and 120 unit groups who seem to do worse than do treatment naïve women. The influence of pretreated women on the trial results is likely due to the fact that this subgroup makes up the largest cohort the trial. The effect of gender is also observed in the total ITT population, which

suggests the overall treatment effect is driven by the size of the pretreated, female subgroup. Among the pre-treated patients, there was a dose related improvement in the total TWSTRS score. There was no relationship between dose and Total TWSTRS score in the treatment naïve group.

Duration of CD at Baseline (Sponsor's Table)

Text Table 10: Duration since First Diagnosis and Estimated Duration of Cervical Dystonia in Subgroups of Treatment-Naïve and Pre-Treated Subjects (ITT Population)

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

Source: Table 14.1.3.2
CD=Cervical Dystonia, SD=Standard Deviation, U=Units

CDTL Comment

The majority of patients enrolled in the study were pre-treated reporting the largest numerical difference using the total TWSTRS score favoring the 240 group over the 120 unit treated group. Pre-treated patients also had a significantly longer duration of disease. However, the baseline disease total TWSTRS scores did not differ significantly between the pre-treated and naïve patients groups. The 240 unit and 120 unit groups also had similar baseline TWSTRS scores.

Secondary Endpoints

TWSTRS Subscale Scores (Sponsor Table)

Text Table 29: Mean Changes from Baseline to Visit 3 in TWSTRS Subscores, Summarized for Treatment-naïve and Pre-treated Subjects (ITT Population; Missing Values Replaced by Baseline Value)

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

Source: 14.2.2.2.1.1, 14.2.3.2.1.1, 14.2.4.2.1.1
LS= Least Square, CI =Confidence Interval, U=Units

Patient Evaluation of Global Response at The Final Visit (Sponsor Table)

Text Table 30 Patient Evaluation of Global Response at Final Visit (ITT Population)

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

Source: 14.2.5.1.1
U=Units

CDTL Comment:

The sponsor selected the individual components (subscales) of the TWSTRS scale as the secondary endpoints. This reviewer does not believe the individual TWSTRS subscale scores add significantly to the evidence supporting effectiveness of NT 201 since, one expects the TWSTRS subscale scores to follow change in the total score. The sponsor included a statement in the indication that Xeomin injections are associated with reduced pain. The claim for reduced pain is supported by the change in the TWSTRS Pain subscale score. A claim for reduced pain was granted to the other approved botulinum toxin type A products for the CD indication. Although, in the Dysport (phase 3) trial the sponsor used the visual analogue scale (VAS) for pain to demonstrate a significant improvement in pain that was not demonstrated using the TWSTRS Pain subscale. Botox, the sponsor's active comparator in study 0013 also

used the VAS to support a claim for reduced pain. It seems reasonable to grant the claim for pain relief in the Xeomin (NT 201) label since significant (statistically) improvement was reported in the NT 201 pivotal trial (except for the 240 unit naïve subgroup p=0.185).

The Patient Evaluation of Global Response (PEGR) can be a useful indicator of the importance patients place on the change in symptoms they experience after treatment with study medication. The sponsor chose to only measure the PEGR at the final visit scheduled, which could be up to 20 weeks post-injection or at the time of repeat injection. It may seem impressive that 43/81 (53% for 240 unit) or 38/78 (49% 120 unit) still reported feeling at least moderately improved at the final visit (whenever that took place). The trial should have incorporated a PEGR at the primary endpoint visit 3 (Week 4) to include the possibility that the benefit gained by reducing CD symptoms was off-set by peak dose adverse effects.

Tertiary Endpoints

Duration of Treatment Effect in CD

Text Table 35: Duration of Treatment Effect in Total ITT Population, Treatment-naïve and pre-treated Subjects

Comparison	Subgroup	Median [95% CI]			p-value
		240 U group N=81	120 U group N=78	Placebo group N=74	
240 U vs. Placebo	Total ITT population	84.0 [71.0;88.0]		61.5 [57.0;71.0]	0.032
	Treatment-naïve Subjects	88.0 [75.0;112.0]		60.0 [57.0;122.0]	0.478
	Pre-treated Subjects	78.0 [65.0;87.0]		63.0 [57.0;71.0]	0.079
120 U vs. Placebo	Total ITT population		85.0 [71.0;91.0]	61.5 [57.0;71.0]	0.052
	Treatment-naïve Subjects		85.0 [71.0;94.0]	60.0 [57.0;122.0]	0.640
	Pre-treated Subjects		85.0 [58.0;92.0]	63.0 [57.0;71.0]	0.053
240 U vs. 120 U	Total ITT population	84.0 [71.0;88.0]	85.0 [71.0;91.0]		0.973
	Treatment-naïve Subjects	88.0 [75.0;112.0]	85.0 [71.0;94.0]		0.347
	Pre-treated Subjects	78.0 [65.0;87.0]	85.0 [58.0;92.0]		0.514

Source: Table 14.2.9.1.1
CI =Confidence Interval, U=Units

CDTL Comment:
The duration of treatment effect was defined using patients and investigator generated data. Patients could receive follow up injections with the blinded fixed dose of NT 201 when they felt the need, the site investigator confirmed that their TWSTRS-Total score ≥ 20 and if at least 6 weeks had passed since the last injection. The duration of the treatment effect was not significantly different between the 120 unit and 240 unit treatment groups. A common clinical believe is that high doses of botulinum toxin are associated with a longer duration of action and a higher number of peak dose side effects.

Study 0013 (CD): Active Comparison to Botox
Study 0013 was a Phase 3, randomized, double-blind, active-controlled study comparing the effect of NT 201 to Botox. Subjects were randomized (1:1) to receive a single IM injection of NT 201 or Botox at the same dose as the most recent dose of Botox (total dose 70 to 300 U).

Subjects were followed for up to 16 weeks. The primary efficacy variable was the change from Baseline to Week 4 in TWSTRS-Severity score.

The secondary efficacy variables were the change from Baseline to Day 28 and Baseline to the Final Visit for the TWSTRS Pain subscore, TWSTRS-Factorial scores, visual analog scale (VAS) pain score(100 mm), and PEGR; Change in TWSTRS-Severity score from Baseline to the Final Visit; percent of subjects with response to treatment (defined as an improvement in TWSTRS Severity score of >20% from Baseline) at Day 28; time to onset and time to waning of treatment effect after injection; duration of effect (defined as the interval between time of injection and the point at which the TWSTRS-Severity score was at least 80% of the Baseline value); and Investigator's global assessment of efficacy.

Trial entry criteria included adults up to 75 years of age with rotational spasmodic torticollis and the following TWSTRS scores: Severity ≥10, Severity (rotation) ≥2, and severity score for rotation greater than score for laterocollis, anterocollis or retrocollis. Only subjects pre-treated with a stable therapeutic dose of Botox (defined as at least two injections into the same muscles, in the same total doses and volumes, with any time interval between injections differing by ≤3 weeks) were eligible to participate. The most recent Botox injection was required to be at least 10 weeks before randomization.

Patient Disposition and Handing of Missing Data

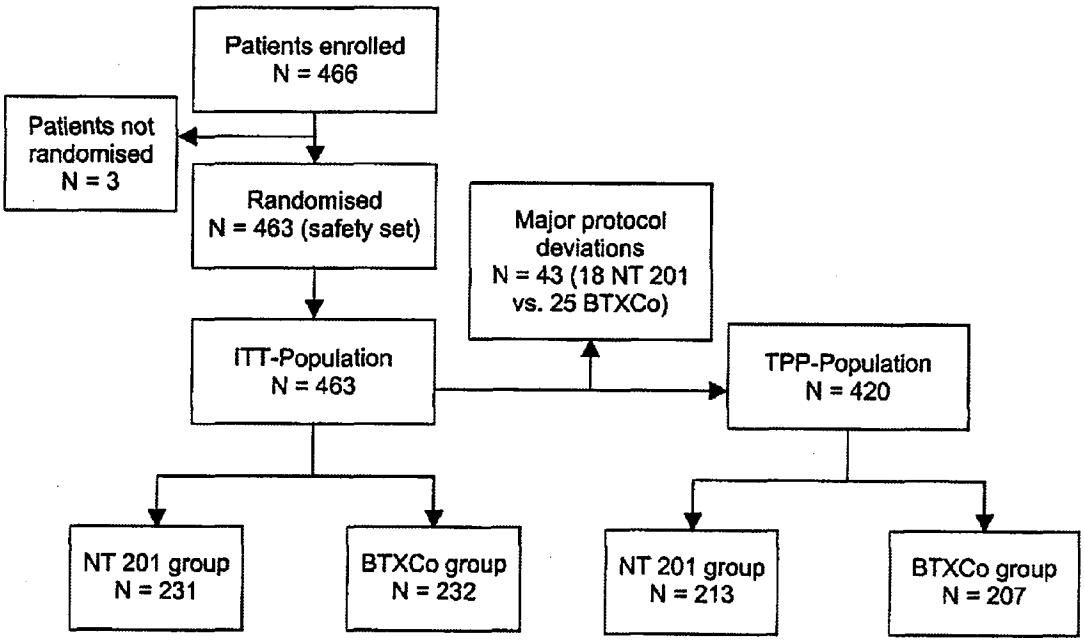
Since the primary efficacy variable was recorded 28 days after treatment, the amount of missing data in both groups was low and no missing data was imputed for the analysis of the primary efficacy variable. In order to perform a sensitivity analysis regarding the influence of missing data, two strategies were to be applied:

- In both treatment groups all missing values of the primary efficacy variable were set to a zero effect (change=0), thus assuming no effect had occurred;
- All missing values of the primary efficacy variable were to be set to the mean value in the respective treatment group calculated for this visit, thus assuming an average effect for these patients.

Patient Disposition

The final ITT population included a total of 463 patients therefore none of the randomized patients discontinued before the trial ended.

Text Figure 1 Patient Disposition (all study patients, N=466)



Data source: Tables 14.1.2.1.1.1 - 4
N = number of patients, ITT = intention-to-treat, TPP = treated per protocol

Statistical Analysis Plan Including the Test Procedure for Non-inferiority

The mean difference between the changes in the TWSTRS - Severity score from baseline was defined as mean of change (NT 201) minus mean change (Botox). Least square means were to be used to calculate the empirical difference between the treatments.

The sponsor's analysis plan would allow the conclusion of non-inferiority if the upper 95% confidence bound of the mean difference between the treatment effects NT 201 compared to Botox (changes in the TWSTRS - Severity score from baseline) was lower than 5%=1.3 points on the TWSTRS - Severity score. NT 201 could be declared superior to Botox, if the upper 95% confidence bound was less than zero. This test procedure held the overall alpha level to 2.5/%.

The non-inferiority study was conducted and analyzed without prior discussion with the FDA. The sponsor did not seek agreement upon the estimate of the NI margins (M1 or M2) for the active comparator (Botox). Furthermore, the design did not incorporate a placebo group to provide conformation that the active comparator or NT 201 was superior to placebo in this trial. The lack of a placebo group and the decision not to use the total TWSTRS score as the primary endpoint for comparison to NT 201 makes it difficult to consider the results of this trial supportive for a claim for effectiveness in CD.

Three models were to be presented in the SAP:

- the full model including all variables and covariates influencing the primary efficacy variable,

- the final model which was to be applied in the confirmatory testing including only those adjusting variables that in a backward selection procedure with significant p=0.2.

- the simple model including the treatment effect only.

Primary Endpoint

Text Table 12 Analysis of TWSTRS - Severity Score at Control Visit (ITT, N=463)

Model	Mean NT 201	Std. Error	Mean BTXCo	Std. Error	Difference NT201 minus BTXCo	Std. Error of Difference	Lower 95% Confidence Limit	Upper 95% Confidence Limit	2-Sided p-Value on Difference
Final Model	-6.84	0.30	-6.54	0.30	-0.29	0.35	-0.98	0.40	0.4060
Full Model	-5.38	1.48	-4.78	1.47	-0.60	0.47	-1.53	0.33	0.2074
Simple Model	-6.55	0.26	-6.32	0.27	-0.23	0.38	-0.97	0.51	0.5367

Data source: Tables 14.2.2.3.1.53 - 54

The sponsor concluded that NT 201 in non-inferior to Botox for the treatment of CD.

Dosing and Duration of Effect

The total amount of study medication (median) used for all muscles treated in the baseline injection session was 120.0 vs. 122.5 units in the NT 201 and Botox groups, respectively. This was in accordance with the recommended amount of total units per session stated in the protocol with a planned range between 70 and 300 units and the doses administered in this study were comparable to data from the literature (156 U of Botox (16).

The median time until waning of effect was at 10.0 weeks following NT 201 versus 11.0 weeks following Botox. Thus, the effect duration (median) was reported as 110 days in the NT 201 group versus 109.5 days in the Botox group. Treatment duration is within the range reported in other trials with Botox: 109 days (58), 107 days (46), 87.5 days (57), 89.2 days (59), and 63 days (13).

CDTL Comment

The sponsor considers study 0013, an active comparator study, a supporting trial for the primary efficacy study (433/1). The active comparator study has two problems, first, it used the TWSTRS severity subscale as the primary endpoint, which differs from the Total TWSTRS score used in the primary efficacy study. Second, the Non-Inferiority (NI) margins were not discussed with the agency prior to initiating the trial. Furthermore, the sponsor does not provide an adequate description (references) of the studies that were used to estimate the NI margin and confidence limits. The calculation of the NI margins may have come from trials that were not adequately powered or the severity subscale, which is often a secondary endpoint in CD trials, may have not have included methods to adjust for multiple comparisons.

Other Reviewers Conclusions
Both the primary DNP reviewer and the statistical reviewer concur that that Xeomin is effective for the treatment of CD at both the 120 unit and 240 unit dose. The 240 unit dose did not demonstrate it was statistically superior to the 120 unit dose for the primary or secondary endpoints.

CDTL Efficacy Conclusion
I agree that the sponsor met the regulatory requirement for effectiveness for the CD indication for the 120 (b) (4) of Xeomin. The placebo controlled CD study (408/1) is supported by a positive efficacy outcome in the placebo controlled trial in blepharospasm (433/1). Both CD and BSP are forms of focal dystonia therefore, it is reasonable to allow the results of their respective clinical trials to support each other. The non-inferiority trials in CD (0013) and BSP (0003) are not adequately design, both used different primary efficacy endpoints compared to their corresponding placebo controlled studies therefore, in my opinion the non-inferiority trials can not adequately support an efficacy claim in CD or BSP.

Blepharospasm
The blepharospasm application primarily relies on the study 433/1 for evidence of effectiveness. The ongoing open label extension (48 weeks) of study 433 provided evidence supporting the long-term safety of Xeomin. The 120-day safety update contains safety data from the first 81 patients to complete 48 weeks of follow up.
Issues that can potentially effect the indication or approvability for blepharospasm are the lack of a fixed dose efficacy trial and the omission of treatment naive patients in the sponsor's clinical trials. The sponsor was aware that these issues could impact the approvability or potentially restrict the claim for blepharospasm (see the meeting discussion below).

During a face to face meeting with the sponsor, the agency was clear in stating their position that the sponsor must provide data in treatment naïve BSP patients to support an indication that did not limit the use of Xeomin to patients who were previously treated with another botulinum toxin product. In addition, the agency required a fixed dose clinical trial in patient with blepharospasm prior to approval.

Excerpts from the June 11, 2007 Sponsor Meeting Minutes

"Question 3 (b) (4) (b) (4) (b) (4)

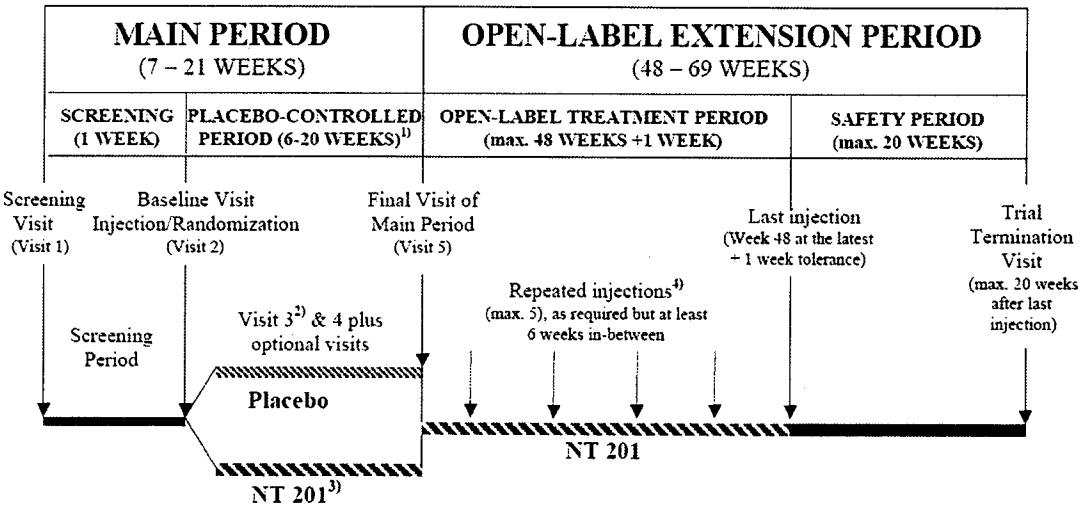
FDA response: (b) (4) (b) (4) (b) (4)

(b) (4)

Blepharospasm Primary Efficacy - Study 433/1

Study 0433/1 (completed) is the primary efficacy trial of NT 201 for the blepharospasm application. The trial design was a randomized, double-blind, placebo-controlled clinical trial. 109 subjects were randomized to NT 201 or placebo in an approximate ratio of 2:1. Only subjects with a confirmed clinical diagnosis of blepharospasm who were previously treated with onabotulinumtoxinA (Botox®) and showed a consistent and satisfactory therapeutic response to Botox for at least 2 injection series were eligible. Subjects could receive up to 50 units of NT 201 per eye, the total dose was 100 units. The selection of dose and injection sites was determined individually for each subject, based on the last Botox injection sessions prior to study entry. The sponsor refers to the double blind portion of study 433 as the Main Period. The Main Period consists of single injection session followed by 6 to 20 weeks post-treatment phase, depending on duration of treatment effect. If a new injection was required, the patient was transitioned to open label extension (OLEX) period lasting 48-69 weeks.

Text Figure 1: Study Design (Main Period and OLEX Period)



1) individual duration of placebo-controlled period per patient – see 9.1.3.1 for determination method
2) telephone contact Day 28-35
3) NT 201 as in the previous two injection sessions
4) control visits 6 weeks after each injection

Primary Endpoint

- The Primary Efficacy variable was the change from baseline in the Jankovic Rating Scale (JRS) Severity sub-score (assessed by a blinded Independent Rater) at Visit 4 (Week 6 ± 3 days) after injection Missing values were replaced using LOCF.

CDTL Comment

The JRS has been used as a primary endpoint in at least 3 peer reviewed clinical trial including one by Dr. Jankovic. The sponsor did not present evidence that the scale has undergone clinometric testing to demonstrate the validity and reliability of the JRS. The Blepharospasm Disability Index (BSDI) was chosen as a secondary endpoint because the JRS rates the frequency and severity of BSP but it does not capture functional impairment.

Secondary efficacy variables:

- Change from baseline in the JRS Severity sub-score (assessed by Subject Diary) at Visit 4 after injection (median score of previous 7 days)

- Change from baseline in Blepharospasm Disability Index [BSDI] at Visit 4 after injection

- Patient Evaluation of Global Response [PEGR] at Final Visit (Visit 5) of the Main Period

Tertiary efficacy variables:

- Change from baseline in the JRS Severity and Frequency sub-scores and in the JRS sum-score (assessed by a blinded Independent Rater) at all other post-baseline visits (except Visit 4 for JRS Severity sub-score).

Study Medication

The subsequent OLEX Period was open-label, non-controlled, with multi-center enrollment. An adjustment of dose was permitted only up to a maximum of 50 U NT 201 per eye. The OLEX Period consists of a treatment section (up to 48 weeks [+ 1 week] with a maximum of 5 injection sessions) and a safety observation section (up to 20 weeks [± 3 days] after the last injection of study medication). The complete OLEX Period covers at least 48 weeks (+ 1 week) up to a maximum of 69 weeks (± 3 days), depending on the time of the last injection of study medication. The minimum interval between two injections was always at least 6 weeks.

Statistical Analysis Plan (SAP)

The sponsor did not finalize the SAP prior to initiating the trial. The SAP was finalized after the Blinded Review Meeting (BRM) the followed completion of The Main Period and prior to unblinding of the data from the Main Period.

Safety Monitoring

An independent Data Safety Monitoring Board [DSMB] monitored both trial periods. The primary purpose of the DSMB was to monitor the overall safety of study subjects and make recommendations regarding subject withdrawals, dose modifications and/or study suspension. Members of the DSMB included outside experts in blepharospasm, an unblinded statistician

not involved with the analysis of the trial data (not a Merz employee) and representatives of Merz were present at the DSMB meetings. The unblinded statistician presented blinded data to the DSMB.

Patient Demographic Information

Text Table 7: Demographic Data (ITT Population)

Parameter	NT 201 group N = 75	Placebo group N = 34	Total N = 109
Gender (n, %)			
Male	26 (34.7)	12 (35.3)	38 (34.9)
Female	49 (65.3)	22 (64.7)	71 (65.1)
Race (n, %)			
American Indian or Alaskan Native	0	0	0
Asian	6 (8.0)	0	6 (5.5)
Black or African American	2 (2.7)	2 (5.9)	4 (3.7)
Hispanic or Latino	8 (10.7)	1 (2.9)	9 (8.3)
Native Hawaiian or other Pacific Islander	0	0	0
White	59 (78.7)	31 (91.2)	90 (82.6)
Other	0	0	0
Smoking (n, %)			
Non-smoker	52 (69.3)	21 (61.8)	73 (67.0)
Smoker	10 (13.3)	2 (5.9)	12 (11.0)
Ex-smoker	13 (17.3)	11 (32.4)	24 (22.0)
Age (years)			
Mean (SD)	61.5 (10.95)	62.6 (8.70)	61.9 (10.27)
Median	61.0	63.0	62.0
Height (in)			
Mean (SD)	65.0 (3.73)	65.0 (4.04)	65.0 (3.81)
Median	65.0	64.0	64.8
Weight (lb)			
Mean (SD)	172.8 (39.88)	171.0 (38.71)	172.2 (39.35)
Median	162.0	163.5	162.0
Body Mass Index [a]			
Mean (SD)	28.6 (5.51)	28.1 (6.09)	28.5 (5.67)
Median	26.9	27.0	26.9

[a] Body Mass Index [BMI] was calculated according to the formula: BMI=(Weight(lb) / Height(in)^2) x 703;
SD=standard deviation
Source: Table 14.1.3.1.1

Baseline Disease Characteristics

The demographic profile of the patients enrolled in study 433/1 was consistent with the gender, age and racial characteristics of patients affected by BSP. There were no other significant imbalanced in the demographic features of the trial population.

Text Table 10: History of Benign Essential Blepharospasm (ITT Population)

	NT 201 group N=75	Placebo group N=34	Total N=109
Diagnosis of BEB (n, %)			
Yes	74 (98.7)	34 (100.0)	108 (99.1)
No	1 (1.3)	0	1 (0.9)
Duration Since First Diagnosis of BEB (months)			
Mean (SD)	58.3 (58.24)	69.5 (63.54)	62.0 (59.86)
Median	42.3	46.0	44.7
Estimated Duration of BEB (months)			
Mean (SD)	96.9 (75.67)	123.9 (113.51)	105.3 (89.55)
Median	84.0	84.0	84.0
Secondary BEB (n, %)			
No	75 (100.0)	34 (100.0)	109 (100.0)
Apraxia of Lid Opening (n, %)			
Yes	0	0	0
No	75 (100.0)	34 (100.0)	109 (100.0)
Previous Eyelid Surgery (n, %)			
Yes	10 (13.3)	6 (17.6)	16 (14.7)
No	65 (86.7)	28 (82.4)	93 (85.3)
Pre-existing Ocular Diseases (n, %)			
Yes	22 (29.3)	8 (23.5)	30 (27.5)
No	53 (70.7)	26 (76.5)	79 (72.5)
Dystonia in Other Muscles (n, %)			
None	51 (68.0)	19 (55.9)	70 (64.2)
Facial	18 (24.0)	7 (20.6)	25 (22.9)
Cervical	6 (8.0)	4 (11.8)	10 (9.2)
Perioral	5 (6.7)	3 (8.8)	8 (7.3)
Mandibular	3 (4.0)	4 (11.8)	7 (6.4)
Other - bilateral hand	1 (1.3)	0	1 (0.9)
Other - cranial dystonia	1 (1.3)	0	1 (0.9)
Other - dysphonia	1 (1.3)	0	1 (0.9)
Other – lingual	0	1 (2.9)	1 (0.9)
Other – Meige	0	1 (2.9)	1 (0.9)
Other - mild dysphonia	1 (1.3)	0	1 (0.9)
Other - mild spasmodic dysphonia (no treatment needed)	0	1 (2.9)	1 (0.9)
Other - spasmodic dysphonia but mild	0	1 (2.9)	1 (0.9)

BEB=benign essential blepharospasm; SD=standard deviation
Source: Table 14.1.3.2

CDTL Comment

There were no significant differences between the two treatment groups with respect to the overall disease characteristics however; most patients had dystonia affecting other body areas. Most patients appear to have dystonia affecting other craniofacial muscles and a few patients had either segmental or perhaps even hemi-dystonia. The study population can not truly be described a having Benign Essential Blepharospasm when in fact the majority of patients appear to have Blepharospasm as part of a broader craniofacial dystonia. I support the recommendation made by he primary reviewer (Dr. Bergmann) changing the sponsor's indication to include patients with Blepharospasm and not Benign Essential Blepharospasm, which is a specific and an anatomically, a more limited focal dystonia syndrome.

Results- Primary End Point-JRS Severity Subscale (Sponsor Table)

14.2.1.2.2.1: Efficacy Data
Jankovic Rating Scale (JRS) Severity Subscale - Independent Rater Assessment
Analysis of Covariance - Change from Baseline in JRS Severity Subscore
Control Visit 4 (Week 6)
ITT Population

Missing Data Handling Method [a]	Model[b]	Variables	p-Value	Treatment Difference LS-Mean (SE) (95% CI) NT 201	Treatment Difference LS-Mean (SE) (95% CI) Placebo	LS-Mean Treatment Difference (95% CI)
Missings Replaced by LOCF	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			
	Simple Model	Treatment	<0.001	-0.8 (0.13) (-1.1,-0.6)	0.2 (0.19) (-0.2,0.6)	-1.0 (-1.5,-0.6)
Observed Cases	Full Model	Treatment	<0.001	-0.7 (0.12) (-1.0,-0.5)	0.2 (0.18) (-0.2,0.5)	-0.9 (-1.4,-0.5)
		Gender	0.043			
		Age	0.081			
		Dose Group	0.877			
		Baseline JRS Severity Subscore	0.017			
		Pooled Center	0.074			
Observed Cases	Final Model	Treatment	<0.001	-0.8 (0.12) (-1.0,-0.5)	0.2 (0.18) (-0.2,0.5)	-0.9 (-1.4,-0.5)
		Gender	0.042			
		Age	0.072			
		Baseline JRS Severity Subscore	0.015			
		Pooled Center	0.071			
	Simple Model	Treatment	<0.001	-0.8 (0.13) (-1.1,-0.6)	0.2 (0.19) (-0.2,0.5)	-1.0 (-1.4,-0.5)
Missings Replaced by Treatment Group Mean Values	Full Model	Treatment	<0.001	-0.7 (0.12) (-1.0,-0.5)	0.2 (0.18) (-0.1,0.6)	-1.0 (-1.4,-0.5)
		Gender	0.064			
		Age	0.058			
		Dose Group	0.928			
		Baseline JRS Severity Subscore	0.003			
		Pooled Center	0.099			
	Final Model	Treatment	<0.001	-0.7 (0.12) (-1.0,-0.5)	0.2 (0.18) (-0.1,0.6)	-1.0 (-1.4,-0.5)
		Gender	0.070			
		Age	0.047			
		Baseline JRS Severity Subscore	<0.001			
		Pooled Center	0.067			
	Simple Model	Treatment	<0.001	-0.8 (0.13) (-1.0,-0.5)	0.2 (0.19) (-0.2,0.6)	-1.0 (-1.5,-0.6)

[a] Missings Replaced by LOCF = Missings were replaced by Last Observation Carried Forward;
Observed Cases = No replacement for missing values;
Missings Replaced by Treatment Group Mean Values = Missing value replaced by mean of the corresponding treatment group.
[b] Full Model = Included all adjusting variables (used for confirmatory testing);
Final Model = Included adjusting variables with an influence of p <= 0.2 in the full model (backward selection);
Simple Model = Included only the treatment effect (used as sensitivity analyses).
Note: Due to missing data for S206G regarding treatment with study medication, the subject was excluded from the analysis.
Source Data: Listing 16.2.2.3.1-2
Data Extraction: 14AUG2008
Table Generation: 26FEB2009 15:02

Key Secondary Endpoint

The Patient Evaluation of Global response (PEGR at the Final Visit (Sponsor Table)

Text Table 21: Distribution of the Patient Evaluation of Global Response at the Final Visit (ITT Population)

Category	NT 201 group N=75 n (%)	Placebo group N=34 n (%)
Complete abolishment of all signs and symptoms	6 (8.0)	2 (5.9)
Marked improvement	19 (25.3)	2 (5.9)
Moderate improvement	19 (25.3)	1 (2.9)
Slight improvement	7 (9.3)	1 (2.9)
Unchanged	10 (13.3)	12 (35.3)
Slight worsening	3 (4.0)	1 (2.9)
Moderate worsening	2 (2.7)	1 (2.9)
Marked worsening	4 (5.3)	10 (29.4)
Very marked worsening	3 (4.0)	1 (2.9)
Missing	2 (2.7)	3 (8.8)

Source: Table 14.2.8.1.1

CDTL Comment

Although the PEGR may be helpful in deciding obtaining some sense that patients valued the effects of NT 201 the rating should have taken place at week 6 (visit 4) in addition to the final visit.

Dose

The median total dose of NT 201 or Placebo administered to patients enrolled in this study was 61.25 U (n=108). This overall median total dose was calculated and used as threshold for dose group in the efficacy analysis. The overall mean total dose of NT 201 or Placebo administered was 64.8 U. The overall mean doses administered in the right and left eye were similar 32.5U and 32.3 U, respectively. The location of injections and dose per muscle was guided by the patient's previous experience receiving Botox injections. The sponsor did not monitor the dose of Xeomin given in each muscle. Instead, investigators were instructed to follow the pattern of the 2 most recent Botox injections. The sponsor then asked the investigators to plot the location of each injection on a standardized diagram of the face. The sponsor presented data for the percentage (min 10% of patients) of patient who received an injection at each location (locations were divided into regions). The data only provided information regarding the frequency of Xeomin injections for the pooled study population within a given region.

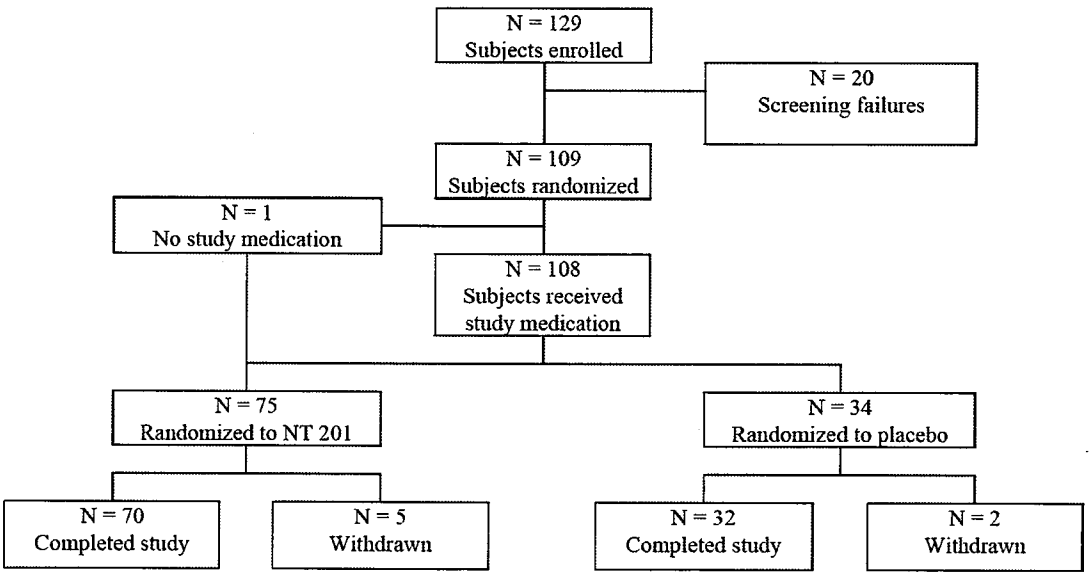
Text Table 39: Summary of Doses Administered (EFS Population)

				Total units of injection				
Treatment	**Side**	**N**	**Nmiss**	**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

Patient Disposition

Text Figure 3: Subject Disposition (All Enrolled Subjects) in the Main Period



Source Data: Table 14.1.1.6

There were relatively few patients who withdrew before completion of the trial in part, because the trial duration was short.

OLEX Phase of Study 433

Upon completion of Final Visit of the Main Period (Visit 5 / Week 6 to Week 20) patients immediately enter the OLEX Period. If a patient felt they needed a new injection and the JRS severity sub-score was ≥ 2 (rated by the blinded independent Investigator), the patient could be treated immediately with NT 201. Upon re-treatment, the patient enrolled in the OLEX

Period. If the severity score was lower than 2 points and the patient did not require a new injection at the Final Visit of the Main Period, the first Open-label Extension Period visit was only scheduled when the patient felt the need for a new injection and the score was 2 or more points. However, the OLEX Period visit could not take place later than 48 weeks (+ 1 week) after the Final Visit of the Main Period.

During the OLEX Period, all patients received NT 201 injections as required (agreed between patient and Investigator), but not sooner than 6 weeks after the last injection. This visit was documented as the first Injection Visit on the OLEX Phase.

Six weeks after each Injection Visit, the patient attended a Control Visit. If the patient received an injection at the Control Visit, this visit was considered the next Injection Visit.

Study 0433 OLEX Period was ongoing, as of June 25, 2009, over half of the 106 subjects (N=81) participating in the Study 0433/1 Main Period and 0433 OLEX Period had received 5 (37.7%) or 6 (34.0%) injections of NT 201. In these studies, the time between doses was variable, but was required to be at least six weeks. As of June 25, 2009, 93 of 106 subjects (87.7%) had been followed for 24 weeks or more after NT 201 exposure, and 81 of 106 subjects (76.4%) had been followed for 48 weeks or more.

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	49.4	66.9	40.7
(SD)	(21.41)	(22.32)	(14.55)
Median Dose	50	65	40
25th and 75th Quartile	36, 60	50, 86	30, 50
Minimum Dose	15	20	15
Maximum Dose	100	100	95

U: units.
Source: Table 1.2.2.1.1, Table 1.2.2.2.1.1, and Table 1.2.2.2.2.1, Section 5.3.5.3, Appendix H.

Dose

All of the subjects in the pooled BSP studies (the Study 0433/1 Main Period and Study 0003) received a single dose of NT 201. The mean and median NT 201 doses were higher in the Study 0433/1 Main Period than in Study 0003. This difference is directly related to the different doses specified in the study protocols. The maximum allowed dose in the Study 0433/1 Main Period was 100 U (50 U per eye) and in Study 0003, 70 U (35 U per eye). Although, the sponsor limited the dose of NT 201 in study 0003 to 35 units per eye the mean and median dose in study 433/1 (Main Phase) where the maximum total dose was 100 units (50 units per eye) also turned out to be 66.9 units (mean) and 65 units (median). This information together with the exposure experience supports a maximum recommended dose of 35 units per eye or a total dose of 70 units.

Duration of Treatment Effect
The duration of treatment effect was only assessed for patients in the Main Phase covering a single injection and follow up. There was no data presented by Merz for the duration of the treatment effect in subjects who received repeated injections in the OLEX Phase because the trial was still ongoing at the time of the 120-day Safety Update. For all subjects who experienced a treatment effect, the duration of treatment effect was defined as the time from injection (Day 0) to re-treatment. For all subjects who did not experience a treatment effect, duration of treatment effect was set to zero days. The Investigator's decision regarding the need for a new injection was based on evaluation of the JRS Severity subscore (assessed by the blinded Independent Rater).

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" (patient and investigator) 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 sub-score assessed by the blinded investigator (score must be $\geq$ 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 occurred 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.

Blepharospasm Study 0003:
The study was a Phase 3, randomized, double-blind, active-controlled study. There were 300 subjects in the ITT Population (148 in the NT 201 group and 152 in the Botox group) and 256 in the TPP Population. A total of 294 subjects completed the study. There were no U.S. sites in study 0003, all 42 enrolling centers were in Europe or Israel. Subjects were randomized (1:1) to receive a single IM dose of NT 201 or Botox (maximum dose $\leq$35 units per eye). The primary efficacy variable was the change in mean JRS sum-score from Baseline to Day 21. Secondary outcome variables were the change in JRS sum-score from Baseline to the Final Visit; change from Baseline in the mean total score for the Function Scale for Patients with BSP at the control and final visits; mean score for Patient Evaluation of Global Response at Day 21 and the Final Visit; Investigator's assessment of efficacy; and time to onset, time to waning.

Patients enrolled in study 0003 were required to have a documented stable therapeutic response to Botox as for the last two previous injection sessions directly before trial entry. Patients must have been injected at least two times in the same injection points, administering the same doses and volumes in the same interval thus resulting in the same satisfactory good therapeutic response evaluated by the investigator and the subjective assessment of the patient. Patients were required to have source documentation of the last two consecutive injection sessions prior to trial entry. The evaluation of previous, stable therapeutic response was judged by both the investigator and patient and included: no change in injection scheme with

respect to injected dose and volume, in time interval between injections (difference < 3 weeks), or in injection points. There were no botulinum toxin (Botox) naïve patients enrolled in the trial.

CDTL Comment
This active control study was designed to demonstrate non-inferiority (NI). Just as in the case for Cervical Dystonia, the sponsor did not seek agreement with the agency regarding the selection of the NI margin. Estimating the NI margin is a more difficult task for BSP because there is little experience using the JRS in clinical trial (most trials enrolled N≤ 30). The sponsor had corrected their original estimate of the relevant treatment difference on the JRS from 1 unit on the JRS to 0.8 units in a protocol amendment and increased the sample size. The SD was estimated to be 2.0 JRS units the sponsor provided no justification for the parameter estimates or justification of the sample size estimate. Therefore, the study is not able to support an effectiveness claim but the data may provide some information regarding dosing and safety.

Dose
Subjects in the NT 201 group received a mean total dose (both eyes) of 41 units, and subjects in the Botox group received a mean total dose of 42 units.

CDTL Comment
Merz provided a rationale as to why they could not provided data to support their dose recommendation in patients with BSP. They also provide their reasoning why toxin naïve patients with BSP could not be studied in clinical trials. The dosing recommendation for toxin naïve patients is based on the assumption that the dose in naïve patients should be less without any sense of what is an appropriate starting dose in toxin naïve patients treated with Xeomin for the first time.

Justification from Merz regarding the decision not to study treatment naïve patients with BSP.

> "The randomized, double-blind, placebo-controlled study (Study 0433/1), as well as the active comparator study (Study 0003), in BSP enrolled only subjects who had previously received a Botulinum toxin. Therefore, the database does not include subjects with BSP who were naïve to Botulinum toxin at the time of initial exposure to NT 201. The low incidence of BEB [Nakashima et al. 1995; Duffey et al. 1998; Defazio et al. 2001; Defazio and Livrea 2002; Nutt et al. 1988], general availability of various Botulinum toxins, and neurologic consensus that Botulinum toxins are effective for the treatment of BSP [Simpson et al 2008a] have combined to make enrollment of Botulinum-naïve subjects very difficult. In addition, the experience in CD (a disorder closely related to BSP, in that both are focal dystonias) indicates that subjects who are Botulinum-naïve have efficacy with NT 201 administration that is similar to the efficacy seen in subjects previously exposed to Botulinum toxin. As a general rule, the starting dose of NT 201 should be lower in patients who are receiving a Botulinum neurotoxin for the first time. (b) (4)
>
> (b) (4)

CDTL Comment

(b) (4) The sponsor should conduct an adequate and well controlled trial to determine the safe and effective dose range and dose interval that can be used to treate botulinum naïve BSP patients. The agency recommended the sponsor include treatment naïve BSP patients in their clinical trials well in advance of the BLA submission. The sponsor agreed to conduct a trial in BSP patients who were naïve to all botulinum toxin products, however they never submitted a study protocol or results to the agency. During the review of the BLA, (b) (4) In addition, they have committed (PMC#9) to conduct a trial examining the dose and safety of Xeomin in patients with BSP who are botulinum toxin naïve.

(b) (4) In addition, all currently approved botulinum toxin products have a statement in their label warning that the potency units of all botulinum toxin products are not interchangeable.

Other Reviewers

The primary DNP reviewer (Dr. Bergmann and the statistical reviewer (Dr. Siddiqi) agree that the sponsor has demonstrate Xeomin is effective for the treatment of BSP.

CDTL Efficacy Conclusion

I concur that the sponsor has provided adequate evidence that Xeomin is effective for the treatment of Blepharospasm.

I recommend restricting the Xeomin blepharospasm indication to patients previously treated with Botox. The starting dose should be 1.25-2.5 units with a maximum dose of 35 units per eye and 70 units in total. (b) (4)

(b) (4) The location of Xeomin injections should be guided by the patient's previous experience receiving Botox injections.

10. Safety

Table of Studies Contributing To the Sponsor's Safety Database (Adapted from Merz)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2	BTC 60201-9801	5.3.5.1	Dose-finding study to determine the therapeutically relevant dose in comparison to the therapeutically effective dose of Botox	Randomized open-label active control multicenter with stepwise inclusion of patients	Patients received either: NT 201 10/20 U NT 201 20/40 U NT 201 30/60 U Botox 30/60 U Intramuscular injection into Sternocleido-mastoid/Splenius capitis muscle	n=53 ITT n=41 TPP	Patients with cervical dystonia (rotational form with hypertrophied Sternocleido-mastoid muscle)	14 days controlled dose-finding period and 106 days follow-up	Finalized ICH
Phase 3	MRZ 60201-0433/1	5.3.5.1	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

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	MRZ 60201-0003	5.3.5.1	Non-inferiority of NT 201 compared to Botox in terms of efficacy and safety in patients with Blepharospasm	Randomized double-blind active-controlled (Botox) 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
Phase 3	MRZ 60201-0408/1	5.3.5.1	Safety and Efficacy of two doses of NT 201 compared with placebo in pre-treated and treatment-naïve subjects with Cervical Dystonia	Randomized, double-blind, placebo-controlled, multicenter study	120 U or 240 U NT 201 or placebo in a 1:1:1 ratio	n=109 ITT	Pre-treated and treatment-naïve patients with Cervical Dystonia	Up to 20 weeks	Finalized ICH
Phase 3	MRZ 60201-0013	5.3.5.1	Non-inferiority of NT 201 compared to Botox in terms of efficacy and safety in patients with Blepharospasm	Randomized double-blind active-controlled (Botox) parallel group multicenter trial to test non-inferiority	70-300 U NT 201 70-300 U Botox intramuscular injection at baseline	n=463 ITT n=420 TPP n=463 EFS	Patients with cervical dystonia Previous successful treatment with Botox in two consecutive sessions directly before trial entry	Up to 16 weeks	Finalized ICH

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	MRZ 60201-0410/1	5.3.5.1	Superiority of NT 201 compared to Placebo in terms of efficacy and safety in patients with post-stroke spasticity of the upper limb	Randomized double-blind placebo-controlled, parallel group multicenter trial to test superiority	170 - 400 U NT 201 or placebo intramuscular injection at baseline	n=148 ITT n=140 TPP n=148 EFS	Naïve and pre-treated patients with post-stroke spasticity of the upper limb	Up to 20 weeks	Finalized ICH
Phase 3	MRZ 60201-0410/2	5.3.5.1	Efficacy and safety of individually dosed, repeated injections of NT 201 over one year in patients with post-stroke spasticity of the upper limb	Open-label, non-controlled, multicenter trial	Up to 400 U NT 201 – repeated treatments with up to 5 injection sessions	n=145 ITT n=145 TPP n=145 EFS	Patients with post-stroke spasticity of the upper limb who participated in the placebo-controlled study MRZ 60201-0410/1	Up to 49 weeks	Finalized ICH
Phase 3	MRZ 60201-0607/1	5.3.5.1	Efficacy and safety of two dilutions of NT 201 (20 or 50 U/mL) in subjects with chronic upper limb spasticity of various etiologies	Phase 3, prospective, observer-blind, randomized, multicenter, controlled study	Up to 400 U NT 201 (20 or 50 U/mL) intramuscular injection at baseline	n=192 ITT n=165 TPP n=192 EFS	Pre-treated or treatment-naïve subjects with spasticity of the upper limb of various etiologies	Up to 20 weeks	Finalized ICH

Exposure Data cervical Dystonia and Blepharospasm for The Number Of Patients Who Received Xeomin Every 12 Weeks or Less for 6 Months (24 weeks) and 1 year (48 months) for The Time of NDA Submission and The 120-Day Safety Update (Sponsor's Tables)

- ***One set for the combined NDA filing and 120 day safety update.***

Number of Blepharospasm Patients Injected with Xeomin
By Total Dose Over 6 months (24 weeks-injected every 12 or less weeks)

	Number of Injection Series		
	1	**2**	**3 or more**
Dose (in units)			
1 to ≤ 49	2	4	12
50 to ≤ 74	8	0	22
75 to ≤ 99	5	0	8
100 or >	7	0	5

Number of Blepharospasm Patients Injected With Xeomin By Total Dose Over 1 year (48 weeks- injected every 12 weeks or less).

	Number of Injection Series			
	1	**2**	**3**	**4 or more**
Dose (in units)				
1 to ≤ 49	0	1	0	5
50 to ≤ 74	2	0	0	4
75 to ≤ 99	1	0	0	2
100 or >	2	0	0	0

Number of Cervical Dystonia Patients Injected with Xeomin
By Total Dose Over 6 months (24 weeks-injected every 12 weeks or less)

	Number of Injection Series		
	1	**2**	**3 or more**
Dose (in units)			
1 to ≤ 119	1	0	0
120 to ≤ 239	16	3	31
240 or more	15	7	36

Number of Cervical Dystonia Patients Injected With Xeomin By Total Dose Over 1 year (48 weeks- injected every 12 weeks or less).

	Number of Injection Series			
Dose (in units)	**1**	**2**	**3**	**4 or more**
1 to ≤ 119	0	0	0	0
120 to ≤ 239	4	0	0	5
240 or more	2	0	0	8

The Number of Patients Injected Every 70-98 Days (10-14 weeks) for Cervical Dystonia From Main period to End of Extension Phase (study 408) (Through 120-day update) Dose ≥120 Units (CDTL Table)

# injection series 70-96 days between injections	N=Patients
1	60
2	35
3	29
4	17
5	9
6	5

* Number of patients who received 3-6 injections given every 70-98 days between injections= 60 (total 155with visits between 70-98 days). A total number = 227 trial participants.

Blepharospasm Exposure (Sponsor Table)

Table 9: Summary of NT 201 Exposure in the Study 0433 Main and OLEX Periods by Dose Group and Exposure Period as of 25-Jun-2009 – 120-Day Safety Update Data

Observation Period	Dose Group		
	10 - 40 U	>40 U	Overall
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.

In this case the sponsor counted exposure based on the mean number of units over the entire duration of follow up. The number of injection within the follow up period is not given. In another table, the sponsor lists the number of injections but does not give the length of follow-up period. The tables will not distinguish if patients received 4 injections in 6 months or 2 injections over an entire year or if they have received 1 injection of 50 units and a second injection of 10 units to achieve a mean of 40 units.

CDTL Comment

Because the interval between injections could vary between each injection series, even within the same patient (i.e., a patient could have the second injection 12 weeks after the first and the 3rd injection 7 weeks later and the 4th injection 15 weeks after the 3rd) it is impractical to count the number of patients who received injections at a fixed interval (every 12 weeks). It is not reasonable to use the average interval since the shortest interval between can as little as 6 weeks with no limit on the interval after the first injection. This reviewer selected an interval of 70 days (10 weeks) to 98 days (14 weeks), which is 12 weeks ±2 weeks, as a reasonable interval between injections. The table above selected a patients who had injections between every 70-98 days and totaled the number of injections each patient had within that interval, so that 29 patients had 3 injections (70-98 days apart), likely at the higher end on the dosing interval (closer to 98days apart). All of the patients in this table were treated with 120 units or greater of Xeomin.

Number of Injections By Dose Given to Any Patient (Any Visit) in the Main and Extension Phases (Through 120-day update) (CDTL Table)

Total Dose Units	N injection visits
	1

120	165
125	2
140	1
220	1
225	1
240	188
400	1

CDTL Comment

This table lists the dose of any injection series administered to any patient at any frequency between doses for study 408 including the Main and Extension Phases. This includes all patients that were unblinded (completed) up through and including those included in the sponsor's 120-day safety update (planned interim analysis). The recommended dose is 120 units (b) (4)

The only other study where patients could receive up to 300 units of Xeomin for the treatment of CD was the active control study (0013), however this was a single dose (16 week) study. After reviewing, the Exposure and Treatments Administered sections of the study it remains unclear if any patients received a dose of 300 units of Xeomin in study 0013.

Exposure For Cervical Dystonia at 120-Day Safety Update (Sponsor's Table)

Table 9: Summary of NT 201 Exposure in the Study 0408 (CD) Main and Extension Periods by Dose Group and Exposure Period as of 25-Jun-2009 – 120-Day Safety Update Data

Observation Period	Dose Group			
	≤120 U	>120 to 240 U	Still Blinded	Overall
<2 weeks	-	1 (0.4%)	-	1 (0.4%)
2 to <7 weeks	1 (0.4%)	2 (0.9%)	-	3 (1.3%)
7 to <13 weeks	1 (0.4%)	4 (1.8%)	-	5 (2.2%)
13 to <21 weeks	4 (1.8%)	8 (3.5%)	-	12 (5.3%)
21 to <24 weeks	-	1 (0.4%)	-	1 (0.4%)
24 to <48 weeks	9 (4.0%)	20 (8.8%)	3 (1.3%)	32 (14.1%)
48 to <72 weeks	25 (11.0%)	60 (26.4%)	25 (11.0%)	110 (48.5%)
72 to <96 weeks	8 (3.5%)	21 (9.3%)	33 (14.5%)	62 (27.3%)
96 to <120 weeks	-	1 (0.4%)	-	1 (0.4%)
Overall	48 (21.1%)	118 (52.0%)	61 (26.9%)	227 (100%)

Data are presented as number of subjects (percent of subjects).
"-" indicates category not applicable.
CD: cervical dystonia; U: units.
Source: Table 1.5, Section 5.3.5.3, Appendix J.

CDTL Comment

The sponsor provided the Exposure table above however they fail to mention in the table in text that the exposure data was based on the average exposure. Merz lists the source of the data in this table as "Source: Table 1.5, Section 5.3.5.3, Appendix J". As a footnote to the source table Merz explains that the dose is based on the average dose,"*: Dose group is calculated from the average total dose over all injection sessions per patient". This is not as critical since patients were randomized to a dose of 120 unit vs. 240 units (or placebo in the Main Phase only). The table does not account for the interval between doses (frequency of injection).

Overall, the number of unique patient exposures for CD are adequate at the recommended dose of 120 units and above (n=155 for approximately 1 year). In BSP, there were approximately 35 patients who received Xeomin at doses of 50 units or more for approximately 6 months and only 11 BSP patients treated with any dose of Xeomin for 1 year. The long-term open label BSP study is still ongoing with approximately 25 patients yet to reach 1 year (at the time of the 120 day safety update). It seems likely that a majority of the patients will receive a dose of less than between 40-70 unit total for 1 year. It is not clear how many injection series a patient will receive over the year or the duration between injections.

Adverse Events

The primary safety Review was conducted by Dr. Lisa Jones, MD, MPH. The following summaries are excerpted from her review.

Deaths

The review by Dr. Jones found six patients who died during clinical trial participation in the Xeomin development program covering all indications. The three of the six deaths occurred in patients who were assigned to Xeomin (NT 201). All of the deaths occurred in patients enrolled in (b) (4) studies, and all three were in the open label 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 the conclusion regarding the cause of death. The determination was apparently based on the patient's medical history.

Serious Adverse Events

Dr Jones's analysis of SAEs in the NT 201 development program found that SAEs were generally similar to 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 (b) (4). Some of these patients were known to have pre-existing epilepsy, but in others, there was no history of epilepsy. All of the patients enrolled I the (b) (4) trial had a history (b) (4). Stroke is a frequent cause of secondary seizure disorder and epilepsy.

There has been a single post-marketing report of "anaphylaxis" the patient was a health care professional who described her symptoms as anaphylaxis. Upon further review, the diagnosis of anaphylaxis was dismissed because the case history did not provide sufficient information to consider it a true case of anaphylaxis.

Non-Serious Adverse Events (From Dr. Jones's Review)

- ***BSP:*** 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%). In the BSP open-label studies, the most common AEs in the repeated dose BSP 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).

- (b) (4) In the placebo-controlled (b) (4) studies, the AEs in the NT 201-treated group with the largest increase compare 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 (b) (4) studies, the

most frequent AEs were muscle spasticity (8.5%), depression (7.0%), upper respiratory track infection (5.6%) and muscular weakness (4.2%).

Discontinuations:
Although the number of discontinuations due to AE was 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.

Drop-Outs In the Repeated-Dose Study
In the Study 0433/2 OLEX period, as of June 25, 2009, a total of 19 subjects dropped out. Only one of these subjects dropped out because of a TEAE. Subject 2007 withdrew because of post-procedural pain and malignant breast lump removal (anesthesia was not permitted per the protocol, and the subject was therefore withdrawn from the study).

Adverse Events of Special Interest

Evidence of Systemic Spread of Toxin Effect:
Dr. Jones found there were no case reports 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 BSP, CD (b) (4) 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 (b) (4) 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 (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 (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).

Alkaline Phosphatase (ALP) (CDTL)

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. In the Xeomin development program, there were no changes in mean ALP levels. A few individual subjects experienced small but non-clinically significant increases in ALP all were < 2 times the upper limit of normal.

Nonserious Adverse Events

Nonserious Adverse Events Cervical Dystonia

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%)

Blepharospasm (Sponsor's Table)

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.

CDTL Safety Conclusion

The deaths and serious adverse events that were reported during the sponsor's clinical trials program do not indicate a significant new safety risk associated with Xeomin. The data from Blepharospasm, CD and spasticity trials were included in Dr. Jones's safety review. The data did not indicate a change in the frequency or type of serious and non-serious adverse events.

Many of the reported AEs were site specific and anticipated with botulinum toxin injection. The exception was dysphagia and dry mouth which was reported in patients who were injected for Blepharospasm (although dysphagia was more frequent in CD) and by patients treated for CD. There was a single case of potential Spread of Toxin Effect in a patient treated for spasticity. There were no cases of spread of toxin effect reported in patients treated for CD or BSP.

Overall, the safety profile of Xeomin appears to be similar to the approved botulinum toxin products. Post-marketing studies addressing the concern for potential spread of toxin effect, elevations of glucose and alkaline phosphatase will apply to this application. The class label language and boxed warning regarding the potential for spread of toxin effect will also be required in the Xeomin Label. Dr. Jones came to same independent conclusion, recommending approval and her review did not find any significant unexpected safety signals compared to other botulinum toxin products currently approved in the United States. The safety team leader Dr. Yasuda provided supervisory concurrence.

11. Advisory Committee Meeting

Not Applicable

12. Pediatrics

Xeomin was granted a waiver for pediatric studies by PeRC (February 24, 2009) on the grounds that children are not typically affected by either cervical dystonia or blepharospasm and clinical trials would be impracticable. (b) (4)

13. Other Relevant Regulatory Issues

The financial disclosures were completed for each of clinical trials referenced in the application. The investigators with disclosable relationships with the sponsor did not enroll a sufficient number of patients to influence the outcome of the trial. There was no indication by the sponsor that the treatment blind was compromised for any of the trials in their clinical development program.

The results of the DSI inspections did not find any violations or deficiencies that would impact the results of the respective clinical trials and no action was indicated for any of the sites inspected.

14. Labeling

Proprietary name- Xeomin approved

Current Status of the Label

The sponsor's initial product label omitted much of the class label language that is common to all of the approved botulinum toxin product labels. The boxed warning regarding the potential for spread of toxin effect and information regarding the lack of interchangeability of the toxins was also missing from the label. The sponsor accepted the boxed warning and other class safety language. The sponsor also accepted the restriction to patients previously treated with Botox for the blepharospasm indication. The sponsor accepted the recommended dose of 120 units with a statement that 240 units did not demonstrate additional efficacy. In the event that a few patients may require a Xeomin dose greater than 120 units the adverse events data the clinical trials data for 240 units will remain in the label.

At the time of this review, the review division and the sponsor are still negotiating the presentation of dose ranges and tables listing the mean dose per muscle (cervical dystonia) or mean dose per region (blepharospasm). The discussion is focused on how best to present the dosing information clearly in the label.

Carton and Container Review Comments from DMEPA

Comments to the Licensee

***A.* GENERAL COMMENTS**

DMEPA notes that the Licensee did not provide revised labels and labeling for all proposed packaging configurations which were previously reviewed. DMEPA recommends implementing all previous recommendation communicated from OSE Review # 2009-1705 dated June 11, 2010 as well as the recommendations below to all packaging configurations for Xeomin. All revised labels and label for each packaging configuration will need to be submitted for review prior to the action date.

B. CONTAINER LABEL (50 units/vial and 100 units/vial retail and physician samples)

1. Ensure the established name is printed in letters that are of a point size and typeface that is as least as prominent as the point size and typeface used in designating the trade name pursuant to 21 CFR 610.62(b) . As currently presented, the small white font on the black background makes the established name, 'IncobotulinumtoxinA' difficult to read.
2. Relocate the strength/potency statement to appear immediately following the presentation of the trade name/established name presentation. The current positioning of the strength statement above the established name at the top of the principal display panel is not the customary presentation with which practitioners are familiar on other injectable products.
3. Delete or reduce the size of the graphic on the principal display panel to allow room for the prominent presentation of important information.

C. CARTON LABELING

1. Increase the prominence of the Medication Guide statement, 'Dispense the enclosed Medication Guide to each patient'. As currently presented, the Medication Guide statement is less prominent than the 'Physician Sample' statement.
2. Relocate the statement, 'For Intramuscular Use' to the principal display panel to appear below the dosage form statement.

3. Remove the statement, [redacted] (b) (4). This information may cause confusion that may lead to dosing errors.

15 Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval in cervical dystonia with 120 units as the recommended dose with information for the 240 unit dose included in the label.

Approval for blepharospasm with 70 units as the maximum recommended dose. The indication should be restricted to blepharospasm patients successfully treated with Botox.

Risk Benefit Assessment

Overall, there is no reason to expect that the safety and efficacy of incobotulinumtoxinA (Xeomin) is materially different from onabotulinumtoxinA (Botox), with the exception being in botulinum toxin naïve patients with blepharospasm. It is reasonable to assume Xeomin is effective in toxin naive blepharospasm patients and non-naive patients. A safe starting dose of Xeomin in toxin naïve blepharospasm patients can not be extrapolated from the existing blepharospasm or cervical dystonia clinical trials data. The active comparator study with Botox does not provide sufficient data to conclude that Botox and Xeomin can be used interchangeably in patients with blepharospasm; also, there were no treatment naïve patients included in this trial. The approved indication for blepharospasm should limit its use to patients previously successfully treated with Botox. [redacted] (b) (4) The 240 unit dose in cervical dystonia appears reasonably safe and a marginal number of patients received repeat injections with 240 units for cervical dystonia. However, the clinical trials data does not indicate that there is additional benefit associated with the 240 unit dose compared to 120 units in patients with cervical dystonia.

[redacted] (b) (4) Given that Xeomin is approved for the treatment of spasticity in foreign markets and the is wide spread off label use of botulinum toxin type A products for the treatment of upper and lower limb spasticity in adults and children, there is a high probability that once marketed Xeomin will be used to treat spasticity in adults and children. Therefore, the agency should require safety study of Xeomin in adult and pediatric patients with upper or lower limb spasticity. We will ask the sponsor to commit to conducting clinical efficacy trials in adult and pediatric upper and lower (separately). The rationale for requiring the upper and lower limb spasticity be studies separately is evaluate the effect that location proximity to the diaphragm in the arm versus the leg can influence the risk for developing distant spread of toxin effect. Also the dose need to treat both the upper and lower limbs is likely to be very large. Preliminary data suggesting that the risk for distant spread of

toxin effect may be increased at doses above those used to treat cervical dystonia. The agency has recommended post marketing studies, some requirement and other as commitment for Xeomin. The sponsor has agreed in to the PMRs and PMCs recommended by the agency to study the safety and efficacy of the use of Xeomin for the treatment of upper and lower limb spasticity in adults and children.

Recommendation for Postmarketing Risk Management Activities
A Postmarketing Risk Evaluation and Mitigation Strategies (REMS) are recommended for Xeomin, which is consistent with all of the approved botulinum toxin products. The REMS will consist of a Medication Guide, a Communication Plan and a REMS Assessment at 1, 3, and 7 years after the initial approval.

The REMS has been presented to the sponsor and there is agreement on the REMS elements and assessment schedule.

DRISK Comments to DNP and the Sponsor Regarding the REMS
The proposed Xeomin® REMS mirrors the REMS requirements of other botulinum toxin products. No additional risks have been identified. Therefore, the Division of Risk Management and the Xeomin® REMS Review Team find the REMS for Xeomin® acceptable once the sponsor accepts the recommended changes in the REMS document and Dear Healthcare Professional Letter (see Appendices A-B attached).
OSE recommends approval of the appended Xeomin® REMS.

We have the following comments for DNP:
We recommend incorporating the information needed for assessment of the REMS into the approval letter.
Information needed for assessment will include but is not limited to:

1. A survey of patients' understanding of the serious risks of Xeomin®.
2. A survey of prescribers' understanding of the serious risks of Xeomin® and the lack of interchangeability of Xeomin® units with those of other licensed botulinum toxin products.
3. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
4. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.
5. An assessment of use data including:
    a. extent of use (denominator estimates)
    b. number of patients by age
6. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with Xeomin®
7. A summary of reports of all medication errors involving interchangeability of Xeomin® units with those of other licensed botulinum toxin products

8. Verification of sources of recipient lists for the Dear Healthcare Provider Letter
9. Number of recipients on each mailing list
10. Date(s) of mailing
11. Copy of document(s) included in the mailing

We have the following comments for the sponsor:

1. Please see attached REMS document and DHCP Letter for track changes (Appendices A-B). Revise the Supporting Document to be consistent with these changes in the REMS.
2. The timetable for submission for REMS assessment communicated in our interim comments was in error; the correct timetable is 18 months, 3 years, and 7 years. This has been corrected in the REMS document.

Current Status of The Medication Guide
At the time of this review, the Medication Guide has been negotiated with the sponsor and agreement has been reached on all major points in the medication guide. The Division and the sponsor are still negotiating final language details.

Postmarketing Requirements (PMR) and Commitments (PMC)

The Sponsor has reviewed and agreed in principle to the following postmarketing studies.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of adverse effects on prenatal and postnatal development or postnatal growth and development, and inadequate potency acceptance criteria. In addition, analysis of spontaneous postmarketing adverse events will not be sufficient to assess signals of serious risk of distant spread of toxin effects in patients with spasticity treated with Xeomin (incobotulinumtoxinA). A case report consistent with spread of toxin effect following treatment with Xeomin (incobotulinumtoxinA) was submitted in this application. In addition, there are several published reports of spread of toxin effect associated with similar botulinum toxin type A products.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3. A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Xeomin (incobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development.

The timetable you submitted on July 8, 2010 states that this study is ongoing and the final report will be submitted according to the following schedule:

PMR #1: Juvenile Rat Toxicology Study	
Milestone	**Date of Submission**
Final Protocol Submission	(b) (4) submitted <insert actual submission date>)
Study Completion Date	September 30, 2010
Final Report Submission	November 30, 2010

4. A prenatal and postnatal development (including maternal function) study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on stages of development and endpoints not evaluated in an embryo-fetal development study, in accordance with guidance set forth in ICH S5(R2): *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005).

PMR #2: Prenatal and Postnatal Development Study	
Milestone	**Date of Submission**
Final Protocol Submission	(b) (4) submitted <insert actual submission date>)
Study Completion Date	May 31, 2010 (completed <insert actual completion date>)
Final Report Submission	November 30, 2010

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a serious risk of distant spread of toxin effects in pediatric and adult patients with spasticity treated with Xeomin (incobotulinumtoxinA).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

5. Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years). Approximately one half of the patients must

be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either the upper or lower limb safety trial, but not both, and they should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these studies, or those commonly used to treat spasticity. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

The timetable you submitted on July 8, 2010 states that you will conduct this trial according to the following schedule:

PMR #3: Safety data assessing distant spread of toxin effects after multiple administrations of XEOMIN in pediatric patients	
Milestone	**Date of Submission**
• Final protocol submission*	July 31, 2012 [Please insert correct date]
• Trial Completion Date	March 31, 2018
• Final Report Submission^	December 31, 2018

*Including protocol of already completed studies, and plans for new analyses of data already submitted to the Xeomin BLA

^ Final Trials reports should be submitted as soon as they are available

6. Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 adult patients. Approximately one half of the patients must be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either an upper or lower limb safety study, but not both, and they should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these studies, or those commonly used to treat spasticity. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

The timetable you submitted on July 8, 2010 states that you will conduct this trial according to the following schedule:

PMR #4: Safety data assessing distant spread of toxin effects after multiple administrations of XEOMIN in adult patients	
Milestone	**Date of Submission**
• Final protocol submission*	December 31, 2011[Please insert correct date]
• Trial Completion Date	September 30, 2016
• Final Report Submission^	June 30, 2017

*Including protocol of already completed studies, and plans for new analyses of data already submitted to the Xeomin BLA

^ Final Trials reports should be submitted as soon as they are available

Submit the protocols to your IND <INSERT IND #>, with a cross-reference letter to this BLA. Submit all final report(s) to this BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated July 12, 2010. These commitments are listed below.

Regarding clinical efficacy in spasticity, you commit to conduct a:

7. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related

to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Final Protocol Submission: by January 31, 2012
Trial Completion Date: by July 31, 2016
Final Report Submission: by March 31, 2017

8. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Final Protocol Submission: by January 31, 2012
Trial Completion Date: by July 31, 2016
Final Report Submission: by March 31, 2017

9. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Final Protocol Submission: by June 30, 2011
Trial Completion Date: by December 31, 2014
Final Report Submission: by September 30, 2015

10. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naïve adults with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Final Protocol Submission: by March 31, 2011
Trial Completion Date: by September 30, 2014
Final Report Submission: by June 30, 2015

11. Randomized, double-blind, adequate and well controlled, parallel group, clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with blepharospasm. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Final Protocol Submission: by July 31, 2011

Trial Completion Date: by January 31, 2016
Final Report Submission: by October 31, 2016

Submit clinical protocols to your IND <INSERT IND #> for this product with a cross-reference letter to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated July 8, 2010. These commitments are listed below.

12. Conduct studies to determine the resistance of *Clostridium botulinum* spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be revalidated in the event the *Clostridium* spores are determined to be more resistant to (b) (4) inactivation than the *Geobacilus stearothermophilus* biological indicator spores. Results of the study should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by August 31, 2010.

13. Add a culture purity test at the end of the (b) (4) as an additional in-process control. The assay should be capable of detecting contaminating anaerobes. Assay qualification data and information should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by December 31, 2010.

14. Re-validate the drug substance release bioburden assay to include the use of (b) (4) of sample volume without dilution. Results should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by December 31, 2010.

15. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by December 31, 2010.

14. Revalidate the microbial ingress test (container closure integrity test) to demonstrate the integrity of the drug product container closure. Determine the sensitivity (minimum detectable leak size) of the test. Information and summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by February 1, 2011.

15. Re-qualify the crimping machine with media filled vials and the revalidated microbial ingress test. Summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by February 1, 2011.

16. Complete shipping validation studies for the drug product vials using the worst shipping temperature and duration. Validation information and summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) at the end of study by October 31, 2011.

17. Develop a container closure integrity test to replace the sterility test in the stability program. Information and summary validation data for the container closure integrity test should be submitted in a Prior Approval Supplement (PAS) by December 31, 2011.

18. Characterize the specificity of the antibody used in the abnormal toxicity test to evaluate whether this antibody recognizes only type A toxin and not other serotypes. Results of this validation study together with the proposed specifications for use in drug product release and in the lot release protocol should be submitted in a Prior Approval Supplement (PAS) by March 31, 2011

19. Characterize the ability of the SE-HPLC assay to accurately assess the aggregate content of the drug substance at release and on stability. This may be established by demonstrating that SE-HPLC provides similar results in aggregate content evaluations as compared to an orthogonal method that is quantitative and does not disrupt weak protein-protein interactions (e.g., AUC or FFF). Results of this validation study should be submitted in a Prior Approval Supplement (PAS) by February 28, 2011.

20. Investigate the development and implementation of a non-animal based potency assay for drug substance, drug product release and stability testing. A summary report together with any proposed modifications to the release and stability specifications should be submitted in a Prior Approval Supplement (PAS) by December 31, 2014.

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